

New Synthetic Approaches to Symmetrical Sulfur-Bridged Carbocycles

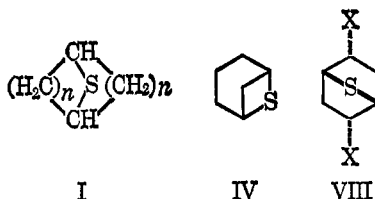
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New syntheses of 7-thiabicyclo[2.2.1]heptane (II) and 9-thiabicyclo[3.3.1]nonane (III) from cyclohexane and cyclooctane derivatives, respectively, are described. One approach involves the reaction of sulfur dichloride with a nonconjugated cyclic diene; the bridging step is the internal addition of S—Cl to C=C in an intermediate cycloalkenylsulfenyl chloride. The other approach depends on internal nucleophilic displacement by sulfur across a carbocyclic ring.

The class of bicyclic compounds which contain a sulfur bridge across a carbocyclic ring has not been subjected to a systematic study despite the fundamental character of such structures. As part of a program of research in this area we have been investigating the synthesis and chemistry of the series designated by I with $n = 1, 2, 3, 4,$ and 5. This paper reports a num-



ber of synthetic routes to two members of the series, 7-thiabicyclo[2.2.1]heptane (II) and 9-thiabicyclo[3.3.1]nonane (III). The former compound has previously been prepared in admixture with the isomeric 6-thiabicyclo[3.1.1]heptane (IV)¹ by a route which is both arduous and inefficient, and the latter substance has been prepared only in small quantities and very poor yield.

Syntheses of 7-Thiabicyclo[2.2.1]heptane (II).—The first synthesis of II which was developed in the present work is summarized in Chart I. The readily available 7-oxabicyclo[2.2.1]heptane² was converted by acid-catalyzed displacement with thiourea to the *trans*-4-hydroxycyclohexyl-S-isothiuronium cation which was hydrolyzed without isolation to *trans*-4-mercaptocyclohexanol (V) (66–92% yield). The mercapto alcohol V underwent selective S-acetylation with acetic anhydride in water at 0° in the presence of an equivalent of alkali to give the hydroxy thioacetate VI, and this was treated (without isolation) with

tosyl chloride to form *trans*-4-acetylthiocyclohexyl tosylate (81%); this upon exposure to alkali underwent saponification of the thiol ester grouping and intramolecular displacement to yield the desired 7-thiabicyclo[2.2.1]heptane (II) in 86% yield. The corresponding sulfone and S-methyl sulfonium iodide were prepared from II and the melting points for these three compounds were in reasonable agreement with those previously reported.¹ In addition the nmr spectra and infrared spectra of II and the various derivatives were fully consistent with assigned structures. Reaction of II with sodium metaperiodate afforded a single sulfoxide, as expected for the *sym*-7-thiabicyclo[2.2.1]heptane nucleus.

A second synthesis of II in two steps from 1,4-cyclohexadiene was devised. Simultaneous slow addition of the diene and sulfur dichloride (by automatic dual-syringe injection) to a large volume of methylene chloride at reflux led to the formation of 2,5-bis-*endo*-dichloro-7-thiabicyclo[2.2.1]heptane (VII) in 68% yield.³ Without the use of a high-dilution procedure polymeric products result almost exclusively. (See Experimental Section for details on a convenient high-dilution method.) Reduction of VII with excess sodium borohydride⁴ in wet dimethylformamide at 50° afforded II in *ca.* 50% yield.⁵ The samples of II obtained by this method were identical with those prepared from 7-oxabicyclo[2.2.1]heptane. The nmr spectrum of the intermediate dichloro-7-thiabicyclo[2.2.1]heptane unequivocally allows assignment of the *endo* orientation to both chlorine atoms as in VII since the observed coupling constant between the vicinal CHCl and bridged protons is *ca.* 3.5 cps., not 0

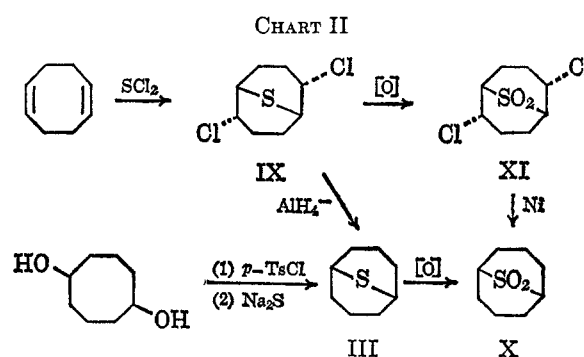
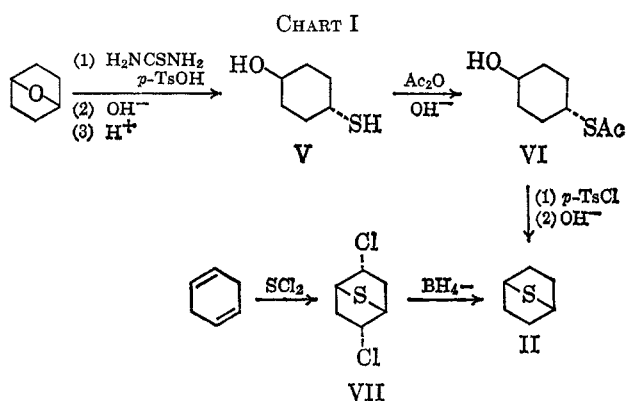
(1) S. F. Birch, R. A. Dean, and N. J. Hunter, *J. Org. Chem.*, **23**, 1026 (1958).

(2) E. A. Fehnel, S. Goodyear, and J. Berkowitz, *J. Am. Chem. Soc.*, **73**, 4978 (1951).

(3) A somewhat analogous reaction is the reported formation of 3,4-dichloro-3,4-dimethyltetrahydrothiophene from 2,3-dimethylbutadiene and sulfur dichloride; see H. J. Backer and J. Strating, *Rec. Trav. Chim.*, **54**, 52 (1935).

(4) H. C. Brown and H. M. Bell, *J. Org. Chem.*, **27**, 1928 (1962).

(5) A number of other experimental conditions were investigated, but all were found to be inferior to those indicated.



as would be expected for the corresponding isomer with *exo*-chlorine orientation. A full explanation of the nmr data is given in the Experimental Section.

