Endocyclic vs. Exocyclic Attack in Nucleophilic Displacement Reactions on Five- and Six-Membered Cyclic Onium Salts

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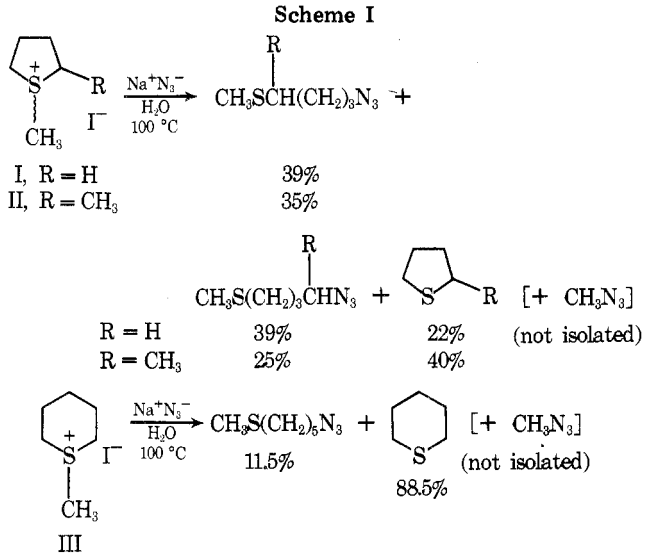
Nucleophilic attack of azide or methanethiolate on *S*-methylthiolanium iodide (five-membered ring) leads mainly to ring opening and to a lesser extent to displacement on methyl. In contrast, the analogous reactions with *S*-methylthianium iodide (six-membered ring) lead largely to displacement of methyl. Similarly, reaction of thiophenolate with *N,N*-dimethylpyrrolidinium tosylate leads largely to ring opening whereas the analogous reaction with *N,N*-dimethylpiperidinium tosylate gives rise only to thioanisole (product of methyl attack). Ring opening of *S*,2-dimethylthiolanium iodide with azide occurs predominantly at the primary (in preference to the secondary) ring carbon and when both α carbons in the ring are secondary, as in the reaction of *S*,2,6-trimethylthiolanium iodides with methanethiolate, displacement occurs nearly entirely at the exocyclic methyl.

In connection with another problem, we had occasion to study the reaction of *S*-methylthiolanium iodide (I) and *S*,2-dimethylthiolanium iodide (II) with sodium azide. We found that the major products in both reactions were those of ring opening, as shown in Scheme I, top. The thiolanes resulting from methyl attack were formed in minor amount. In contrast, the reaction of *S*-methylthianium iodide (III) with azide gave largely methyl azide and thiane, the products of methyl attack, and only a small amount of ring-opened product (Scheme I, bottom).

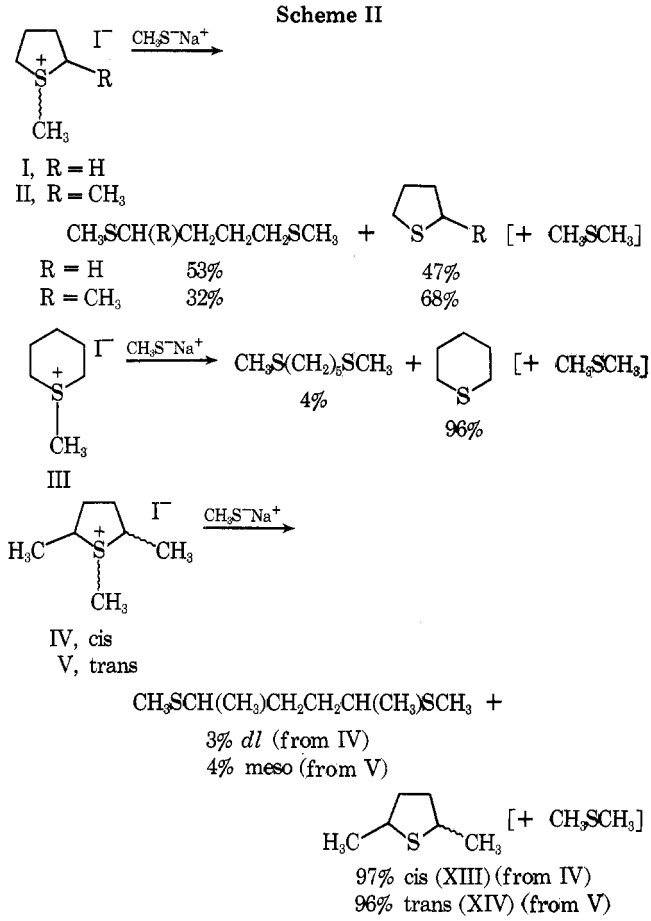
Scheme I



Predominant attack of the nucleophile on the ring in preference to the exocyclic methyl group in compounds I and II is a cause for surprise. The reaction of a good nucleophile such as azide on a thiolanium salt is most probably of the SN2 type[1] and therefore should follow the usual preference[2] $CH_3 > CH_2 > CH$. Indeed, for the specific case of displacement of hydroxide on acyclic sulfonium salts $RSMe_2^+$ or R_2SMe^+ it was found[3] many years ago that methyl is displaced faster than ethyl (with isopropyl the reaction changes over to SN1). In the present work it was shown that reaction of $(CH_3CH_2CH_2)_2SCH_3^+$ with CH_3S^- gives 18 times as much $(CH_3CH_2CH_2)_2S$ (and CH_3SCH_3), after correction for statistical factors, as $CH_3SCH_2CH_2CH_3$.

