Reactions of a Bridgehead Sulfonium Salt with Nucleophiles. The Proton Nuclear Magnetic Resonance Spectra of Hexahydro-1,1-dimethyl-3*H*-2,4,7-ethanylylidene-1*H*-cyclopenta[*c*]thiopyrilium Bromide and Its Derivatives[1a]

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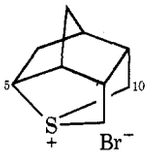
On reaction with a series of nucleophiles, the bridgehead sulfonium salt hexahydro-1,1-dimethyl-3*H*-2,4,7-ethanylylidene-1*H*-cyclopenta[*c*]thiopyrilium bromide (3) affords β-elimination products in a higher proportion than substitution products. Proton nmr chemical shift assignments are presented for the salt 3, its progenitors, and its elimination and substitution products. Specifically deuterated compounds 9–12 and 14 have been prepared to assist in the nmr analysis. The anomalous downfield chemical shift of the exo methyl of 13 and the exo cyanomethyl of 16 are attributed to the proximity of the sulfur lone electron pair.

In recent years in this laboratory there has been considerable interest in the synthesis and reactivity of conformationally rigid bicyclic sulfonium salts in which the sulfonium function is located at a bridgehead position. Many examples of this type of sulfonium compound[2-5] have been found to possess biological activity as alkylating agents.[6] In 1965 the synthesis of the bridgehead sulfonium salt 1 was reported.[7] Subsequently the study was extended[8] and it was found that nucleophilic attack occurs at C-5 or C-10. No products arising from β-elimination reactions were observed. Similar results have been reported[9] for sulfonium salt 2. The synthesis of the bridgehead sulfonium compound 3 and an examination of its reactivity as an alkylating agent is the subject of the present study.



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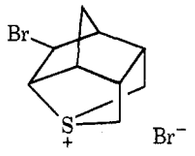

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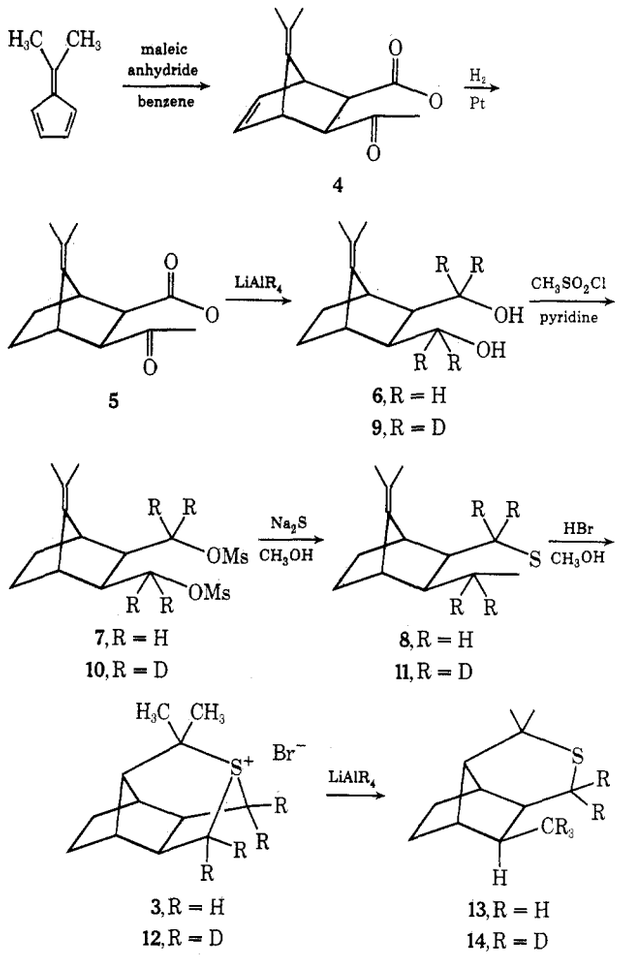
The synthesis of sulfonium salt 3 is described in Scheme I. Dimethylfulvene and maleic anhydride reacted in boiling benzene to give the exo adduct 4. This adduct was hydrogenated over platinum catalyst to give 5 which, in turn, afforded *exo*-7-isopropylidenebicyclo[2.2.1]heptane-2,3-dimethanol (6) on reduction with $LiAlH_4$. Reaction of the diol 6 with methanesulfonyl chloride gave the methanesulfonate diester 7, and the sulfide 8 was then prepared by a modification of the method of cylization of Owen and Peto[10] using sodium sulfide nonahydrate. With refluxing 48% HBr solution, the sulfide 8 afforded the cyclic bridgehead sulfonium salt 3. For the nmr analysis to be described below, the specifically deuterated sulfonium salt 12 and its several progenitors were prepared by the method in Scheme I except for the use of $LiAlD_4$. Sulfide 14 was obtained directly from 12 by reaction with $LiAlD_4$.

Scheme I



Results and Discussion

The reactions with nucleophiles were carried out in refluxing aqueous medium with the sodium or potassium salt of the nucleophile, with the exceptions of *N*-methylaniline and $LiAlH_4$. The product mixtures were separated by preparative glpc, and the assignment of structures was based largely upon interpretation of their nmr spectra. The product distributions for these reactions, the percentages of which were determined by analytical glpc, are summarized in Table I.

Inspection of the distribution of elimination and substitution products reveals no immediate clear-cut pattern, other than a predominance of elimination over substitution. This predominance is typical for straight- and branched-chain alkylsulfonium salts under the conditions employed, but is in contrast to results of studies in this laboratory for similar cyclic bridgehead sulfoniums.[8,9] At the outset of these experiments it was demonstrated that the salt 3 does not undergo unimolecular elimination; namely, in one experiment an aqueous solution of 3 was refluxed for 48 hr without change and similar results were found for refluxing ethyl ether.

The investigation of the sulfonium salt 3 as an alkylating agent presented two problems: (1) the determination

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NMR SPECTRA

In the case of the six symmetrical norbornane derivatives the assignment of proton chemical shifts is straightforward except that the resonances for the protons at C_5 and C_6 are partially obscured by the isopropylidene methyl resonance. The synthetic route to the sulfonium salt 3 provides a series of norbornane derivatives in which one part of the molecule is altered at a time with a corresponding change in one set of proton resonances. The spectral features have been assigned on the basis of chemical shift, magnitude of coupling constants, and spin decoupling experiments. In the case of broad peaks, chemical shifts are assigned as the position of band centers.