The dichloride VII was converted smoothly to the corresponding sulfone with peracetic acid. Reaction of the dichloro sulfide VII with silver trifluoroacetate in trifluoroacetic acid at -5° or with trifluoroacetic acid alone at reflux gave 2,5-bis-*endo*-trifluoroacetoxy-7-thiabicyclo[2.2.1]heptane (VIII, X = OCOCF₃) stereospecifically and in high yield. The stereochemistry of this product follows from the nmr spectrum (see Experimental Section). Furthermore, treatment of VIII, X = OCOCF₃, with methanol in the presence of sodium methoxide as catalyst afforded the diol VIII, X = OH, which proved to be identical with a substance synthesized *via* a different and unequivocal route by Craig and Berchtold and assigned structure VIII, X = OH, by them.⁶ The dichloride VII gave the diacetate VIII, X = OCOCH₃, upon heating at reflux with acetic acid.

Syntheses of 9-Thiabicyclo[3.3.1]nonane (III).—The reaction of 1,5-cyclooctadiene with sulfur dichloride proceeded extremely well to give 2,6-dichloro-9-thiabicyclo[3.3.1]nonane (IX, 96% yield) even without the use of high dilution techniques (Chart II). The stereochemistry of this product follows from the nmr spectrum (see Experimental Section). Reaction of IX with methanol led to stepwise replacement of chlorine by methoxy, the first substitution being considerably faster than the second. Reduction of the dichloride IX by lithium aluminum hydride in ether afforded a product which is assigned structure III in 94% yield. The structural assignment rests on a second independent (and unequivocal) synthesis of III from *cis*-cyclooctane-1,5-diol as outlined in Chart II. Furthermore, catalytic hydrogenolysis of dichloro-sulfone XI gave sulfone X, identical with that prepared from III, eliminating the possibility of skeletal rearrangement during lithium aluminum hydride reduction of IX. The sulfoxide and S-methylsulfonium iodide derivatives have also been prepared from III as described in the Experimental Section.

Discussion

There are a number of points in connection with the synthetic work described above which are of special interest. The first is that the reaction of sulfur dichloride with nonconjugated dienes under proper dilu-

tion conditions represents a new and valuable route to sulfur-bridged carbocyclic systems. The stereochemistry of this reaction also is noteworthy: the stereospecific formation of VII and IX from 1,4-cyclohexadiene and 1,5-cyclooctadiene, respectively, indicates the probable involvement of 1,2-*epi*-sulfonium ion intermediates. Assuming the intermediacy of the sulfonium ion intermediates XII and XIII, it is



clear that there is positional as well as orientational specificity in the attachment of the second chloro group such as to give the symmetrical sulfur-bridged carbocycle in each case.⁷ Lastly, the stereochemistry and the fast rates of the solvolytic substitution reactions of the dichlorides VII and IX are an indication that ions XII and XIII intervene as intermediates in the solvolysis of these bridged β -chloro sulfides.

Experimental Section⁸

***trans*-4-Mercaptocyclohexanol (V).**—In a 5-l. three-necked flask fitted with reflux condenser, addition funnel, and mechanical stirrer, a mixture of 7-oxabicyclo[2.2.1]heptane (220 ml, 2.2 moles, bp 119.5–120°; synthesized by the procedure of Fehnel²), *p*-toluenesulfonic acid (625 g, 3.3 moles), thiourea (253 g, 3.3 moles), and 1 l. of 95% ethanol was brought to reflux.⁹ After 21 hr the homogeneous solution¹⁰ was cooled to room temperature and under nitrogen, with vigorous stirring, concentrated aqueous sodium hydroxide (280 g in 320 ml of distilled water, 7 moles) was added rapidly. The mixture was gently refluxed for

(7) See (a) M. Hanack and W. Kaiser, *Angew. Chem. Int. Ed. Engl.*, **3**, 583 (1964), A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *J. Am. Chem. Soc.*, **87**, 3130 (1965), for bridging carbon; (b) R. Köster, G. Griasnow, W. Larbig, and P. Binger, *Ann.*, **672**, 1 (1964), for bridging boron; (c) S. Wawzonek and P. J. Thelen, *J. Am. Chem. Soc.*, **72**, 2118 (1950), for bridging nitrogen; all for the cyclooctane series.

(8) Elemental analyses were performed by the Scandinavian Micro-analytical Laboratories, Herlev, Denmark. Exact molecular weights were determined on an AEI MS9 double-focusing mass spectrometer. Molecular weights were also determined using a Mechrolab vapor pressure osmometer, Model 301A. Mass spectra were determined on the mass spectrometer mentioned above. All melting points are corrected. Nuclear magnetic resonance (nmr) spectra were obtained on a Varian A-60 nmr spectrometer with tetramethylsilane as internal standard. Spin decoupling was accomplished using a Varian Associates Model V-6058 spin decoupler in conjunction with a Varian A-60 nmr spectrometer. Infrared spectra were obtained on a Perkin-Elmer 137 spectrophotometer and ultraviolet data were obtained from a Perkin-Elmer Model 202 spectrophotometer in ethanol as solvent.

(9) For related procedures, see L. A. Subluskey and L. C. King, *J. Am. Chem. Soc.*, **73**, 2647 (1951), and F. G. Bordwell and H. M. Andersen, *ibid.*, **75**, 4959 (1953). For other acid-catalyzed displacement reactions of 7-oxabicyclo[2.2.1]heptane, see L. R. Haeefe, Ph.D. Thesis, University of Illinois, 1958.

(10) *trans*-4-Hydroxycyclohexyl-S-isothiuronium tosylate could be isolated from this solution as a colorless solid, mp 184–185°, with spectral data in complete agreement with this structure.

(6) T. W. Craig, Ph.D. Thesis, Massachusetts Institute of Technology, 1965. We are grateful to Drs. Craig and Berchtold for communicating their results and for providing a reference sample.

1.5 hr in a nitrogen atmosphere and then the ethanol was removed by distillation. With vigorous stirring, ice-cold aqueous sulfuric acid (165 ml of concentrated sulfuric acid, 3.1 moles, was diluted to 900 ml with distilled water) was added slowly to the chilled flask contents. A slightly yellow oil [186 g (66%)] could be isolated from the reaction mixture.¹¹ Purification by vacuum distillation gave V as a colorless, foul-smelling viscous oil, bp 90° (1.5 mm). The infrared spectrum showed $\lambda_{\text{max}}^{\text{neat}}$ 2.96 (s), 3.94 (w, thiol band), and 9.37 μ (s). The nmr spectrum (CDCl₃) showed broad peaks at δ 1.30, 1.90 (nine protons including a sharp peak at δ 1.62 likely due to the thiol proton), δ 2.65, 3.45, and a sharp peak at δ 3.97 (each of the last three peaks integrated for a single proton). The exact molecular weight determined mass spectrometrically was 132.0601 (calcd for C₆H₁₀OS: 132.0609).