To check whether there was anything unusual about azide displacement, we repeated the reaction with methyl thiolate, including in the series also the *cis*- and *trans*-2,6-dimethylthiolane derivatives IV and V. The results are shown in Scheme II. (Attack at the CH_2 and CHR position in II cannot be distinguished in this case.) Although the

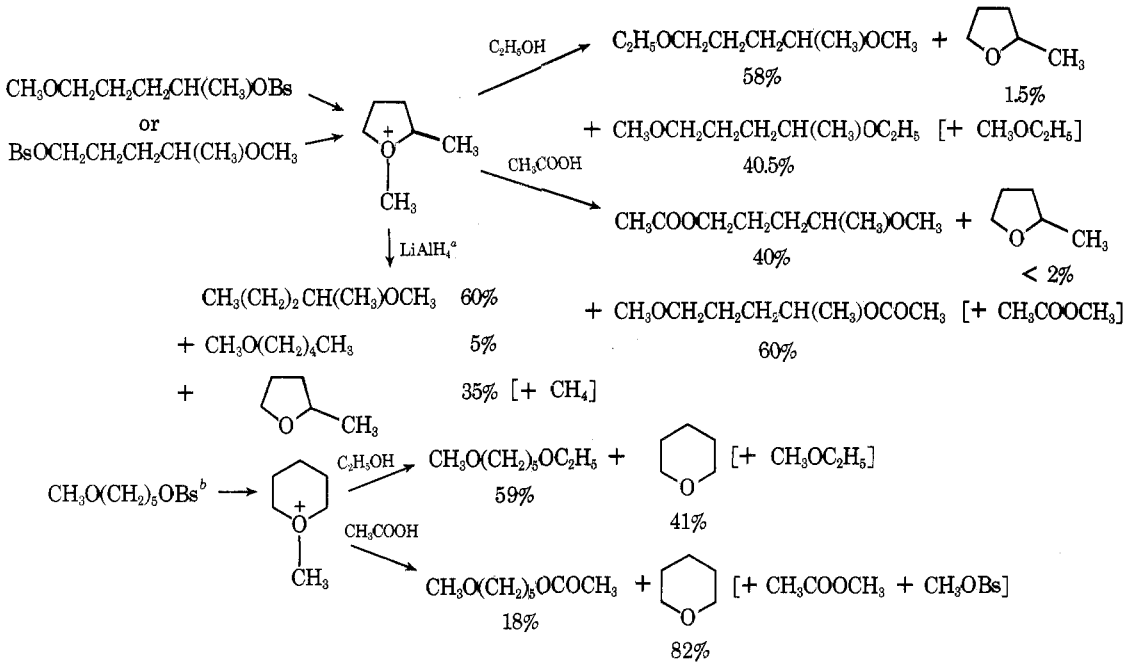
Scheme II



exact proportions of ring opening and methyl attack are somewhat different for methyl thiolate and azide displacement, the overall picture is the same: in the five-membered ring, ring opening at a CH_2 position (but not at a CHMe position) is preferred to methyl displacement whereas in the six-membered ring methyl displacement is by far the preferred mode of nucleophilic attack.

At this juncture, three hypotheses suggested themselves. One, based on analogy with other reactions of sulfonium salts,[4] was that a tetracovalent sulfurane intermediate might be involved and that, for geometrical reasons,[5] such a sulfurane might preferentially undergo ring opening when the ring is five membered but methyl loss when the ring is six membered. A second possibility was that the reactions had some SN1 character in the five-membered ring and that therefore methylene attack should predominate over methyl attack. This hypothesis could essentially be

Scheme III



[a] 10% neighboring group participation from 4-methoxy-1-pentyl brosylate, 30% from 5-methoxy-2-pentyl brosylate. [b] 59% participation in ethanolysis, 98% in acetolysis. The 5-methoxypentyl ethyl ether yield in the ethanolysis includes material which has not passed through the cyclic ion.

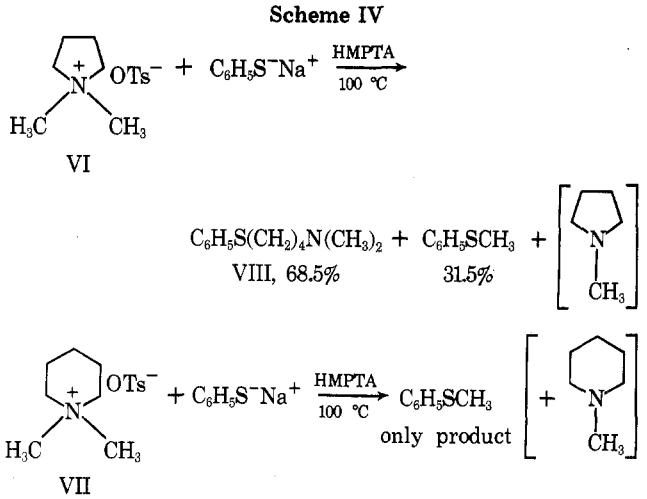
ruled out, at least for the CH_3S^- nucleophile, since it was found that attack at a secondary center (as in II, IV, and V) was not favorable. (Additional counterarguments are discussed below.) The third hypothesis is that the strain of the five-membered ring, reinforced by the absence of eclipsing in nucleophilic attack on that ring, should promote ring opening; in contrast, the lack of strain in the six-membered ring, combined with the likelihood of eclipsing of the nucleophile with ring hydrogens occurring in the transition state to ring opening, would lead to a preference for exocyclic attack.

To distinguish between the first and third hypotheses, it became important to decide whether there is anything unusual about sulfur as the leaving group. It turns out that experiments to this end are already available: Winstein and Allred[6] have studied the behavior of five- and six-membered cyclic methyl oxonium ions, formed through neighboring group participation processes, in ethanolysis, acetolysis and (in the case of the five-membered compound) lithium aluminum hydride reduction. The published results are summarized in Scheme III.