For the series of compounds 4-8, the position of the isopropylidene methyl resonance (sharp singlet) remains constant, as these protons are well removed from the changes in magnetic environment in the rest of the molecule. The position of the resonance for the C_5 and C_6 endo- and exo-protons also appears to be constant (with the exception of the olefinic protons of compound 4) for the entire series.

It has not been possible to assign conclusively the exo- and endo-$C_{5,6}$ resonances, although the upfield doublet may tentatively be assigned to the endo-protons on the basis of assignments made for similar compounds.[8,9,13] The 1,4-bridgehead proton resonances for the compounds 4-8 are readily identified by their appearance as a downfield irregular triplet with a separation (S) between the outer lines of ~ 5 Hz. These protons are allylic to the isopropylidene double bond in all cases and also allylic to the Δ^2- double bond in compound 4. They are coupled to the 5- and 6-exo-protons in compounds 5-8 and to the 5- and 6- olefinic protons in compound 4.

The 1,4-bridgehead proton resonances are found 0.5-0.7 ppm further upfield in compounds 5-8 indicating that they were deshielded by the carbonyl functions of the anhydrides 4 and 5. These results are in agreement with those found by Kaneznwa for 5,6-dicarboxy-2-norbornene derivatives.[14]

The 2,3-endo-methine (bridgehead) proton resonances are in all cases found at higher field than the 1,4-bridgehead resonances, even in compounds 4 and 5 in which they are deshielded by the exo-carbonyl functions. They exhibit coupling with the adjacent exo-methylene groups in compounds 6-8, giving rise to broadened peaks which become sharper when the exo-methylene proton resonances are irradiated during spin-decoupling experiments.

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The spectrum of diol 6 was run on a DMSO-d_6 solution due to negligible solubility of the compound in $CDCl_3$. The hydroxyl proton resonance is quite broad ($W_{1/2}$ = 12Hz), indicating a slow exchange rate which is probably the result of extensive hydrogen bonding (the IR spectrum exhibits a broad OH band at 3200 cm^{-1}). The adjacent methylene proton resonances appear as a broad multiplet ($W_{1/2}$ = 18Hz), probably due to magnetic non-equivalence of the two methylene protons resulting from restricted rotation imposed by the hydroxyl hydrogen bond. They also appear to be coupled to the endo-methine protons, although the endo-methine resonance is partially obscured by the isopropylidene methyl resonances. The spectrum of the dimethanesulfonate ester 7 is much the same in appearance, except that both the methylene and endo-methine resonances appear further downfield. Here the endo-methine resonance can be clearly distinguished as an imperfect triplet (J = 6Hz).

The spectrum of the sulfide 8 exhibits magnetic nonequivalence for the *methylene protons adjacent to sulfur. An irregular triplet* (J = 9Hz) integrating for two protons appears at 2.96 δ, while a broad absorption integrating for four protons appears centered at 2.20 δ. Irradiation of either of these resonances causes sharpening of the other. One may designate two of the four methylene protons flanking the sulfur atom as syn to the isopropylidene group and the other two as anti to the isopropylidene group. One may tentatively assign the 2.20 δ envelope to the syn methylene protons (shielded by the isopropylidene double bond) overlapped by the two endo-methine proton resonances. The 2.96 δ resonance is then assigned to the anti-methylene protons. (Note: Since the conformation of the 5-membered sulfide ring is not known with certainty, it is possible that the nonequivalence of the methylene protons is due in part to their orientation with respect to the sulfur lone pairs. It is possible that the H-C-H angle of the methylene protons may not be bisected by one of the sulfur lone pairs, but rather, one set of methylene protons (either the syn or anti) may be more nearly eclipsed by an adjacent lone pair than the other set.[15-18] This type of orientation could lead to anisotropy about the C-S-C bonds which would be reflected in a chemical shift difference for the two sets of methylene protons).

The above assignments are supported by the spectrum of the deuterated compound 11, in which the 2.96 δ resonance is absent while there remains a broad singlet integrating for two protons at 2.22 δ for the endo-methine protons. The spectrum of the oxygen analogue 24 is similar, except that the two methylene triplets (J = 8Hz) are shifted downfield and no longer overlap any other proton resonances. Irradiation of the 2.20 δ multiplet collapses both methylene triplets to a doublet (J = 8Hz), while irradiation of either triplet collapses the other triplet to a broad doublet (J = 8Hz) as well as sharpening the 2.20 δ multiplet. It is apparent that each methylene triplet arises from fortuitous overlap of two doublets, one caused by geminal coupling between the non-equivalent methylene protons (J = ~8Hz), and one caused by vicinal coupling (J = 8Hz) with the endo-methine protons. In both compounds 8 and 24, the 1,4-bridgehead protons appear as a characteristic imperfect triplet at 2.44 δ (S = 5Hz).

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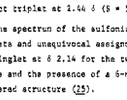
Due to complexity of the spectrum of the sulfonium bromide 3, it has not been possible to make complete and unequivocal assignment of proton resonances. The appearance of a sharp singlet at δ 2.14 for the two methyl groups confirms the symmetry of the molecule and the presence of a 6-membered cyclic sulfonium moiety rather than a 5-membered structure (25).



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The spectrum of the deuterated salt 12 exhibits a broad singlet at 3.32 δ for the endo-methine protons, a poorly-resolved triplet at 2.90 δ for the norbornane 1,4-bridgehead protons, and a broad singlet for the norbornane bridge proton. Resonances for the norbornane C_5 and C_6 protons appear at δ 1.92 and 2.02, partially obscured by the methyl singlet. The 3.32 δ resonance appears as an irregular triplet in the parent salt 3, indicating coupling with the methylene protons adjacent to sulfur.