The diacetate of V was obtained in practically quantitative yield by reaction with acetic anhydride-sodium acetate at 130–150°: mp 66.6–68.0°; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.81 and 5.94 μ and no hydroxyl or thiol absorption.

Anal. Calcd for C₁₀H₁₆O₃S: C, 55.52; H, 7.46; O, 22.19; S, 14.82. Found: C, 55.54; H, 7.54; O, 22.21; S, 14.71.

trans-4-Acetylthiocyclohexyl Tosylate.—Vacuum-distilled V (1.29 moles, 170 g) was dissolved in 750 ml of distilled water containing 1.29 moles of sodium hydroxide. Then at 0° with vigorous stirring 121.2 ml (1.29 moles) of purified acetic anhydride was added during 10 min.¹² The solution¹³ was saturated with sodium chloride and extracted with methylene chloride. The carefully dried methylene chloride solution was transferred to a 5-l. three-necked flask equipped with mechanical stirrer, addition funnel, and nitrogen inlet outlet. After cooling to –20° in a nitrogen atmosphere, a solution of 296 g of *p*-toluenesulfonyl chloride (1.55 moles) in 510 ml (5 equiv) of dry pyridine and 350 ml of dry methylene chloride was added with stirring during 15 min. Stirring was continued at 0° for 34 hr. Crushed ice was then added and stirring was resumed for 30 min. After extensive washing of the organic phase with dilute hydrochloric acid and copper nitrate solution to remove pyridine, 342.2 g (81%) of a colorless, practically odorless solid, mp 96–105° (with decomposition), could be isolated. Recrystallization from ethyl acetate-*n*-hexane afforded a colorless solid with mp 109–110° (with decomposition); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.92, 7.42, 8.41, and 8.50 μ ; the nmr spectrum (CDCl₃) showed methylene protons at δ 1.2–2.2 (br) overlapping with methyl peaks at δ 2.30 and 2.46 (both sharp), tertiary protons at δ 3.4 and 4.5 (both br, one proton each), and an aromatic quartet (four protons) centered at δ 7.64. The molecular weight determined mass spectrometrically was 328.0809 (calcd for C₁₅H₂₀O₄S₂: 328.0804).

7-Thiabicyclo[2.2.1]heptane (II).—In a 1-l. three-necked flask equipped with stirrer, gas inlet-exit tube, and a rubber sleeve attached to a 250-ml erlenmeyer flask was placed a solution of 6 g of sodium (0.26 mole) in 400 ml of absolute methanol. The flask was chilled to 12–13° in an argon atmosphere and during 30 min 82.0 g of *trans*-4-acetylthiocyclohexyl tosylate (0.25 mole) was added from the erlenmeyer flask. Stirring was continued at 13° for 48 hr. Methyl acetate was saponified by stirring for 5 hr at 25° with a solution of 50 g of sodium hydroxide in 250 ml of distilled water. The reaction mixture was then extracted with trichlorofluoromethane and after washing with water, drying over anhydrous magnesium sulfate, and concentrating the organic phase through a Vigreux column, 24.6 g (86.4%) of II, a colorless waxy solid (mp 118–127°, sealed tube), was isolated by sublimation at 50° and atmospheric pressure. A resublimed sample of II, having a camphoraceous odor, had mp 126.5–127.5° (sealed tube; with sublimation; lit.¹ mp 127.5–128.5°). The molecular weight determined mass spectrometrically was 114. The very simple infrared spectrum had $\lambda_{\text{max}}^{\text{CCl}_4}$ 3.33 (s), 3.45 (sh), 6.89 (m), 7.62 (m), 8.07 (m) (all sharp peaks), 8.8–9.4 and 11.3–11.6 μ (two sets of three weak peaks each); the nmr spectrum (CFCl₃) showed two peaks, δ 1.63 (four protons) and δ 3.76 (one proton); the ultraviolet spectrum had λ_{max} 247 m μ (ϵ 43).

Anal. Calcd for C₆H₁₀S: C, 63.08; H, 8.83; S, 28.07. Found: C, 63.11; H, 8.90; S, 27.98.

(11) Yields as high as 92% have been realized when larger excesses of sulfuric acid and thiourea are employed.

(12) The method of S-acetylation utilized is that of L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 817 (1952).

(13) The infrared spectrum of the methylene chloride solution indicated the presence of thioacetate carbonyl (5.92 μ) and the complete absence of acetate carbonyl (5.78 μ). From this solution product VI could be isolated in good yield as a colorless liquid.

7-Thiabicyclo[2.2.1]heptane 7,7-Dioxide.—Compound II [2.8 g (24.6 mmoles)] in 10 ml of glacial acetic acid was treated at 18° with 58 ml (10 equiv) of peracetic acid ("Becco 40%") during 30 min. The mixture was stirred overnight at 25°, for 4 hr at 50°, and then concentrated *in vacuo*. The residual solid, after dissolving in methylene chloride, washing with brine, drying, and concentrating, was recrystallized from methylene chloride-*n*-hexane to afford 3.0 g (81%) of colorless, practically odorless needles: mp 252° (lit.¹ mp 253–254°); infrared $\lambda_{\text{max}}^{\text{CHCl}_3}$ 7.72 and 8.78 μ ; the nmr spectrum (CDCl₃) showed two peaks, δ 2.03 (four protons; an AB quartet with geminal $J_{\text{exo-endo}}$ = 10 cps) and δ 2.88 (one proton; br singlet). The molecular weight determined mass spectrometrically was 146.0406 (calcd for C₆H₁₀O₂S: 146.0401).

7-Thiabicyclo[2.2.1]heptane 7-Monoxide.—To a solution of 5.00 g (44 mmoles) of II in 150 ml of methanol at 0° was added 50 ml of an aqueous solution containing 10.4 g (47.5 mmoles) of sodium metaperiodate.¹⁴ The heterogeneous mixture was stirred vigorously at 0° for 24 hr and then allowed to warm to 25° overnight. The methanol was removed *in vacuo* after removal of the solid sodium iodate and unreacted sodium metaperiodate by centrifugation. The residual liquid was saturated with sodium chloride and extracted with chloroform (8 × 20 ml). Drying and concentrating the organic phase afforded (after drying *in vacuo*) 4.64 g (81%) of a practically colorless, odorless solid, mp 207.3–208.8° (with sublimation). A sample sublimed at 110° and atmospheric pressure had mp 208.3–209.9° (with sublimation) and showed a single spot on thin layer chromatography: infrared $\lambda_{\text{max}}^{\text{CCl}_4}$ 9.40 μ ; the nmr spectrum (CDCl₃) showed a multiplet at δ 1.3–2.7 (four protons) and a singlet at δ 3.37 (one proton; appears at δ 3.25 in CCl₄ as solvent). The molecular weight determined mass spectrometrically was 130.0452 (calcd for C₆H₁₀OS: 130.0452).