In the five-membered ring, acetolysis and ethanolysis give rise almost exclusively to ring opening. However, attack at the methylene and methine side of the ring occurs to nearly the same extent, suggesting that the reaction is SN1 like. Indeed, the intervention of open carbonium ions in a similar case (but involving a double bond in the ring) has been demonstrated.[7] Hydride reduction does not suffer from this drawback but only 10–30% of the reaction proceeds by neighboring group participation, i.e., via the cyclic oxonium salt. In the six-membered ring, both ethanolysis and acetolysis led to appreciable methyl attack; the quantitative interpretation of these results for our purposes is, however, complicated by incomplete participation in the ethanolysis and internal return in the acetolysis.

While the work of Winstein and Allred makes it very unlikely that the results we observed have anything to do with the presence of sulfur, we felt that it would be worthwhile to study a reaction which was clearly SN2 and involved a first-row element in the leaving group. Since nucleophilic displacements on preformed oxonium salts would involve considerable experimental difficulties, we opted instead to look at the cyclic ammonium salts *N,N*-dimethylpyrrolidinium tosylate (VI) and *N,N*-dimethylpiperidinium tosylate (VII). The results of nucleophilic displacement reactions of VI and VII with sodium thiophenolate in hexamethylphosphoric triamide[8] at 100 °C (the reaction did not proceed at an appreciable rate in boiling water) are shown in Scheme IV. Once again, reaction with the five-membered ring involves predominantly (68.5%) ring opening whereas the six-membered ring led exclusively to attack on methyl and formation of thioanisole. (The expected product of ring opening was produced by an independent synthesis and was shown, by gas chromatography, to be totally absent from the reaction products.)

Scheme IV



A summary of ring vs. methyl attack in various five- and six-membered methyl onium salts with various nucleophiles is given in Table I. The results are corrected for statistical factors where pertinent. It is clear that in all cases studied, ring opening occurs to a substantial extent in the

Scheme V

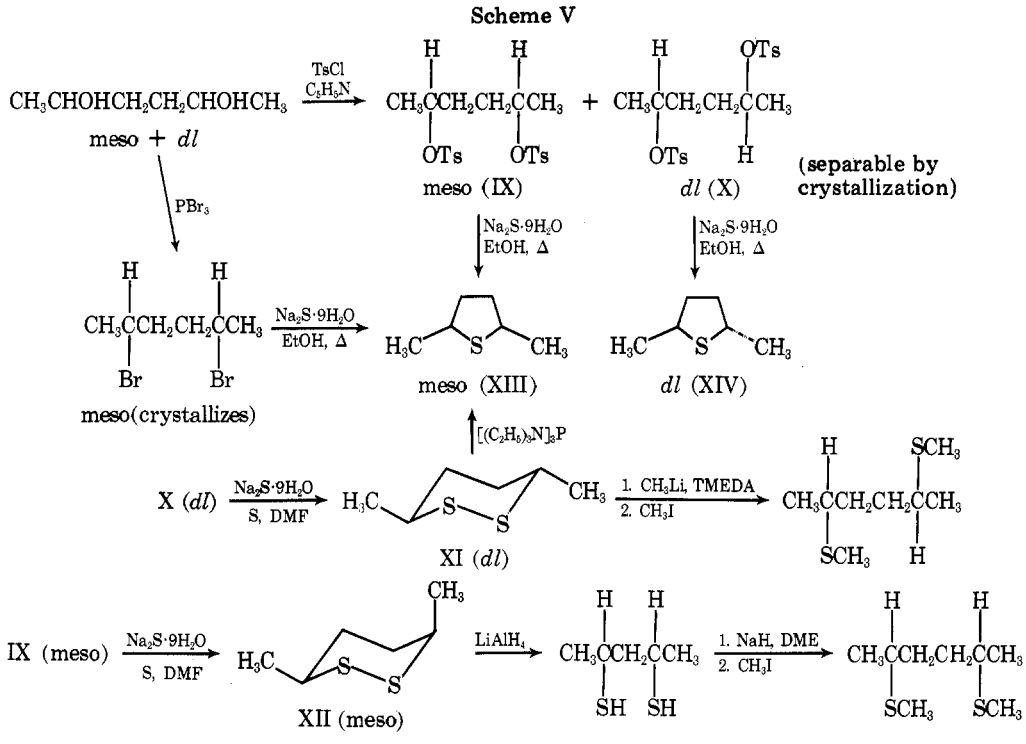
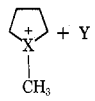
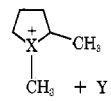
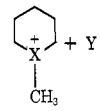


Table I. Ratio of Methylene to Methyl Displacement in Cyclic Onium Salts[a]

X	Y			
S	N_3^-	1.77	0.88[b]	0.065
S	CH_3S^-	0.56	0.47	0.02
O	C_2H_5OH	n.a.[c]	38.7[d]	Small[e]
O	CH_3COOH	n.a.	>20.0[f]	0.11
O	$LiAlH_4$	n.a.	1.71[g]	n.a.
NCH_3	$C_6H_5S^-$	2.17	n.a.	0

[a] Corrected by statistical factor of 2 for compounds having one XCH_3 and two ring methylene positions. The results for X = O are from ref 8, the others from the present study. [b] Ratio of methylene to methine attack ca. 1.4. [c] Not available. [d] Ratio of methylene to methine attack 1.43. [e] This ratio is less than 0.70—probably considerably less since most of the product of apparent ring opening is in fact formed by direct nucleophilic displacement on the precursor of the cyclic onium salt without participation of the methoxy group. [f] Ratio of methylene to methine attack 0.67. [g] Ratio of methylene to methine attack 12.

five-membered rings, so much so that the reaction may be of preparative usefulness. In contrast, very predominant or exclusive attack on exocyclic methyl occurs in the six-membered ring. The transition state in an SN2 reaction presumably involves substantial progress along the reaction coordinate and the concomitant bond breaking of the endocyclic bond in the five-membered ring entails substantial relief of strain whereas no such relief occurs in the nearly strainless six-membered ring. In addition, inspection of models indicates that attack of a nucleophile from the rear of the ring X–C bond in a five-membered ring places the nucleophile in the favored staggered position with respect to the hydrogens of the adjacent CH_2 group. In contrast, such attack in the six-membered ring would lead to eclipsing of the nucleophile with one of the adjacent C–H bonds. Both factors may contribute to the observed preference for ring cleavage in the five- as contrasted to the six-membered ring.