The nmr spectra of the two derivatives of octahydro-1,1-dimethyl-4,7-methanocyclopenta[c]thiopyran (13 and 16) constitute the primary evidence in support of their assigned structures. Many of the spectral features of these two compounds are similar. The 8-methyl derivative 13 exhibits a distinct singlet for each methyl group. This demonstrates the nonequivalence of the gem-dimethyl groups in the 6-membered thiane ring resulting from the dissymmetry of the molecule itself and the rigidity of the thiane ring. The proton resonance for the 8-methyl group appears as a doublet (J = 2Hz) at 1.30 δ, coupled with the adjacent endo-methine proton whose resonance appears in an envelope centered at 1.94 δ. The noteworthy feature of this resonance is its extreme downfield position, about 0.7 further downfield than the exo-methyl groups (0.8 δ, J = 8Hz) of compound 23.

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The nature of the downfield shift may be either steric or anisotropic. The steric shift may result from interaction of the methyl protons with a non-bonded electron pair on sulfur oriented toward it, or from steric repulsion with the neighboring gem-dimethyl group (the possibility of severe steric repulsion between these two methyl groups is believed to be partly responsible for locking the thiane ring in the conformation shown. Examination of molecular models demonstrates that if the thiane is bent out of its chair conformation so that sulfur moves away from the 8-methyl group, the neighboring gem-dimethyl group must rotate toward the 8-methyl group and incur severe steric interaction. Examination of models also suggests that the distance between the 8-methyl carbon and the sulfur atom is not appreciably greater than the bonding distance between the adjacent methylene carbon and the sulfur atom in sulfonium salt 3).

A second marked feature of the nmr spectrum of compound 13 is the appearance of four doublets between δ 3.00 and 2.20, integrating for a total of two protons. These resonances arise from the methylene protons adjacent to sulfur in the following way: because of the rigid conformation of the thiane ring, the methylene protons are nonequivalent, one being axial (δ 2.90) and the other equatorial (δ 2.34). These methylene protons exhibit geminal coupling (J = ~12Hz) to give a pair of doublets, and vicinal coupling with the adjacent endo-methine proton to further split each line of the pair of doublets, thus giving rise to two pairs of doublets for the two methylene protons. The vicinal coupling constants are not equal for each methylene proton; the adjacent endo-methine proton is equatorial with respect to the thiane ring, and thus should couple to a greater extent with the equatorial methylene proton than with the axial methylene proton, as predicted by the Karplus relationship. Accordingly, the vicinal coupling constant for the upfield methylene proton is 4Hz. It should be noted that the axial methylene proton is subject to 1,3-steric repulsion with the axial methyl group.

The 1.94 δ envelope (integrating for three protons) contains the norbornane 1,4-bridgehead resonances and the resonance for the endo-methine proton adjacent to the 8-methylene group. The above assignments have been confirmed by spin-decoupling and deuterium-labeling experiments. Irradiation of the pair of doublets centered at 2.90 δ collapses the 2.34 δ pair of doublets to one doublet (J = ~3Hz, from coupling with the adjacent endo-methine proton) as well as sharpens the 1.94 δ envelope. Irradiation of the 1.94 δ envelope collapses the vicinal coupling in both pairs of methylene doublets, leaving a doublet centered 2.90 δ and one centered 2.34 δ for the geminally-coupled methylene protons (J = ~12Hz). The deuterium-labeled compound 14, in which the 8-exo-methyl and the 8-methylene groups are pardeuterated, exhibits an nmr spectrum identical to the unlabeled compound 13, *except for the absence of a methyl resonance at* 1.30 δ and the absence of any resonances downfield from 2.0 δ. A broad singlet at 1.66 δ which was obscured by overlap with the 8-methyl resonance in the parent compound is discernible in the deuterated derivative and may tentatively be assigned to the proton of the norbornane bridge, which is equatorial in the thiane ring. The 1.94 δ envelope is considerably sharpened in the deuterated compound due to absence of coupling between the deuterated 8-methylene and the adjacent endo-methine proton.

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Similarities between the nmr spectrum of the cyano-derivative 16 and compound 13 were of considerable aid in assigning its structure. The methyl groups again appear as singlets at δ 1.24 and 1.46. The cyanomethylene protons appear as a doublet (J = 8Hz) centered at 3.34 δ. Comparison of this chemical shift with a value of ~ 2.5 δ reported for cyanomethylene protons in alkyl cyanides[19] suggests that these methylene protons experience an anomalous downfield shift similar to that of the analogous 8-methyl protons in compound 13.

The endo-methine proton adjacent to the cyanomethyl group appears as a broad doublet (J = 8Hz) centered 1.88 δ. Irradiation of this signal causes collapse of the cyanomethylene doublet to a singlet.

The appearance of the cyanomethylene protons as a sharp doublet suggests that rotation for this group is rapid on the nmr time scale. Hindered rotation would render these two protons magnetically non-equivalent, giving rise to two pairs of doublets through geminal and vicinal coupling as is the case for the 8-methylene protons.

The 8-methylene protons appear in the 90-MHz spectrum as two pairs of doublets similar to those of compound 13 (in the 60 MHz spectrum, the furthest upfield doublet partially overlaps the envelope centered 2.18 δ). One pair of doublets is centered 3.06 δ and the other pair is centered 2.48 δ. The gemdinal coupling constant is ~13Hz. The downfield doublets show vicinal coupling of 2Hz, while the upfield doublets exhibit 5Hz coupling. The upfield doublets are assigned to the proton equatorial in the thiane ring, as previously discussed for *compound* 13.

The nmr spectrum of the 8-elimination product 15 exhibits a singlet at δ 1.74 for the isopropenyl methyl group, and a broad singlet at δ 4.90 for the vinyl protons. Irradiation of the vinyl protons causes considerable sharpening of the methyl signal as evidenced by a 30% gain in peak height (while integration remains the same). This peak sharpening is caused by elimination of allylic coupling between the methyl and vinyl protons, which is expected to have a value of ~1 to ~2Hz.

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The 8-methylene protons again show separate resonances for the syn- and anti-protons at δ 2.98 (imperfect doublet, S = 2Hz) and 2.84 (sharp singlet). These resonances cannot be assigned unequivocally as the isopropenyl group would be expected to be subject to hindered rotation and its exact orientation is unknown. The conformation of the 5-membered sulfide ring is also not certain, nor is the orientation of the methylene protons with respect to the sulfur lone pairs. The upfield resonance may tentatively be assigned to the protons syn to the isopropenyl group, assuming a net shielding contribution for that group.