7-Methyl-7-thiabicyclo[2.2.1]heptane Sulfonium Iodide.—To 1.00 g of II (8.77 mmoles) in 3 ml of acetonitrile at 0° was added with stirring 2.70 ml of methyl iodide (a fivefold molar excess). The mixture was stirred at 0° for 24 hr and then warmed to room temperature during 0.5 hr. Excess ether was added and, after centrifuging, washing the product several times with ether, and air drying, 1.38 g (62%) of a colorless, crystalline solid, mp 134.5–135.5° (with decomposition) was isolated.¹⁵ An analytical sample prepared by recrystallization from absolute methanol had mp 135.5–136.0° (with decomposition; lit.¹ mp 138–139°). The nmr spectrum (CF₃COOH) showed peaks at δ 2.30 (doublet, eight protons), δ 2.77 (singlet, three protons), and δ 4.68 (singlet, two protons).

Anal. Calcd for C₇H₁₃IS: C, 32.82; H, 5.12; I, 49.54; S, 12.52. Found: C, 32.66; H, 5.07; I, 49.72; S, 12.64.

2,5-Bis-*endo*-dichloro-7-thiabicyclo[2.2.1]heptane (VII).—A 10-l. three-necked flask was fitted with stirrer, a Friedrichs condenser, and inlets for 1.5-mm-o.d. Teflon tubing from two-syringe drives (JKM Instrument Co., Durham, Pa.), each of which was fitted with a 100-ml syringe. During 24 hr, solutions of 10.0 ml of 1,4-cyclohexadiene¹⁶ and 7.0 ml of freshly distilled sulfur dichloride¹⁷ each in 60 ml of dry methylene chloride were simultaneously added to 5 l. of gently refluxing anhydrous methylene chloride. The syringes were refilled twice so that a total of 30.0 ml of 1,4-cyclohexadiene (0.315 mole) and 21.0 ml of sulfur dichloride (0.322 mole) had been added after 3 days. The deep yellow solution was then concentrated to about 200 ml, shaken with dilute acid and saturated salt solution, dried over magnesium sulfate, and added dropwise to 1 l. of *n*-pentane to precipitate 5.6 g (10%) of a white, odorless, highly insoluble polymer.

Concentration of the pentane filtrate yielded, after sublimation at aspirator vacuum and 95°, 38.9 g (68%) of a colorless, waxy solid with a distinctive odor, mp 93.0–94.3° (sealed tube); the infrared spectrum was sharp and relatively simple; the nmr

(14) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(15) In another run in which the above reaction mixture was stirred at 24° for 23 hr a 95% yield of 7-methyl-7-thiabicyclo[2.2.1]heptane sulfonium iodide was obtained contaminated with about 2% trimethylsulfonium iodide. When the bicyclic sulfonium salt was heated to its melting point it was converted into a compound which spectral data suggest was *trans*-4-iodocyclohexyl methyl sulfide. This latter compound, probably formed even at room temperature, could then react with methyl iodide to give 1,4-diiodocyclohexane and the observed trimethylsulfonium iodide.

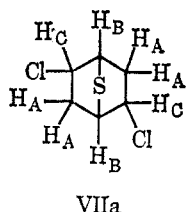
(16) A. P. Krapcho, Ph.D. Thesis, Harvard University, 1957; A. P. Krapcho and A. A. Bothner-By, *J. Am. Chem. Soc.*, **81**, 3658 (1959).

(17) G. Brauer, "Handbuch der Präparativen Anorganischen Chemie," Vol. 1, Ferdinand Enke Verlag, Stuttgart, 1960, p 336.

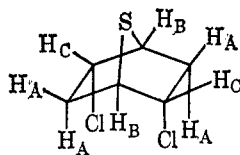
spectrum (CDCl_3) showed peaks at δ 2.40 (doublet of quartets, four protons), δ 3.64 (sextet, two protons), and δ 4.45 (sextet, two protons). The molecular weight determined mass spectrometrically was 181.9723 (calcd for $\text{C}_6\text{H}_8\text{Cl}_2\text{S}$: 181.9724).

Anal. Calcd for $\text{C}_6\text{H}_8\text{Cl}_2\text{S}$: C, 39.35; H, 4.40; Cl, 38.73; S, 17.51. Found: C, 39.11; H, 4.27; Cl, 38.75; S, 17.77.

Stereochemistry of VII as Determined by Spin Decoupling.—The nmr spectrum of VII in deuteriochloroform shows the protons labeled H_A (see VIIa below) as a multiplet at δ 2.40, H_B , a multiplet at δ 3.64, and H_C , a multiplet at δ 4.45. Saturation of protons H_A results in the collapse of protons H_B to a doublet ($J_1 = 3.4$ cps) and protons H_C to a doublet ($J_2 = 2.5$ cps; poor resolution, less accurate J value). J_1 and J_2 may be assigned to J_{BC} . Saturation of protons H_B results in the collapse of protons H_A to a doublet ($J_3 = 7.2$ cps) and protons H_C to a triplet ($J_4 = 7.5$ cps). J_3 and J_4 may be assigned to J_{AC} . Saturation of protons H_C results in the collapse of protons H_B to a triplet ($J_5 = 1.9$ cps). Poor resolution prevented an examination of the fine structure of protons H_A . J_5 may be assigned to J_{AB} .



VIIa



VIIb

The following conclusions may be drawn based on the above results. (1) In VII the *exo*- and *endo*-methylene protons are effectively magnetically equivalent and act as a single system of spin 1 or 0 in coupling to the H_B and H_C protons in the molecule.¹⁸ In VII the magnetic equivalence of the *exo*- and *endo*-methylene protons follows not only from the simplifications found on spin decoupling but also from the values of the coupling constants. In the norbornyl system¹⁹ the observed coupling constant between the *exo*-methylene protons and the vicinal bridgehead proton is 3.0–6.0 cps, whereas that for the corresponding *endo* methylene protons is 0 cps. From Table I it can be seen that J_{AB} in compound VII is 1.9 cps, in good agreement with the value calculated from the formula¹⁸ $J_{AB} = [J_{AendoB} + J_{AexoB}]/2$. (2) The stereochemistry of the chlorines is *bis-endo* as shown in VIIb. This follows from the value of 3.4 cps for J_{BC} , indicating that H_C must be *exo*.