The syntheses of the methyl ethers of *meso*- and *dl*-2,5-hexanedithiol, the free meso dithiol, *trans*- and *cis*-3,6-dimethyl-1,2-dithiane (XI, XII), and *cis*- and *trans*-2,5-dimethylthiolane (XIII, XIV) are summarized in Scheme V and are described in the Experimental Section. It is of interest that *cis*-2,5-dimethylthiolane (XIII) can be prepared either from *meso*-2,5-hexanediol ditosylate (IX) by a reaction (with sodium sulfide) involving two inversions or from the *dl*-ditosylate X by reactions involving three inversions in all (cyclic disulfide formation by Na_2S_2 followed by internal nucleophilic displacement triggered by hexaethylphosphorous triamide).[9]

Experimental Section

***meso*- and *dl*-2,5-Hexanediol Di-*p*-toluenesulfonates (IX, X).** Solutions of 88.7 g (0.75 mol) of 2,5-hexanediol (Aldrich) in 150 ml of pyridine and 310 g (1.63 mol) of *p*-toluenesulfonyl chloride in 450 ml of dry pyridine were cooled to 0 °C and then slowly mixed with cooling in an ice bath. After 3 days at 0 °C the solution was poured, with rapid stirring, onto a mixture of 700 g of ice, 400 ml of water, and 50 ml of concentrated hydrochloric acid. The precipitated solid was collected and washed thoroughly with water. Drying in a vacuum desiccator gave 239 g of off-white crystals. Four recrystallizations from methanol yielded 30 g of *meso*-2,5-hexanediol ditosylate (IX), mp 115.5–117 °C (lit.[10] 112–115 °C). One further recrystallization raised the melting point to 116–117 °C. The filtrates upon concentration yielded an additional 1.8 g. Further crystallization of the concentrated mother liquors followed by repeated recrystallization yielded 34.3 g of *dl*-2,5-hexanediol ditosylate (X), mp 80–83 °C (lit.[10] 81–91 °C, but for the optically active material).

***meso*-2,5-Dibromohexane** was prepared as described in the literature,[11] yield 40.8%, mp 39–40 °C (lit.[11] 39 °C).

***cis*-2,5-Dimethylthiolane (XIII).** A solution of 36.6 g (0.1 mol) of sodium sulfide nonahydrate in 500 ml of 95% ethanol was prepared and half of it placed in a 3-l. three-necked flask equipped with two dropping funnels and a condenser. The solution was heated to reflux and the remaining half of the solution and a solution of 42.7 g (0.1 mol) of *meso*-2,5-hexanediol ditosylate (IX) in 100 ml of dry dimethylformamide (DMF) were simultaneously added from the two addition funnels over a period of 1.5 h. The mixture was refluxed for 40 h and then steam distilled. The distillate was diluted with water and extracted with four portions of methylene chloride which were combined, cleared with water (three times), dried over $MgSO_4$, and concentrated on a rotary evaporator. Distillation of the residue yielded 8.2 g (70%) of *cis*-2,5-dimethylthiolane (XIII), bp 62–63 °C (45 Torr) [lit.[12] 60 °C (45 Torr)].

In a second preparation, the yield was 76%. The same material could be prepared in the same way in 74% yield starting with *meso*-2,5-dibromohexane. The product was further purified by distillation at reduced pressure from sodium metal.

NMR δ_{Me_4Si} ($CDCl_3$) 1.20–2.60 (m, 4 H, CH_2CH_2), 1.40 (d, 6 H, J = 7 Hz, CH_3), 3.80 ppm (m, 2 H, CHS).

***trans*-2,5-Dimethylthiolane (XIV).** This material was prepared similarly as the cis isomer but starting with the *dl*-ditosylate X, yield 63%, bp 78–82 °C (90 Torr) [lit.[12] 58 °C (44 Torr)].

NMR δ_{Me_4Si} ($CDCl_3$) 1.20–2.60 (m, 4 H, CH_2CH_2), 1.35 (d, 6 H, J = 7 Hz, CH_3), 3.78 ppm (m, 2 H, CHS).

***trans*-3,6-Dimethyl-1,2-dithiacyclohexane (XI).** The procedure was adapted from that of Dodson and Nelson.[10] To a solution of 12.0 g (0.05 mol) of sodium sulfide nonahydrate and 1.61 g (0.05 g-atom) of sulfur in 200 ml of DMF was added 22.3 g (0.05 mol) of *dl*-2,5-hexanediol ditosylate (X). The dark solution was heated with stirring at 80 °C for 21.5 h and was then poured with stirring onto 100 g of ice and 400 ml of water. The organic material was extracted with four portions of methylene chloride which were combined, cleared with three portions of water, dried over $MgSO_4$, and concentrated. Distillation of the residue afforded 4.13 g (56%) of pale yellow product, bp 36–40 °C (0.75 Torr). Redistillation gave 3.97 g of colorless liquid which was analyzed by GLC (10-ft 20% Carbowax 20M, temperature 122–160 °C, 15 °C/min rise) and shown to contain the trans (XI) and cis (XII) isomers in a 93:7 ratio. The material was purified to 99% purity by low-temperature recrystallization from petroleum ether (bp 30–60 °C) at −20°. The NMR spectrum agreed with that reported.[13]