The 5,6-exo and endo protons of 15 appear at δ 1.14 and 1.50. The upfield are assumed to be endo. The remaining protons appear in an envelope from δ 1.64 to 1.18, which appears to arise from the overlap of at least two resonances, one centered at 2.48 δ and the other centered at 2.22 δ.

The isomeric structure 19 has been eliminated from consideration due to the absence of two separate methyl resonances for the nonequivalent methyl groups and the absence of the characteristic splitting pattern for the methylene protons adjacent to sulfur as exhibited by compounds 13 and 16. One would also expect the vinyl protons to show two distinct resonances as one would be directed toward and the other would be oriented away from the thiane ring. The appearance of a broad olefinic singlet at δ 4.90 is suggestive of neither non-equivalence nor anomalous deshielding as exhibited in compounds 13 and 16.

EXPERIMENTAL

GENERAL. Melting points and boiling points are uncorrected. Analyses are by Atlantic Microlab, Atlanta, Georgia, Galbraith Laboratories, Knoxville, Tennessee, or M-H-W Laboratories, Garden City, Michigan. Glpc analyses were carried out on a Varian-Aerograph Series 1200 gas chromatograph using 5 ft x 1/8 in. columns; preparative glpc separations were performed on an Aerograph Autoprep Model A-700 equipped with 10 ft x 1/4 in. columns (200 ml min^{-1} He flow). Nmr spectra were obtained from a Varian A-60 or T-60 spectrometer (TMS internal standard); decoupling experiments were performed on the T-60. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Mass spectra were determined on an MS-902 mass spectrometer (courtesy of the Research Triangle Mass Spectrometry Center, Research Triangle Park, N. C.) or a DuPont C.E.C. 21-490 instrument.

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DIMETHYLFULVENE.-- Dimethylfulvene was prepared according to the method of Crane[20], with the following modification. To a solution of 310 g (4.7 mole) of cyclopentadiene and 275 g (4.8 mole) of reagent grade acetone at 0° was added dropwise from an addition funnel 120 *ml of 20% ethanolic KOH*. The yield was 412 g (3.9 mole, 83%) of yellow liquid, bp 50-54°/11 mm (reported bp 54-57°/12 mm).

exo-7-ISOPROPYLIDENEBICYCLO[2.2.1]HEPTANE-2,3-DICARBOXYLIC ACID ANHYDRIDE (5) was prepared according to the method of Alder and Rühman.[21] To a solution of 170 g (1.7 mole) of maleic anhydride in 1.5 l of benzene was added 160 g (1.5 mole) of dimethylfulvene. The solution was refluxed 15 min and allowed to cool to room temperature. The solid adduct (a 50:50 mixture of endo- and exo-isomers) was filtered. The exo-adduct (less soluble) was separated by fractional crystallization from ethyl acetate to yield 117 g of colorless needles, mp 134-136° [literature:[21] exo 137° (needles), endo 112° (plates)]; nmr ($CDCl_3$) δ 6.60 (2H), 3.90 (2H), 3.22 (2H), 1.58 (6H).

The adduct 4 was hydrogenated in ethyl acetate over PtO_2 catalyst in a Parr hydrogenator. The product (5) melted at 132-134° (lit.[21,22] mp 138°, 132.5-134°); nmr ($CDCl_3$) δ 3.20 (2H), 3.00 (2H), 1.65 (6H), ~1.68 (2H), ~1.56 (2H).

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exo-7-ISOPROPYLIDENEBICYCLO[2.2.1]HEPTANE-2,3-DIMETHANOL (6).-- To a 3 l round-bottomed three-necked flask equipped with a Soxhlet extractor, drying tube, and magnetic stirrer, was suspended 43 g (1.1 mole) of $LiAlH_4$ in 1.5 l of anhydrous ethyl ether (dried over sodium). To the thimble was added 140 g (0.70 mole) of the selectively reduced dimethylfulvene-maleic anhydride adduct, and reflux was maintained for three days. Excess $LiAlH_4$ was decomposed by the dropwise addition of 10% aqueous NH_4Cl (the product has been found to be acid-sensitive). The ether layer was decanted and the solid residue was washed with 500 ml of ether. The combined ether layers were dried over magnesium sulfate and evaporation of the solvent yielded 97 g (74%) of colorless crystals, mp 134-135° (lit.[22] mp 135-136°); nmr (DMSO-d_6) δ 4.30 (2H), 3.20 (4H), 2.50 (2H), 1.66 (6H), ~1.55 (2H), ~1.43 (2H).

exo-7-ISOPROPYLIDENEBICYCLO[2.2.1]HEPTANE-2,3-DIMETHANOL DIMETHANESULFONATE (7).-- In a 1 l round-bottomed three-necked flask equipped with a thermometer, drying tube, addition funnel, and magnetic stirrer, was placed 300 ml of dry pyridine (distilled over BaO). The flask was cooled to 0° in an ice-salt bath, and 50 ml (74 g, 0.65 mole) of methanesulfonyl chloride was added to the stirred pyridine at such a rate that the temperature of the mixture did not exceed 5°. exo-Diol (6) (34 g, 0.28 mole) dissolved in 250 ml of dry pyridine was added dropwise through an addition funnel to the stirred, chilled methanesulfonyl chloride-pyridine solution (the temperature was maintained below 5°). When addition was complete, the mixture was stirred for one hour at 0° and then placed in a refrigerator overnight (12 hours, 5°). The reaction mixture was then poured with stirring *into a 3-l beaker containing* 600 ml of 10% HCl diluted with ice to 1.5 l. The pH of the mixture was adjusted to 1 by the addition of concentrated HCl. The product, which precipitated readily, was filtered and stirred with 300 ml of water to remove excess pyridine. The crude methanesulfonate diester was recrystallized from hot absolute methanol (with addition of Norite) to yield 82.6 g (85%) of crystals, mp 75-76°; nmr ($CDCl_3$) δ 4.10 (4H), 3.00 (6H), 2.66 (2H), 2.20 (2H), 1.66 (6H), ~1.58 (2H), ~1.48 (2H).