Reduction of VII to II.—A solution of 400 mg of VII (2.2 mmoles) in 2 ml of dimethylformamide was added dropwise during 15 min to a vigorously stirred slurry of 3.5 g of sodium borohydride¹ (92 mmoles) in 6 ml of dimethylformamide containing 0.5 ml of dilute aqueous sodium hydroxide (pH ca. 11) at 50°. Vigorous gas evolution occurred; rapid stirring and slow addition were necessary to prevent foaming. After 3 hr at 50° the reaction mixture was treated with 100 ml of saturated aqueous sodium potassium tartrate (to destroy excess borohydride) and extracted with trichlorofluoromethane. The organic phase was shaken with water, dried, and concentrated through a short Vigreux column; the residue was sublimed at 50° and atmospheric pressure giving 122 mg (49%) of a waxy solid spectrally identical with sulfide II prepared from 7-oxabicyclo[2.2.1]heptane. In a parallel reduction of VII, the reduction product was shown not to depress the melting point of an authentic sample of II.

A variety of other methods were investigated for effecting the reduction of VII to II. Lithium aluminum hydride in refluxing ether or tetrahydrofuran after 2 days gave recovered VII and traces of decomposition products. The addition of 1–4 equiv of aluminum chloride to ethereal lithium aluminum hydride gave a low yield (ca. 20%) of II from VII after 24 hr at reflux temperatures. Other reducing agents such as dissolving metals, di-*n*-butyl tin dihydride, diborane, and aluminum borohydride proved ineffectual or resulted in the complete destruction of VII.

Oxidation of VII to 2,5-Bis-endo-dichloro-7-thiabicyclo[2.2.1]heptane 7,7-Dioxide.—Compound VII (2.75 mmoles, 500 mg) in 2 ml of glacial acetic acid was treated at 15° with 4 ml of "Becco 40%" peracetic acid during 15 min. After stirring over-

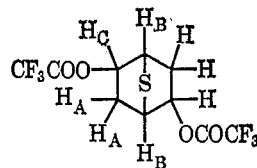
night at 25° and for 4 hr at 60°, the mixture was concentrated *in vacuo*. The residue was dissolved in methylene chloride, washed with aqueous alkali, dried, and concentrated giving 597 mg (97%) of a colorless solid, mp 190–192°. A doubly recrystallized sample had mp 195.5–195.8°; the infrared spectrum showed $\lambda_{\text{max}}^{\text{CHCl}_3}$ at 7.60 and 8.62 μ ; the nmr spectrum (CDCl_3) showed peaks at δ 2.7 (multiplet, two protons), δ 3.33 (triplet, $J = 3.5$ cps; one proton), and δ 4.89 (quintet, one proton). Molecular weight determined mass spectrometrically was 213.9626 (calcd for $\text{C}_6\text{H}_8\text{Cl}_2\text{O}_2\text{S}$: 213.9622). Refluxing the dichlorosulfone with saturated ethanolic silver nitrate for 3 days did not give a precipitate of silver chloride.

2,5-Bis-endo-trifluoroacetoxy-7-thiabicyclo[2.2.1]heptane (VIII, X = Trifluoroacetoxy).—To a solution of 200 mg (1.1 mmoles) of VII in 5 ml of trifluoroacetic acid at -5 to -10° was added with vigorous stirring 500 mg of silver trifluoroacetate (1 equiv; Chemicals Procurement Laboratories, Inc.) in 8 ml of trifluoroacetic acid during 30 min. An immediate white precipitate appeared. Stirring was continued for 45 min at 30° and, after removal of the silver chloride by centrifugation, the solution was concentrated *in vacuo*. An ethereal solution of the residue was washed with water and saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* giving 324 mg (87%) of a very slightly yellow, mobile liquid. Distillation of the crude product at 0.07 mm and 85° (bath temperature) gave a colorless liquid having a slight odor, n_D^{25} 1.4165, and molecular weight determined mass spectrometrically, 338.0043 (calcd for $\text{C}_{10}\text{H}_8\text{F}_6\text{O}_4\text{S}$: 338.0047). The infrared spectrum (neat) showed a strong carbonyl peak at 5.60 (μ) (trifluoroacetate) and two very intense peaks between 8.2 and 8.6 μ (trifluoromethyl group). The nmr spectrum (CCl_4) showed methylene protons at δ 1.9–2.83 (complex multiplet, two protons), bridgehead protons at δ 3.85 (triplet with $J = 4$ cps, one proton), and protons geminal to trifluoroacetate at δ 5.38 (complex multiplet of 11 peaks, one proton).

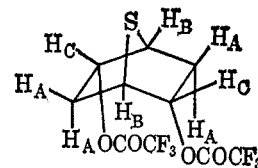
The bistrifluoroacetate can also be conveniently synthesized simply by refluxing VII with a slight excess of trifluoroacetic acid for several hours. For example 2.00 g (11 mmoles) of VII was refluxed with 5 ml of trifluoroacetic acid (67 mmoles) for 11 hr (the reaction was 90% complete after 6.5 hr). Bistrifluoroacetate, 3.34 g (90%) (identical with product from silver trifluoroacetate run), was isolated from the reaction mixture as described above.

Anal. Calcd for $\text{C}_{10}\text{H}_8\text{F}_6\text{O}_4\text{S}$: C, 35.53; H, 2.39; S, 9.49. Found: C, 35.74; H, 2.66; S, 10.01.

Stereochemistry of VIII (X = Trifluoroacetoxy) as Determined by Spin Decoupling.—The nmr spectrum of VIII (X = trifluoroacetoxy) in deuteriochloroform showed H_A , a complex multiplet at δ 1.9–2.83, H_B , a triplet at δ 3.85, and H_C , a complex multiplet at δ 5.38 (see VIIIa below for labeling). Saturation of protons H_A results in the collapse of protons H_B to a doublet ($J_1 = 3$ cps). J_1 may be assigned to J_{BC} . Saturation of protons H_B results in the collapse of protons H_C to a quartet ($J_2 = 3$ cps, $J_3 = 10$ cps). J_2 may reasonably be assigned to J_{AendoC} and J_3 to J_{AexoC} . Saturation of protons H_C results in the collapse of protons H_B to a doublet ($J_4 = 3.6$ cps). J_4 may be assigned to J_{AexoB} . Saturation of protons H_B and H_C resulted in the partial simplification of protons H_A but these methylene protons were still too complex for analysis.



VIIIa



VIIIb

It may be concluded that the stereochemistry of the trifluoroacetoxy groups is *bis-endo* as shown in VIIIb; this follows from the fact that $J_{BC} = 3.8$ cps indicating that H_C must be *exo*. It can be seen that the triplet observed for the bridgehead protons in the bistrifluoroacetate nmr spectrum ($J = 4.0$ cps) is due to the overlapping of two doublets of very similar J values (3.8 and 3.6 cps).