***cis*-3,6-Dimethyl-1,2-dithiacyclohexane (XII)** was prepared similarly from 11.15 g (0.025 mol) of the meso ditosylate IX and was obtained in 61% yield, bp 78–80 °C (5 Torr). The crude product, analyzed as indicated above, indicated a cis/trans ratio of 96:4 plus two contaminants of lower retention time, one of which appeared to be XIII or XIV. The NMR spectrum of the material agreed with that reported.[13]

Reaction of *trans*-3,6-Dimethyl-1,2-dithiacyclohexane (XI) with Hexaethylphosphorous Triamide. The general procedure of Harpp et al.[9] was employed. A solution of 1.483 g (10 mmol) of XI and 2.73 g (11 mmol) of the triamide[14] $[(C_2H_5)_2N]_3P$ in 10 ml of dry benzene was stirred at room temperature for 12 h. Since no reaction appeared to have occurred (GLC analysis), the solution was boiled at reflux for 18.5 h. Still only 10% reaction had occurred. The benzene was removed and the residue heated at 150 °C. Even after 35 h reaction was not complete, so 10 additional drops of $(Et_3N)_3P$ were added and heating continued for 11.5 h. At this point GLC showed absence of starting material. The reaction mixture was diluted with water and extracted four times with petroleum ether (bp 30–60 °). The combined organic layers were cleared with water, dried ($MgSO_4$), and concentrated and the residue distilled to give 0.53 g (45.7%) of *cis*-2,5-dimethylthiolane (XIII), identical in NMR spectrum with the material described earlier.

***meso*-2,5-Hexanedithiol.** A solution of 4.44 g (30 mmol) of XII in 10 ml of anhydrous ether was added dropwise to a stirred slurry of 0.864 g (22.8 mmol) of lithium aluminum hydride in 20 ml of anhydrous ether over a 15-min period. The mixture was refluxed for 1.0 h, cooled, cautiously hydrolyzed with water, and treated with 10% sulfuric acid until clear. The layers were separated and the aqueous phase extracted with two portions of ether. The combined ether layers were cleared with water, dried ($MgSO_4$), and concentrated. Distillation of the residue afforded 4.08 g (91%) of a colorless product, bp 76–78 °C (5 Torr) [lit.[15] 87–88 °C (12 Torr) for a mixture of diastereomers]. GLC analysis similar to that described earlier indicated two close peaks (presumably meso and *dl* isomers) in a 97.9:2.1 ratio.

***meso*-2,5-Bismethylthiohexane.** To a solution of *meso*-2,5-hexanedithiol (3.00 g, 20 mmol) in 50 ml of dimethoxyethane, cooled in an ice bath, sodium hydride (1.854 g of 57% dispersion in oil, 1.056 g, 44 mmol) was added in portions. After stirring for 15 min, 6.38 g (45 mmol) of methyl iodide was added portionwise over 30 min and the mixture was stirred for an additional 2 h in the ice bath followed by warming to room temperature (3 h). The mixture was poured into 500 ml of water and extracted four times with ether. The combined ether layers were cleared three times with water, dried over $MgSO_4$, and concentrated. Distillation of the residue afforded, after a forerun, 1.85 g (52%) of product, bp 68–70 °C (0.7 Torr). Analysis by GLC essentially as described above indicated a purity of only 79%. The material was purified (GLC criterion) by redistillation, at reduced pressure, from a mixture of sodium and sodium hydroxide.

NMR δ_{Me_4Si} (C_6H_6) 1.13 (d, J = 7 Hz, 6 H, CCH_3), 1.56 (skew t, 4 H, CH_2), 1.80 (s, 6 H, SCH_3), ca. 2.4 ppm (flat, broad, ca. 2 H, CHS).

Anal. Calcd for $C_8H_{18}S_2$: C, 53.87; H, 10.17. Found: C, 53.78; H, 10.30.

***dl*-2,5-Bismethylthiohexane.** To ca. 1.6 g (10 mmol) of tetramethylethylenediamine cooled to 10 °C in a flask equipped with magnetic stirrer was added 4.4 ml of 2.3 M methyllithium in ether by means of a syringe through a septum; a white precipitate formed. Then 1.48 g (10 mmol) of XI (95% pure) was added through a syringe and the syringe was rinsed with 2 ml of anhydrous ether which was also added to the flask. Stirring was continued at 10–15 °C for 2 h, after which time methyl iodide (1.7 g, 12 mmol) in 10 ml of anhydrous ether was added gradually from a syringe over a 20-min period. Stirring was continued at 10–15° for 1 h and then at room temperature for 2 h. The mixture was then poured into 50 ml of water and extracted three times with ether. The combined ether layers were twice cleared with water, dried over $MgSO_4$, and concentrated. Distillation of the residue from sodium afforded 1.04 g (60%) of product, bp 78–80 °C (1 Torr).

NMR δ_{Me_4Si} (C_6H_6) 1.13 (d, J = 7 Hz, 6 H, CCH_3), 1.57 (broad t, 4 H, CH_2), 1.80 (s, 6 H, SCH_3), 2.3–2.6 ppm (broad, ca. 2 H, CHS).

Anal. Calcd for $C_8H_{18}S_2$: C, 53.87; H, 10.17. Found: C, 53.98; H, 10.40.