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Anal. Calcd for $C_{13}H_{24}O_6S_2$: C, 47.72; H, 6.82. Found: C, 47.67; H, 6.72.

exo-OCTAHYDRO-8-ISOPROPYLIDENE-4,7-METHANOBENZO[c]THIOPHENE (8).-- To 83 g (0.23 mole) of dimesylate (7) dissolved in 600 ml of hot absolute methanol was added 60 g (0.25 mole) of sodium sulfide nonahydrate. The reaction mixture was stirred under reflux for 24 hours and was then poured into 1.5 l of water to dissolve inorganic salts and to precipitate the product. The crude product was filtered, washed with water, and recrystallized from absolute methanol, yielding 40 g (88%) of sulfide 8, mp 88.5-90°; nmr ($CDCl_3$) δ 2.96 (2H), 2.44 (2H*), ~2.20 (4H), 1.64 (6H), 1.50 (2H), 1.30 (2H*).

Anal. Calcd for $C_{14}H_{22}S$: C, 74.28; H, 9.28. Found: C, 74.19; H, 9.30.

In a subsequent reaction Compound 8 was prepared in comparable yield using HMPA solvent according to the method of Paquette.[23]

A methiodide salt was prepared by dissolving the sulfide in anhydrous ethyl ether and adding excess methyl iodide: mp 182-183° on recrystallization from absolute methanol.

Anal. Calcd for $C_{15}H_{25}IS$: C, 46.43; H, 6.25. Found: C, 46.31; H, 6.42.

HEXAHYDRO-1,1-DIMETHYL-3H-2,4,7-ETHANYLYLIDENE-1H-CYCLOPENTA[c]THIOPYRILIUM BROMIDE (3).-- To a solution of 49 g (0.20 mole) of sulfide 8 in 80 ml of absolute ethanol was added 98 ml (0.80 mole) of 48% HBr. The reaction was stirred under reflux for 24 hours and the product was isolated by addition of anhydrous ethyl ether until solid no longer precipitated. The salt was purified by solution in hot absolute methanol, followed by the addition of anhydrous ethyl ether to effect precipitation. The yield was 35 g (62%) of white crystals, mp 350-351° in a sealed tube (the compound sublimes at 335°); nmr (D_2O, TMS capillary) δ 3.30 (2H), 2.94 (2H*), 2.54 (1H), 2.14 (6H), 2.02 (2H), 1.92 (2H).

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Anal. Calcd for $C_{15}H_{25}BrS$: C, 52.3u; H, 6.91. Found: C, 51.99; H, 6.72.

A picrate was prepared by dissolving the sulfonium bromide in absolute ethanol and adding a saturated ethanolic picric acid solution; mp 231-232° (dec) on recrystallization from absolute ethanol.

Anal. Calcd for $C_{21}H_{28}N_3O_7S$: C, 51.06; H, 4.96. Found: C, 51.16; H, 4.88.

REACTION OF SULFONIUM BROMIDE 3 WITH LITHIUM ALUMINUM HYDRIDE. PREPARATION OF OCTAHYDRO-1,1,8-TRIMETHYL-4,7-METHANOCYCLOPENTA[c]THIOPYRAN (13).-- To a stirred suspension of 10 g (0.26 mole) of $LiAlH_4$ in 250 ml of anhydrous ethyl ether was added 16 g (0.06 mole) of sulfonium bromide 3. The mixture was heated under reflux for 72 hours before excess $LiAlH_4$ was decomposed by the dropwise addition of 10% aqueous NH_4Cl. The ether layer was decanted and the solid residue was washed with 50 ml ethyl ether. The ether layers were combined and dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to yield a light yellow oil. Analytical glpc on a 10% carbowax 20M column at 180° suggested the presence of 2 major components. Preparative glpc on a 20% carbowax 20M column at 150° effected a separation of the mixture into 2 components in a ratio of 85:15. The major component (shorter retention time) was identified as sulfide 8 by comparison of mp, glpc, and nmr data with those of an authentic sample. The *minor component was identified as* octahydro-1,1,8-trimethyl-4,7-methanocyclopenta-[c]thiopyran (13), bicro bp 264° dec; nmr (benzene) δ 2.90 (1H), 2.34 (1H), 1.86 (3H), 1.52 (3H), 1.42 (3H), 1.22 (3H).

Anal. Calcd for $C_{14}H_{24}S$: C, 73.50; H, 10.24; S, 16.26. Found: C, 73.36; H, 10.29; S, 16.38.

REACTION OF SULFONIUM BROMIDE 3 WITH SODIUM ACETATE IN ACETIC ACID.-- A sample of 1.4 g (0.005 mole) of the sulfonium bromide 3 and 1.5 g (0.023 mole) of anhydrous sodium acetate was heated under reflux for 48 hours in 25 ml of glacial acetic acid. The reaction mixture was poured into 100 ml of water, neutralized with sodium carbonate, and extracted with three 25-ml portions of ethyl ether. The ether extracts were combined and dried over $MgSO_4$, and the solvent was evaporated to yield a single product identified as octahydro-8-isopropylidene-4,7-methanobenzo[c]thiophene (8) by comparison of its mp, nmr, and glpc retention time with those of an authentic sample.

REACTION OF SULFONIUM BROMIDE 3 WITH SODIUM PHENOXIDE. PREPARATION OF exo-OCTAHYDRO-8-ISOPROPENYL-4,7-METHANOBENZO[c]THIOPHENE (15).-- A sample of 2.4 g (0.005 mole) of the sulfonium bromide 3 was heated under reflux for 25 hours in a

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solution of 3.4 g (0.06 mole) of KOH and 5.7 g (0.06 mole) of phenol in 40 ml of water. The reaction mixture was then extracted with three 20-ml portions of ethyl ether. The ether extracts were combined and washed with 10% NaOH (to remove phenol) and then with saturated NaCl solution until washings were neutral. Finally, the extracts were dried over $MgSO_4$ and solvent was removed. Analytical glpc of the product on a 10% carbowax 20M column at 180° indicated the presence of two components in equal amounts (53:47). Preparative glpc on a 20% carbowax 20M column at 140° effected separation. The first component (shorter retention time) was identified as sulfide 8 by comparison of its nmr and glpc retention time with those of an authentic sample. The second component was identified as exo-octahydro-8-isopropanyl-4,7-methanobenzo[c]thiophene (15), mp 39-40°; nmr ($CDCl_3$) δ 4.90 (2H), 2.92 (4H), 2.48 (3H), 2.22 (2H), 1.74 (3H), 1.50 (2H), 1.26 (2H). The infrared spectrum exhibits a strong olefinic band at 1640 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}S$: C, 74.22; H, 9.30; S, 16.48. Found: C, 74.31; H, 9.36; S, 16.34.