2,5-Bis-endo-acetoxy-7-thiabicyclo[2.2.1]heptane (VIII, X = Acetoxy).—The chlorine atoms in VII may be easily replaced by acetate by refluxing VII for several hours with glacial acetic

(18) For a discussion of the phenomenon of virtual coupling, see J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

(19) For a summary of coupling constants in the norbornyl system, see P. Laszlo and P. von R. Schleyer, *J. Am. Chem. Soc.*, **86**, 1171 (1964).

acid. The crystalline product so obtained in good yield (83% crude, 51% recrystallized, mp 63–64.1°) has spectral properties very similar to VIII (X = trifluoroacetoxy) (*e.g.*, the nmr spectrum is essentially identical with that of the bistrifluoroacetate except for the acetate methyl protons and a slight chemical shift) and is considered to be 2,5-bis-*endo*-acetoxy-7-thiabicyclo[2.2.1]heptane.

2,5-Bis-*endo*-hydroxy-7-thiabicyclo[2.2.1]heptane (VIII, X = Hydroxy).—Crude VIII (1.929 g, 5.7 mmoles) (X = trifluoroacetoxy) was dissolved in 25 ml of absolute methanol containing a trace of sodium methoxide. Removal of methanol and methyl trifluoroacetate by distillation through a short Vigreux column and recrystallization of the crude solid residue (0.788 g) from boiling benzene gave 0.725 g (87%) of a colorless, odorless solid, mp 249–253° (with sublimation and decomposition); the nmr spectrum (deuterioacetone) showed peaks at δ 2.03 (quartet, $J_1 = 6$ cps, $J_2 = 2.3$ cps; two protons), δ 3.30 (quartet, $J = 2.5$ cps, one proton), δ 4.12 and 4.40 (overlapping broad peaks, two protons). The nmr spectrum in pyridine was very different from that in deuterioacetone owing to the absence of virtual coupling (present in the latter solvent): δ 2.0–2.85 (complex multiplet of 17 peaks, one proton), δ 3.58 (triplet, $J = 4$ cps; one proton), δ 4.87 (multiplet, one proton), and δ 6.59 (br singlet; overlap with pyridine peaks prevented accurate integration). Sublimation of the diol at 100° (0.07 mm) gave a product having infrared: $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.70 (μ), 2.8–2.9 (μ), and 9.52 (μ (s)). The molecular weight determined mass spectrometrically was 146.0410 (calcd for $\text{C}_6\text{H}_{10}\text{O}_2\text{S}$: 146.0401), and a mixture melting point with authentic 2,5-bis-*endo*-hydroxy-7-thiabicyclo[2.2.1]heptane⁶ showed no depression; spectral data supported the identity of the two samples.

Anal. Calcd for $\text{C}_6\text{H}_{10}\text{O}_2\text{S}$: C, 49.29; H, 6.89; O, 21.89. S, 21.93. Found: C, 49.27; H, 6.84; O, 22.01; S, 21.88.

2,6-Dichloro-9-thiabicyclo[3.3.1]nonane (IX).—To a mixture of 125 ml of 1,5-cyclooctadiene (1.02 moles; treated with alumina and distilled from sodium *in vacuo*) and 1 l. of reagent methylene chloride at -50° in a nitrogen atmosphere in a 2-l. three-necked flask (fitted with stirrer, addition funnel, and nitrogen inlet-outlet) was added with vigorous stirring a solution of 65 ml (1.02 moles) of freshly distilled sulfur dichloride¹⁷ in 500 ml of reagent methylene chloride. The addition was carried out during 90 min. The slightly yellow, cloudy solution was allowed to warm to 0° during 30 min, filtered from trace amounts of side products, shaken several times with cold brine, dried, and concentrated to give, after air drying, 204.9 g (96.6%) of a very faintly yellow solid, mp 97.9–99.9°. Sublimation at 48° (0.05 mm) gave colorless crystals with a mild odor, mp 98.1–99.6°. The infrared spectrum was sharp and relatively simple showing, in particular, $\lambda_{\text{max}}^{\text{CHCl}_3}$ at 6.75 (μ (s)) in addition to the normal methylene band at 6.95 (μ (m)).²⁰ The nmr spectrum (CHCl_3) showed peaks at δ 2.34 (multiplet), δ 2.80 (multiplet; the total area of these two overlapping peaks was five protons), and δ 4.68 (sextet, one proton). The molecular weight of the sublimed solid determined osmometrically was 217 ± 3 , determined mass spectrometrically, 210, and calculated, 210 (for ^{35}Cl). Treatment of an ethanolic solution of IX with ethanolic silver nitrate at room temperature gave immediately an abundant white precipitate.

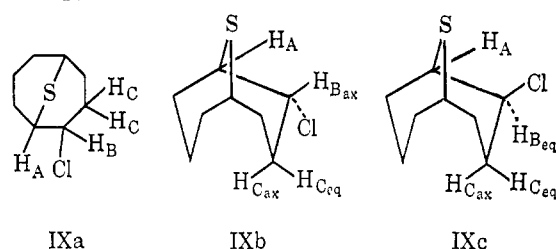
Anal. Calcd for $\text{C}_8\text{H}_{12}\text{Cl}_2\text{S}$: C, 45.48; H, 5.73; Cl, 33.60; S, 15.18. Found: C, 45.29; H, 5.73; Cl, 33.92; S, 15.32.

Stereochemistry of IX as Determined by Spin Decoupling.—A saturated solution of IX in chloroform at 50° was examined by double resonance nmr spectroscopy. Saturation of the multiplet at δ 2.80 (H_A) resulted in the collapse of the δ 4.68 sextet (H_B) to a triplet ($J = 8$ cps); therefore, $J_{BC} = 8$ cps (see IXa below for labeling). Saturation of the multiplet at δ 2.34 (H_C) resulted in the collapse of the H_B signal to a doublet ($J = 3$ cps); therefore, $J_{AB} = 3$ cps. Values for J_{AB} and J_{BC} could also be calculated from the H_B peak and the results are summarized below in Table I.