Preparation of Thiolanium and Thianium Methiodides. The preparation of thiolanium, 2-methylthiolanium, and thianium methiodides (I, II, III) has been described previously.[2,16] The methiodides of XIII and XIV were prepared analogously in refluxing ether, 2-day reaction time, IV, 54% yield (presumably the anti isomer), mp 190–192 °C dec; V, 51% yield, mp 186–189 °C dec (lit.[12] reports vaporization at 140–142 and 141–143 °C, respectively).

***N,N*-Dimethylpyrrolidinium *p*-Toluenesulfonate.** To a solution of 6.3 g (0.074 mol) of *N*-methylpyrrolidine in 80 ml of sodium-dried benzene was added 16 g (0.086 mol) of methyl *p*-toluenesulfonate. An additional 200 ml of benzene was added and the solution heated to incipient boiling for 10 min. After cooling the crude product was collected, washed with several portions of benzene, and dried, yield 17.66 g of yellow crystals. Recrystallization from ethanol–ethyl acetate yielded 14.34 g (71.5%) of product as white crystals, mp 163 °C.

***N,N*-Dimethylpiperidinium *p*-Toluenesulfonate.** A solution of 6.93 g (0.07 mol) of *N*-methylpiperidine and 13.1 g (0.07 mol) of methyl *p*-toluenesulfonate in 50 ml of absolute methanol was heated, with stirring, to incipient boiling for 10 min. After cooling the crystalline product was collected, washed with several portions of cold ethanol, and dried to give 18.34 g of crystalline product. Recrystallization from ethanol–ethyl acetate afforded 14.34 g (71.9% yield) of white crystals, mp 160 °C.

Reaction of Sulfonium Salts with Sodium Methylmercaptide. A solution of sodium hydroxide (15 mmol, 600 mg) in 25 ml of water was placed in a thick-walled tubular vessel containing a small stirring bar. A solution of 5 mmol of the sulfonium iodide in 25 ml of water was added, nitrogen was bubbled through the solution for several minutes, and the solution was then frozen, connected to a vacuum line, and degassed by at least three freeze–thaw cycles at 1 mm or less. To the frozen solution 3.0 ml of methanethiol (cooled by dry ice) was added, nitrogen flow was resumed, and the mixture was allowed to melt and mix with stirring; then 1.5 ml of additional methanethiol was added. Sitrring was continued at room temperature under nitrogen for several hours to allow evaporation of excess methanethiol. (The solution is 0.1 M in sulfonium salt and 0.3 M in CH_3SNa.) The solution was then again degassed and the vessel sealed off under vacuum. It was placed in an oil bath for periods of time ranging from 48 to 66.5 h, cooled to room temperature, frozen, and opened, and 10–15 ml of *n*-hexane containing exactly 5 mmol of diphenylmethane or decane as internal standard was added. After thorough shaking the hexane layer was subjected to gas chromatography. Each analysis was carried out at least five times; analysis on 10 ft × 0.125 in. 20% Carbowax 10% KOH on Chromosorb W column; columns were programmed for a temperature rise, over 60 min, from 80–110 °C lower limit to 200 °C upper limit.

The analytical results (response factors in parentheses) were as follows: I, thiane (1.689) 42%, thioether (1.060) 48%; II, thiane (1.601) 68–70%, thioether (1.002) 32–30%; III, thiane (1.688) 96%, thioether (0.981) 4%; IV, thiane XIII (1.422) 90%, thioether (0.948) 3.3%; V, thiane XIV (1.359) 91%, thioether (0.935) 3–9%; $(CH_3CH_2CH_2)_2SCH_3{}^+I^-$, $(CH_3CH_2CH_2)_2S$ (1.346) 82%, $CH_3SCH_2CH_2CH_3$ (2.069) 18%.

Reaction of Cyclic Ammonium Salts with Sodium Thiophe-

nolate. The dry *N,N*-dimethylpyrrolidinium or *N,N*-dimethylpiperidinium salt (0.1 mol) and 1.2 g (0.03 mol) of NaOH were dissolved in 50 ml of hexamethylphosphoramide (HMPA) in a 100-ml tubular thick-walled vessel containing a small stirring bar. Nitrogen was passed through the solution for 1 h after which 3.30 g (0.03 mol) of previously distilled thiophenol was added. The mixture was thus 0.2 M in the ammonium salt and 0.6 M in thiophenolate. Nitrogen flow was continued for 15 min and the mixture was then degassed by at least three freeze–dry cycles at 2 mm. The vessel was sealed under vacuum and placed in an oil bath at 100 °C for 48 h. The tubes were then removed, cooled, frozen, and opened. The contents were diluted with 180 ml of distilled water and extracted continuously with 150 ml of pentane for 24 h. To the extract was added exactly 0.01 mol of dodecane as internal standard and analysis was carried out by GLC using a 10% UCW-98 column programmed between 150 and 200 °C. A second extraction of the HMPA solution with pentane led to extraction of no additional product, as shown by GLC. Salt VI gave thioanisole (response factor relative to internal standard 1.63), 32% and amino thioether VIII (response factor 0.93), 68% in a total yield of 86%; salt VIII gave only thioanisole in 93% analytical yield.

1-Phenyl-6-methyl-6-aza-1-thiaheptane. A mixture of 27.1 g (0.1 mol) of *N,N*-dimethylpyrrolidinium tosylate, 12 g (0.3 mol) of NaOH, and 100 ml of HMPA was placed in a three-necked flask fitted with a reflux condenser and stirred for 1 h while nitrogen gas was passed through. Previously distilled thiophenol (32.5 g, 0.295 mol) was added and the solution heated to 100 °C for 24 h. The solution was then cooled, diluted with 300 ml of water, and extracted continuously with 250 ml of petroleum ether (bp 30–60 °C) for 48 h. The petroleum ether layer was cleared several times with water and several times with 10% aqueous hydrochloric acid, dried over $MgSO_4$, and concentrated. Distillation gave 1.3 g (13.7%) of thioanisole. The acidic water layer was made basic with 10% aqueous sodium hydroxide and extracted several times with portions of diethyl ether. The ether layer was dried and concentrated. Distillation of the residue afforded 8.81 g (42%) of product, bp ca. 160 °C (25 Torr), about 95% pure by GLC analysis. The material was purified by preparative gas chromatography for elemental analysis and response factor determination.