REACTION OF SULFONIUM BROMIDE 3 WITH POTASSIUM CYANIDE. PREPARATION OF OCTAHYDRO-1,1-DIMETHYL-8-CYANOMETHYL-4,7-METHANOCYCLOPENTA[c]THIOPYRAN (16).-- To a solution of 7.8 g (0.12 mole) of KCN in 40 ml of water was added 2.8 g (0.010 mole) of sulfonium bromide 3. The reactants were heated under reflux for 48 hours. The reaction mixture was extracted with three 25-ml portions of ethyl ether. The extracts were combined, dried over $MgSO_4$, and the solvent was removed. Analytical glpc (10% carbowax 20M column, 180°) indicated the presence of three products. Preparative glpc (20% carbowax 20M column, 150°) effected separation of the mixture into three components in a ratio of 40:10:50.

The first component (40%, shortest retention time) was identified as sulfide 8 by comparison of its glpc retention time, nmr spectrum, and mp (87-88°) with those of an authentic sample. The second component (10%) was identified as exo-octahydro-8-isopropenyl-4,7-methanobenzo[c]thiophene (15) by comparison of its ir and nmr spectra and glpc retention time with those of an authentic sample. The third component (50%, longest retention time) was identified as octahydro-1,1-dimethyl-8-cyano-methyl-4,7-methanocyclopenta[c]thiopyran (16), micro bp 250° dec; nmr ($CDCl_3$) δ 3.34 (2H), 3.04 (1H), 2.48 (1H), 2.12 (3H), 1.46 (3H), 1.24 (3H); ir 2220 cm^{-1}, weak (C≡N); mass spectrum m/e (rel intensity) 221 (17),206 (100), 194 (4), 165 (10), 121 (7).

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Anal. Calcd for $C_{13}H_{19}NS$: C, 70.60; H, 8.66; N, 6.33. Found: C, 70.77; H, 8.72; N, 6.43.

REACTION OF SULFONIUM BROMIDE 3 WITH METHYLANILINE.-- Sulfonium bromide 3 (1.4 g, 0.005 mole) was refluxed for 48 hours with 6 g (0.06 mole) of methylaniline in 25 ml of 95% ethanol. Anhydrous ethyl ether (30 ml) was added to the reaction mixture, and 1.35 g (98%) of starting material (mp 320° dec.) was recovered. The ether layer was washed with three 25 ml portions of 10% HCl and then with satd. NaCl solution until washings were neutral. The ether layer was dried over $MgSO_4$ and solvent was removed, yielding a trace amount of sulfide 8, identified by glpc retention time and mp (87-88°).

PREPARATION OF exo-7-ISOPROPYLIDENEBICYCLO[2.2.1]HEPTANE-2,3-bis(METHANOL-d_2) (5).-- The reaction of 18.6 g (0.090 mole) of exo-7-isopropylidenebicyclo[2.2.1]-heptane-2,3-dicarboxylic acid anhydride (4) and 5.0 g (0.12 mole) of $LiAlD_4$ was carried out according to the procedure for the preparation of exo-7-isopropylidenebicyclo[2.2.1]heptane-2,3-dimethanol (6). The yield was 7.7 g (44%) of colorless crystals, mp 130-132°. The compound was identified by comparison of its mp, glpc retention time, and infrared spectrum with those of the unlabeled compound (6). The presence of deuterium was confirmed in the infrared spectrum (strong doublet, 2120 cm^{-1}) and the mass spectrum (molecular ion 200).

exo-7-ISOPROPYLIDENEBICYCLO[2.2.1]HEPTANE-2,3-bis(METHANOL-d_2) DIMETHANESULFONATE (10).-- The reaction of 5.0 g (0.025 mole) of the deuterated diol (5) and 7.2 g (0.063 mole) of methane sulfonyl chloride was carried out according to the procedure described above for the preparation of dimethanesulfonate 7. Recrystallization of the oil from absolute methanol yielded 7.0 g (80%) of white solid, mp 74.5-75.5°. The compound was identified by comparison of its mp, nmr spectrum, and glpc retention time with those of the unlabeled compound (7); nmr ($CDCl_3$) δ 3.00 (6H), 2.64 (2H), 2.20 (2H), 1.66 (6H), ≈1.58 (2H), ≈1.48 (2H).

exo-OCTAHYDRO-1,3-d_4-8-ISOPROPYLIDENE-4,7-METHANOBENZO[c]THIOPHENE-1,3-d_4 (11).-- The reaction of 7.0 g (0.020 mole) of the deuterated dimethanesulfonate ester (10) and 15 g (0.360 mole) of sodium sulfide nonahydrate in 70 ml of absolute methanol was carried out according to the procedure described above for the preparation of sulfide 8. The crude product was recrystallized from absolute methanol to yield 2.0 g (53%) of colorless crystals, mp 87.5-88.0°. The

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compound was identified by comparison of its mp, glpc retention time, and nmr spectrum with those of the unlabeled sulfide 8: nmr ($CDCl_3$) δ 2.44 (2H), 2.24 (2H), 1.64 (6H), 1.50 (2H), 1.34 (2H).