The following conclusions may be inferred from these results.
(1) Both chlorines are *endo* and *trans* to the carbon–sulfur bond.
(2) Protons H_C are virtually equivalent. The 9-thiabicyclo-

(20) All of the 9-thiabicyclo[3.3.1]nonane derivatives studied showed the same characteristic methylene band at about 6.75 (μ (1481 cm^{-1})) reported for the chair–chair conformation of bicyclo[3.3.1]nonanes (ref 20a), reported value, 1490 cm^{-1}) but missing in the infrared spectrum of bicyclo[4.2.1]nonane (ref 20b). (a) W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964); G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965). (b) see ref 7a—paper by A. C. Cope, *et al.*

Coupling constant	Spin decoupling value, cps	Spectrum anal. value, cps
J_{AB}	3.0	4
J_{BC}	8.0	8



[3.3.1]nonane system is presumably in a chair–chair (cyclohexane) conformation.²⁰ Thus the values of coupling constants for cyclohexane derivatives could be applied: $J_{\text{ax-ax}} = 9\text{--}13$ cps, $J_{\text{ax-eq}} = 2\text{--}4$ cps, and $J_{\text{eq-eq}} = 2.7\text{--}4$ cps.²¹ Then for IXb, $J_{\text{BaxC}} = [J_{\text{BaxCax}} + J_{\text{BaxCeq}}]/2 = 5.5\text{--}8.5$, and for IXc, $J_{\text{BecC}} = [J_{\text{BecCax}} + J_{\text{BecCeq}}]/2 = 2.35\text{--}4$ cps. The value of 8 cps for J_{BC} indicates that the correct stereochemistry for IX is IXb.

Reaction of IX with Methanol.—The chlorine atoms of IX appear to be unequally reactive towards replacement by the methoxy group. When IX was boiled with methanol for several minutes, an oil was obtained in which the ratio of methoxy group to chlorine as determined by nmr was *ca.* 1:1; after 7 hr of refluxing IX with methanol this ratio was 3:1.

Compound IX (2.37 mmoles) (500 mg) was refluxed for 60 hr with 10 ml of methanol containing 0.57 ml of 2,6-lutidine (5 mmoles). After 60 hr the methanol was distilled off, the product washed with dilute acid and brine, dried, and concentrated giving 386 mg (81%) of a colorless oil of good purity (the infrared spectrum was identical with that of distilled product). Distillation at 110° (0.1 mm) gave a colorless oil with $\lambda_{\text{max}}^{\text{CHCl}_3}$ 3.52 (CH_3O), 6.76 (μ), 6.86 (μ , sh), 6.95 (μ), 9.15 (μ (s)); the nmr spectrum (CCl_4) showed peaks at δ 1.6–2.4 (multiplet of area eight), δ 2.6–2.8 (quartet of area two), δ 3.17 (singlet of area three) and δ 3.6 (septet of area two); n_D^{20} 1.5203.

Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_2\text{S}$: C, 59.37; H, 8.97; O, 15.82; S, 15.85. Found: C, 59.51; H, 8.98; O, 15.97; S, 15.54.

The infrared band at 6.76 μ suggests that the 9-thiabicyclo[3.3.1]nonane skeleton remains²⁰ and a likely structure for the dimethoxy product would be 2,6-dimethoxy-9-thiabicyclo[3.3.1]nonane.

9-Thiabicyclo[3.3.1]nonane (III).²²—Anhydrous ether (350 ml) in a 2-l. three-necked flask equipped with a 5-cm stirring bar, reflux condenser, addition funnel, and nitrogen inlet-outlet was presaturated with 30.3 g of lithium aluminum hydride (0.8 mole) and then treated with a solution of 170 g of IX (0.8 mole) in 1300 ml of anhydrous ether at such a rate as to maintain gentle reflux (45 min required for addition). After the addition was completed, the mixture was gently refluxed for 2.5 hr. Excess reducing agent was destroyed by the cautious addition of water and the product was then filtered through a mat of Celite. The granular solid was washed several times in the funnel with ether. The combined organic phase was washed with brine, dried, and concentrated giving 108 g (94%) of a colorless solid having a camphor-like odor, mp 168.6–173.1° (sealed tube; with sublimation), and giving a single spot on thin layer chromatography on several different supports. Sublimation at 70° and atmospheric pressure gave a colorless solid with mp 167.7–168.6° (sealed tube; with sublimation); the infrared spectrum was sharp and simple showing, in particular, a $\lambda_{\text{max}}^{\text{CHCl}_3}$ at 6.75 (μ (m)); the nmr spectrum (CDCl_3) displayed two partially overlapping peaks at δ 1.4–2.3 (br, seven protons) and δ 2.84 (br, one proton). The molecular weight determined mass spectrometrically was

(21) F. A. Bovey, *Chem. Eng. News*, 43, 98 (1965). For coupling constants in the bicyclo[3.3.1]nonane system, see R. Lygo, *et al.*, *Chem. Commun.*, 15, 356 (1965).

(22) Compound III, itself, has been previously prepared in very poor yield: S. F. Birch, T. V. Cullum, and R. A. Dean, *Chem. Eng. Data Series*, 3, 359 (1958). The syntheses of several compounds possessing the 9-thiabicyclo[3.3.1]nonane skeleton have been reported: A. H. Frazer and W. P. O'Neill, *J. Am. Chem. Soc.*, 85, 2613 (1963); V. Horák, J. Závada, and A. Piskala, *Acta Chim. Acad. Sci. Hung.*, 21, 97 (1959); *Chem. Ind. (London)*, 1113 (1958).

142. The ultraviolet spectrum showed λ_{\max} at 235 $m\mu$ (sh, ϵ 167).

Anal. Calcd for $C_8H_{14}S$: C, 67.52; H, 9.93; S, 22.54. Found: C, 67.08; H, 9.81; S, 22.47.

***cis*-1,5-Cyclooctanediol Ditosylate.**—*cis*-1,5-Cyclooctanediol was prepared by hydroboration of 1,5-cyclooctadiene according to the method of Sharma.²³ To a solution of 0.8 g (5.55 mmoles) of the diol in 8 ml of anhydrous pyridine was added, at 0°, 2.56 g (1.2 equiv) of *p*-toluenesulfonyl chloride. The solution was stirred under nitrogen at 0° for 34 hr. Water (1 ml) was added and the mixture was stirred for an additional 30 min at 0°. The cold mixture was poured onto 7 ml of concentrated hydrochloric acid mixed with crushed ice and extracted with chloroform (3 × 10 ml) and ether (10 ml). The organic layer was washed with ice-cold 3 *N* hydrochloric acid (3 × 50 ml), 2 *N* copper sulfate solution (2 × 40 ml), and 5% aqueous sodium carbonate (40 ml), dried with anhydrous magnesium sulfate, and concentrated. Recrystallization of the crude product from methanol gave 2.12 g (83.5%) of colorless crystalline *cis*-1,5-cyclooctanediol ditosylate. An analytical sample had mp 83.1–84.3° (with decomposition). The infrared spectrum did not show hydroxyl absorption but did show the characteristic tosylate bands; the nmr spectrum ($CDCl_3$) showed peaks at δ 1.7 (six protons; methylene protons), δ 2.40 (three protons, methyl group), δ 4.5 (one methine proton), and δ 7.5 (four protons, aromatic quartet).