Anal. Calcd for $C_{12}H_{19}NS$: C, 68.90; H, 9.09. Found: C, 68.96; H, 9.21.

^1H NMR 1.6 (CH_2CH_2, m, 4 H), 2.1 (NMe_2 and CH_2S, m, 8 H), 2.85 (CH_2NMe_2, t, 2 H), 7.2 ppm (aromatic, m, 5 H).

Reaction of *meso*-*S*,2,5-Trimethylthiolanium Iodide with Sodium Mercaptide. A boiling solution of 25.2 g (0.63 mol) of sodium hydroxide in 500 ml of water was purged by bubbling through nitrogen for 2 h. After an additional 3 h at room temperature with N_2 purging, the solution was frozen, 40 ml of CH_3SH (cooled) was added, and the flask was allowed to warm to room temperature under nitrogen. An additional 10 ml of CH_3SH was added, followed by 54.4 g (0.21 mol) of the sulfonium salt IV. With continuing nitrogen blanketing the solution was boiled for 59 h, cooled, and extracted three times with methylene chloride. The combined methylene chloride layers were washed with water, dried over $MgSO_4$, and concentrated. Distillation of the residue afforded 16.8 g (69%) of *cis*-2,5-dimethylthiolane (XIII), bp 93–95 °C (160 Torr), spectrally identical with an authentic sample. GLC analysis (10-ft Carbowax 20M column) showed only traces of 2,5-bismethylthiohexane. Distillation of the pot residue afforded 0.86 g (2.3%) of 2,5-bismethylthiohexane, bp 68–71 °C (1 Torr), containing only traces of 2,5-dimethylthiolane, as indicated by GLC. Analysis by NMR (XL-100) using mixtures of authentic *dl*- and *meso*-2,5-bismethylthiohexane isomers for comparison demonstrated the product to be very largely the *dl* isomer (ca. 90–95%) with but a small amount (ca. 5–10%) of the meso isomer present.

7-Methyl-1-phenyl-7-aza-1-thiaoctane. 2-Phenylthiotetrahydropyran. A solution of 44.0 g (0.40 mol) of thiophenol in 65.6 g (0.80 mol) of dihydropyran containing a few crystals of *p*-toluenesulfonic acid was boiled at reflux for 2 h in a 250-ml flask. The mixture was cooled and neutralized with anhydrous potassium carbonate and the excess dihydropyran was removed by distillation at reduced pressure. The product was collected at 89–90 °C (0.5 Torr), yield 68.2 g (87%).

5-Phenylthio-1-pentanol.[17] Following an earlier-described procedure,[18] 133.5 g (1.0 mol) of aluminum chloride was dissolved, by slow addition with stirring, in 500 ml of dry ether cooled to 0 °C (ice–salt bath) in a 1-l. three-necked flask equipped with a reflux condenser, mechanical stirrer, and addition flask (later replaced by an addition funnel). After 30 min of stirring, 9.5 g (0.25 mol) of lithium aluminum hydride was added and the solution stirred for an additional 30 min. A solution of 68 g (0.35 mol) of 2-thiophenyltetrahydropyran in 200 ml of dry ether was then added over a 1-h period with stirring. The solution was boiled for 3 h and cooled, and 50% aqueous sodium hydroxide added dropwise with vigorous stirring until a fine white precipitate had formed. The mixture was filtered and the residue extracted for 3 h with ether in a Soxhlet extractor. The combined ether solution was dried over sodium sulfate, filtered, and concentrated and the residue distilled, bp 150–151 °C (0.5 Torr), yield 51 g (70%).

5-Phenylthio-1-bromopentane. To a solution of 51 g (0.26 mol) of the above alcohol in 50 ml of dry CCl_4 cooled to −5 °C in a 250-ml round-bottomed flask was added, dropwise, 70.2 g (0.26 mol) of PBr_3 over a period of 1 h. The flask was equipped with a reflux condenser with drying tube and the solution was allowed to warm to room temperature overnight. It was then heated on a steam bath for 1 h, cooled, and poured onto ice. After stirring for 1 h, the oily bottom layer was separated, washed with two 50-ml portions of 5% aqueous sodium carbonate followed by two 50-ml portions of water, and dried over Na_2SO_4. The drying agent was filtered and the product distilled, bp 145–146 °C (0.5 Torr), yield 85%.

7-Methyl-1-phenyl-7-aza-1-thiaoctane. A solution of 7.13 g (0.0275 mol) of the above bromide in 50 ml of ethanol was placed in a flask fitted with an ice–methanol condenser. The flask was cooled to 0 °C and 12.5 g (0.275 mol) of chilled anhydrous dimethylamine was added. After 4 h at 0 °C the solution was allowed to come slowly to room temperature. After standing for 48 h the reaction mixture was diluted with 200 ml of water, made basic with 10% aqueous sodium hydroxide, and extracted several times with ether. The combined ether extracts were dried over K_2CO_3 and concentrated and the residue distilled in a Kugelrohr apparatus. GLC of the product (10% UCW98) showed three components. The material was dissolved in 100 ml of 10% hydrochloric acid and the aqueous layer extracted with ether and then made basic with 10% aqueous NaOH. The ether layer was dried (K_2CO_3) and concentrated and the residue distilled in a Kugelrohr apparatus, yield 2.85 g (46.5%), bp ca. 250 °C (25 Torr).