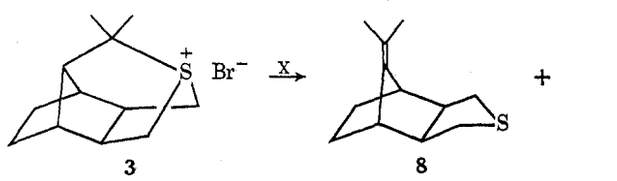
HEXAFLUORO-1,3-DIMETHYL-1H-2,4,7-ETHANYLYLIDENE-1H-CYCLOPENTA[c]THIOPYRYLIUM-3,3,9,9-d_4, BROMIDE (12).-- The unlabeled sulfide (11) (2.20 g, 0.01 mole) was reacted with 6.0 ml of 48% HBr and 4.0 ml of absolute ethanol according to the procedure previously described for the preparation of sulfonium bromide 3. The crude salt was precipitated, filtered, and thoroughly washed with 20 ml of anhydrous ethyl ether. The yield was 1.4 g (50%) of a white solid, subliming at 325° dec. No further purification or characterization was attempted. NMR (D_2O, TMS capillary) δ 3.32 (2H), 2.90 (2H), 2.52 (1H), 2.12 (6H), 2.02 (2H), 1.92 (2H).

OCTAHYDRO-3-d-1,1-DIMETHYL-8-(METHYL-d_4)-4,7-METHANOCYCLOPENTA[c]THIOPYRAN-3-d (14).-- A sample of 1.5 g (0.0054 mole) of the deuterated bromosulfonium salt (12) was reacted with 1.00 g (0.024 mole) of $LiAlD_4$ in 25 ml of anhydrous ethyl ether according to the procedure described above for the preparation of octahydro-1,1,8-trimethyl-4,7-methanocyclopenta[c]thiopyran (13). Analytical glpc (10% carbowax 20M, 180°) indicated 3 major components: octahydro-3-d-1,1-dimethyl-8-(methyl-d_4)-4,7-methanocyclopenta[c]thiopyran-3-d (compound 14, 83%), octahydro-1,3-d_2-8-isopropylidene-4,7-methanobenzo[c]thiophene (compound 11, 12%), and 5% of a component not identified. Separation was effected by preparative glpc (20% SE-30, 155°). Compound 11 was identified by comparison of its glpc retention time and nmr spectrum with those of an authentic sample; compound 14 was identified by comparison of its glpc retention time and nmr spectrum with those of the unlabeled compound (13); nmr ($CDCl_3$) δ 1.94 (3H), 1.70 (1H), 1.40 (3H), 1.22 (3H); mass spectrum molecular ion 201.

exo-cis-2,3-DIMETHYL-7-ISOPROPYLIDENEBICYCLO[2.2.1]HEPTANE (23).-- Compound 23 was prepared by reduction of the dimethanesulfonate ester 7 with $LiAlH_4$ according to the method of Winston.[22] The product had a melting point (135-136°) identical to the reported value.

exo-OCTAHYDRO-8-ISOPROPYLIDENE-4,7-METHANOBENZO[c]FURAN (24).-- An authentic sample previously prepared in this laboratory[24] was used after purification by sublimation, mp 61-62°.

Table I
Product Distribution

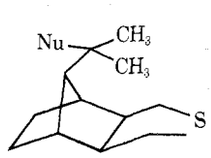


3 8 15 16, Y = CN 18, Y = Nu

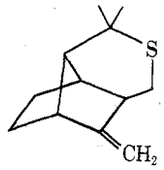
X	% 8	% 15	% 13 or 16
OAc^-	100	0	0
$PhNHCH_3$	Trace[a]	0	0
PhO^-	53	47	0
$LiAlH_4$	85	0	15
CN^-	40	10	50

[a] Starting material was recovered quantitatively.

of its ability to alkylate nucleophiles of varying nucleophilicity and (2) the determination of the position of substitution during alkylation. Inherent in the cyclic sulfonium structure is the possibility for competition between substitution and elimination reactions, which could give rise to a mixture of five possible products, namely, 8, 15, 17, 18, and 19.



17



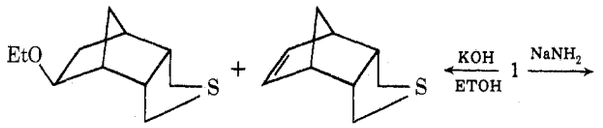
19

The symmetry of the sulfonium bromide 3 reduces the modes of ring opening in substitution to two possibilities: the positive sulfonium moiety can be displaced at the dimethyl-substituted carbon or at either of the equivalent methylene carbons.

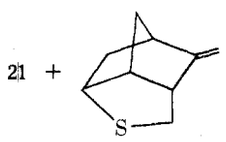
One would expect to see only small amounts of product 17 relative to 18, as the *gem*-dimethyl groups would both shield the adjacent carbon sterically from an incoming nucleophile and reduce (by electron release) its positive character relative to the methylene carbons. The same expectation would hold on a purely statistical basis, since product 18 may arise from two independent pathways while product 17 may arise from only one. The results tabulated in Table I bear out these predictions.

On statistical grounds, one would expect to see products 8, 19, and 15 in a ratio of 1:2:6. This would most certainly not be the case, as it is necessary to take into consideration the relative acidities and accessibilities of the various β protons. With alkyl onium compounds the dominating influence governing orientation in eliminations is the inductive influence (electron releasing) of any β-alkyl groups which might be present.[11] Thus, the least substituted olefin is formed preferentially because the β carbon with the fewest alkyl substituents has the most acidic β protons. The predominance of elimination product 8 is an exception to this trend.

Other studies in this laboratory have demonstrated that sulfonium salts 1 and 2 react with nucleophiles to give only substitution products.[8,9] In the initial investigation of the reaction of 1 with a variety of nucleophiles, only



20 95% 21 4.5%

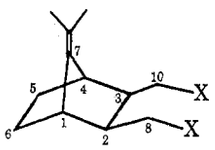


22 50% 50%

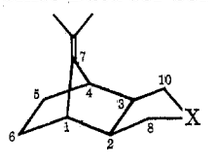
two examples were found[12] in which a β-elimination occurred to form 21 and 22.