Anal. Calcd for $C_{22}H_{28}O_6S_2$: C, 58.40; H, 6.24; O, 21.21; S, 14.17. Found: C, 58.28; H, 6.18; O, 21.19; S, 14.35.

Synthesis of III from *cis*-1,5-Cyclooctanediol Ditosylate.—In 18 ml of dimethyl sulfoxide 1.07 g (4.4 mmoles) of sodium sulfide nonahydrate and 1.00 g (2.2 mmoles) of *cis*-1,5-cyclooctanediol ditosylate were dissolved and the heterogeneous mixture was stirred at 27° in a nitrogen atmosphere for 100 hr. The reaction mixture was diluted with 100 ml of water and extracted with pentane (3 × 33 ml). The pentane layer was washed with water and 10% aqueous potassium hydroxide, dried over anhydrous magnesium sulfate, and concentrated at 0° *in vacuo* giving 272 mg of crude product. Purification of this crude product by passage through 200 mg of grade I Woelm alumina gave 224.5 mg (72%) of a white solid with a camphoraceous odor. A sublimed sample gave a single spot on thin layer chromatography with the same R_f value as the sulfide III prepared by reduction of IX and had mp 168.2–168.6° (sealed tube), undepressed by admixture with sulfide III prepared from IX. The nmr and infrared spectra of the two samples of III were identical.

9-Thiabicyclo[3.3.1]nonane 9,9-Dioxide (X).—Utilizing the procedure followed in the synthesis of 7-thiabicyclo[2.2.1]heptane-7,7-dioxide, 0.30 g of III gave 0.36 g (98%) of a colorless, odorless crystalline solid with mp 297–299° (with sublimation and decomposition); the infrared spectrum showed $\lambda_{\max}^{CHCl_3}$ at 7.75 and 9.00 μ (sulfone bands; the spectrum was characteristically simple) in addition to a band at 6.75 μ . The nmr spectrum (CF_3COOH) revealed methylene protons at δ 1.6–2.9 overlapping with bridgehead protons at δ 3.12. Thin layer chromatography indicated the presence of a single compound. The molecular weight determined mass spectrometrically was 174.0713 (calcd for $C_8H_{14}O_2S$: 174.0714).

(23) R. K. Sharma, B. A. Shoulders, and P. D. Gardner, *Chem. Ind. (London)*, 2087 (1962).

2,6-Dichloro-9-thiabicyclo[3.3.1]nonane 9,9-Dioxide (XI).—Compound IX (0.5 g) (2.37 mmoles) was oxidized (as in the synthesis of X) to 0.5 g (91%, after recrystallization) of XI, fine, colorless crystals, mp 171.2–173.5° (with sublimation). The infrared spectrum showed $\lambda_{\max}^{CHCl_3}$ at 6.75 μ in addition to sulfone bands at 7.9 and 8.9 μ ; the nmr spectrum (CF_3COOH) displayed a methylene proton peak at δ 2.1–2.8 (br, four protons), a bridgehead proton peak at δ 3.42 (one proton), and a tertiary proton geminal to chlorine at δ 4.78 (one proton). Thin layer chromatography indicated the presence of a single compound. The molecular weight determined mass spectrometrically was 241.9929 (calcd for $C_8H_{12}Cl_2O_2S$: 241.9935).

Treatment of XI with silver nitrate in boiling ethanol did not give a precipitate of silver chloride.

An analytical sample prepared by sublimation at 80° and 0.01 mm had mp 173.9–174.9° (with sublimation).

Anal. Calcd for $C_8H_{12}SO_2Cl_2$: C, 39.52; H, 4.98; S, 13.19; O, 13.16; Cl, 29.16. Found: C, 39.54; H, 5.01; S, 13.21; O, 12.68; Cl, 29.56.

Conversion of XI to X.—Compound XI (125 mg) (0.51 mmoles) was stirred with 2.5 g of Raney nickel in 25 ml of absolute dioxane in a hydrogen atmosphere at 50° for 18 hr. Concentration of the filtered dioxane solution afforded 92 mg of a colorless solid which, according to nmr analysis, still contained chlorine. Recrystallization of the crude product twice from carbon tetrachloride gave in 27% yield a colorless solid, mp *ca.* 295° (with decomposition), whose infrared and nmr spectra were identical with those of sulfone X prepared from III.

9-Thiabicyclo[3.3.1]nonane 9-Monoxide.—To a solution of 1.00 g of sulfide III (7.05 mmoles) in 35 ml of methanol at 0° with stirring was added 30 ml of 50% aqueous methanol, 0.25 *M* in sodium metaperiodate (7.5 mmoles of oxidant). The solution was stirred for 13 hr at 0° and 25 hr at 24° and then extracted with methylene chloride. The organic phase was washed with water, dried, and concentrated to give 800 mg (73%) of a colorless solid, mp 241–253° (with sublimation and decomposition). A sublimed sample, showing a single spot on thin layer chromatography, had mp 252–255°; infrared $\lambda_{\max}^{CHCl_3}$ 6.73 (m), 9.49 μ (s, sulfoxide band); the nmr spectrum ($CDCl_3$) showed peaks at δ 1.4–2.8 (multiplet, six protons) and δ 2.95 (singlet, one proton). The molecular weight determined mass spectrometrically was 158.0762 (calcd for $C_8H_{14}OS$: 158.0765).

9-Methyl-9-thiabicyclo[3.3.1]nonane Sulfonium Iodide.—Methyl iodide (1.1 ml) (17.8 mmoles) was added to 0.50 g of III in 4 ml of acetonitrile at 26°. A crystalline precipitate appeared within several minutes. The mixture was stirred overnight at 25° and for 3 hr at 60° under a reflux condenser. Excess ether was added and, after centrifuging, washing the product several times with ether, and air drying, 0.95 g (95%) of a colorless crystalline solid, mp *ca.* 263° (sealed tube; decomposition to III occurs) was obtained: infrared λ_{\max}^{KBr} at 6.78 μ ; the nmr spectrum (CF_3COOH) showed peaks at δ 1.7–2.7 (br, *ca.* 14 protons), δ 2.98 (sharp, three protons), and δ 3.75 (br, two protons).

Acknowledgment.—We are indebted to the National Institutes of Health and the National Science Foundation for Predoctoral Fellowships to Eric Block, 1962–1965.