The product distribution of Table I probably reflects nucleophilic strength more than any other single factor. Those cases in which substitution was observed ($LiAlH_4$ and KCN) employed reagents of high nucleophilicity and small size. It should be noted that the $LiAlH_4$ reaction was carried out in relatively nonsolvating, low-boiling ethyl ether, which would be expected to promote substitution. The absence of any appreciable reaction with *N*-methylaniline, which is a good nucleophile but a poor

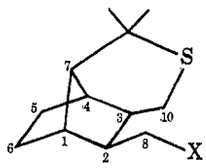
Table II
Proton Chemical Shift Data for Some Norbornane Derivatives[a]



6, 7, 23



4, 5, 8, 24



13, 16

Compd	X	Chemical shift, δ[b] 1,4	2,3 endo	5,6 exo[c]	5,6 endo[c]	8	10	CH_3
4	O[d]	3.90	3.22	6.60[e]		*d*	*d*	1.58[f]
5	O[d]	3.20	3.00	~1.66	~1.56	*d*	*d*	1.66[f]
6	OH[g,h]	2.50	1.85	~1.55	~1.45	3.20	3.20	1.66[f]
7	OSO_2CH_3[i]	2.66	2.20	~1.58	~1.48	4.10	4.10	1.66[f]
23	H	2.20	1.80	~1.50	~1.40	0.80[j]	0.80[j]	1.66[f]
8	S	2.44	2.20	~1.50	1.30	2.96[k]	2.20[k]	1.64[f]
24	O	2.46	2.20	~1.50	1.38	3.00[k]	4.04[k]	1.66[f]
13	H[l]	1.94	1.94	*m*	*m*	1.52[j]	2.90[k]	1.22[n]
							2.34[k]	1.42[n]
16	CN[l]	2.12	1.88[k]	*m*	*m*	3.34	3.04[k]	1.24[n]
							2.48[k]	1.46[n]

[a] The compounds are numbered as norbornane derivatives for convenience in tabulating chemical shifts. [b] Relative to TMS (δ 0.00) in $CDCl_3$. [c] Assignment is indefinite and may be reversed. [d] Compounds **4** and **5** are anhydrides. [e] The 5,6 linkage is olefinic. [f] Isopropylidene methyl. [g] In DMSO-d_6. [h] OH protons at δ 4.50 (2 H). [i] OSO_2CH_3 protons at δ 3.00 (6 H). [j] *exo*-CH_3 protons. [k] See discussion. [l] C-7 proton resonance obscured by other resonances. [m] Resonances obscured. [n] *gem*-CH_3 protons.

base, may reflect that reagent's inability to get at the sites for substitution.

The chemical shift data for a series of compounds containing the norbornane skeleton are summarized in Table II.

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Registry No.—**3**, 51510-22-6; **3** picrate, 51703-25-4; **4**, 51510-23-7; *exo*-**5**, 51606-73-6; *endo*-**5**, 51606-74-7; **6**, 51510-24-8; **7**, 51510-25-9; **8**, 51510-26-0; **8** methiodide, 51606-75-8; **9**, 51510-27-1; **10**, 51510-28-2; **11**, 51703-29-8; **12**, 51606-76-9; **13**, 51510-29-3; **14**, 51606-77-0; **15**, 51510-30-6; **16**, 51510-31-7; **23**, 51510-32-8; **24**, 51510-33-9; dimethylfulvene, 2175-91-9.

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References and Notes

(1) (a) Taken in part from the Dissertations of L. A. F.-O. and G. A. D. submitted to the Graduate School of Duke University in partial fulfillment of the requirements for the Ph.D. degree (1965 and 1973, respectively). The partial support of this research by a grant (CA-4298) from the National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged. (b) National Science Foundation Trainee, Duke University, 1969–1970; Allied Chemical Corp. Predoctoral Fellow, 1971–1972.
(2) V. Prelog and E. Cerkovnikov, *Justus Liebigs Ann. Chem.*, **537**, 214 (1939).
(3) V. Prelog and D. Kohlbach, *Ber.*, **72**, 672 (1939).
(4) W. F. Cockburn and A. F. McKay, *J. Amer. Chem. Soc.*, **76**, 5703 (1954).
(5) R. H. Eastman and G. Kritchevsky, *J. Org. Chem.*, **24**, 1428 (1959).
(6) M. A. Stahmann, J. S. Fruton, and M. Bergmann, *J. Org. Chem.*, **11**, 704 (1946).
(7) P. Wilder, Jr., and L. A. Feliu-Otero, *J. Org. Chem.*, **30**, 2560 (1965).
(8) P. Wilder, Jr., L. A. Feliu-Otero, and J. M. Shepherd, *Int. J. Sulfur Chem., Part A*, **1**, 169 (1971).
(9) P. Wilder, Jr., and R. F. Gratz, *J. Org. Chem.*, **35**, 3295 (1970).
(10) L. N. Owen and A. G. Peto, *J. Chem. Soc.*, 2383 (1955).
(11) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, pp 659–666.
(12) L. A. Feliu-Otero, Ph.D. Dissertation, Duke University, 1965.
(13) P. Laszlo and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964).
(14) N. Kamezawa, K. Sakashita, and K. Hayamizu, *Org. Magn. Resonance*, **1**, 405 (1969).
(15) C. C. Price, *J. Org. Chem.*, **38**, 615 (1973).
(16) E. L. Eliel and R. O. Hutchins, *J. Amer. Chem. Soc.*, **91**, 2703 (1969).
(17) H. T. Kalff and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 467 (1966).
(18) N. S. Zefirov, V. S. Blagoveshchensky, I. V. Kazimirchik, and N. S. Surova, *Tetrahedron*, **27**, 3111 (1971).
(19) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1967, pp 136–137.
(20) G. Crane, C. E. Boord, and A. L. Henne, *J. Amer. Chem. Soc.*, **67**, 1237 (1945).
(21) K. Alder and R. Rühmann, *Justus Liebigs Ann. Chem.*, **566**, 1 (1950).
(22) A. Winston, Ph.D. Dissertation, Duke University, 1955.
(23) L. A. Paquette, R. E. Wingard, Jr., J. C. Philips, G. L. Thompson, L. K. Read, and J. Clardy, *J. Amer. Chem. Soc.*, **93**, 4508 (1971).
(24) C. F. Culberson, Ph.D. Dissertation, Duke University, 1959.