Anal. Calcd for $C_{13}H_{21}NS$: C, 69.95; H, 9.41. Found: C, 69.74; H, 9.50.

NMR δ 1.5 ($CH_2CH_2CH_2$, m, 6 H), 2.2 (NMe_2 and CH_2S, m, 8 H), 2.8 (CH_2NMe_2, t, 2 H), and 7.1 ppm (aromatic, m, 5 H).

Reaction of 1-Methylthiolanium Iodide (I) and 1-Methylthianium Iodide (III) with Sodium Azide in Water. Water solutions, 0.1 M in sulfonium iodide and 0.3 M in sodium azide or 1.0 M in sulfonium iodide and 2.0 M in azide, were used for the analytical and preparative runs, respectively. The solutions were placed in 100-ml, thick-walled tubes and degassed by three freeze–evacuate–thaw cycles and the tubes sealed and placed in an oil bath at 100 °C for 48 h, then removed from the bath, cooled, and opened. In the analytical runs, 20–30 ml of diethyl ether was added, the water layers extracted by shaking, and the ether layer separated, dried, and analyzed by GLC on a 6 ft × 0.125 in. 10% UC-W-98 on Chromosorb W (80–100 mesh) column at 110 (I) or 125 °C (III), flow rate 120 ml/min He. Product compositions are summarized in Table II. In the preparative runs, the contents of the tubes were transferred to a small separatory funnel with the aid of some ether and extracted with ether. The ether layer was separated, dried over sodium sulfate, filtered, and concentrated and the residue distilled through a short Vigreux column. Yields and properties of products are included in Table II.

Reaction of *S*,2-Dimethylthiolanium Iodide (II) with Sodium Azide. The reaction was carried out on both analytical and preparative scales, as described for I above. The analytical run showed a ratio of azides to 2-methylthiolane of 1.52:1 corresponding to 60% azide(s) and 40% thiolane. (This value is approximate since it is based on the response ratio of 1.391 of the products of azide displacement on III. The corresponding ratio for I is 1.376.) The preparative experiment produced, upon distillation of the product, a forerun of 2-methylthiolane, identified by infrared spectrum, and a fraction of bp 95–105 °C (18 Torr) which displayed a broad band at 5.2 μm in the ir (azide). The NMR spectrum suggested the presence of two components (two methyl doublets at 1.30 and 1.32 ppm, $CHCH_3$, J = 6.5 Hz, two methyl singlets at 2.08 and 2.10 ppm, SCH_3). All attempts to separate the two components by GLC failed. Reduction of 6 g of the apparent azide mixture with a fourfold excess of ethereal $LiAlH_4$ yielded ca. 4 g of a mixture of two amines which could be analyzed on a 12 ft × 0.125 in. Theed (5% on Chromosorb W) column, ratio ca. 40:60. The amines were separated on a 12 ft × 0.375 in. preparative Theed (5% on Chromosorb A) column and identified as the reduction

Table II

Salt	Products	Yield, % Analytical	Yield, % Preparative	Bp, °C (Torr)
I	$(CH_2)_4S$	22	15	118–122[a]
	$CH_3S(CH_2)_4N_3$	78	68	86–87 (15)[b,c]
III	$(CH_2)_5S$	88.5	75	140–145[d]
	$CH_3S(CH_2)_5N_3$	11.5	~6	98–100 (15)[e,f]

[a] Lit. 119–120°C (760 Torr). [b] Calcd for $C_5H_{11}N_3S$: C, 41.35; H, 7.64. Found: C, 41.16; H, 7.53. [c] NMR $\delta^{(CDCl_3)}_{Me_4Si}$ 1.67 (4 H, m, CCH_2CH_2C), 2.08 (s, 3 H, SCH_3), 2.50 (distorted t, SCH_2), 3.28 ppm (distorted t, CH_2N_3). [d] Lit. 140–142°C (760 Torr). [e] Identical with authentic sample; see below. [f] NMR $\delta^{(CDCl_3)}_{Me_4Si}$ 1.6 [6 H, broad m, $C(CH_2)_3C$], 2.02 (s, 3 H, SCH_3), 2.45 (distorted t, 2 H, SCH_2), 3.23 ppm (distorted t, 2 H, CH_2N_3).

products of the expected two azides by their NMR spectra (10% $CDCl_3$ solution).

2-Amino-6-thiaheptane, $CH_3SCH_2CH_2CH_2CH(CH_3)NH_2$: δ 1.06 (d, 3 H, J = 6.5 Hz, $CHCH_3$), 1.56 (broad s, 2 H, exchanges with D_2O, NH_2), 1.39–1.78 (m, 4 H, $CH_2CH_2CHMeNH_2$), 2.07 (s, 3 H, CH_3S), 2.48 (distorted t, 2 H, $J \approx 7$ Hz, CH_3SCH_2), 2.87 ppm (approximate sextet, $J \approx 6.2$ Hz, $CH_2CHMeNH_2$).

1-Amino-4-methyl-5-thiahexane, $CH_3SCH(CH_3)CH_2CH_2CH_2NH_2$: δ 1.25 (d, 3 H, $CHCH_3$, J = 6.5 Hz), 1.54 (m, 4 H, CH_2CH_2CHMe), 1.67 (broad s, 2 H, exchanges with D_2O, NH_2), 2.03 (s, 3 H, CH_3S), 2.67 (m, 3 H, CH_2NH_2 and $CH_2CHMeSCH_3$).

1-Azido-6-thiaheptane. 6-Thiaheptan-1-ol.[18] To 500 ml of ether contained in a 1-l. three-necked round-bottom flask equipped with a mechanical stirrer, dropping funnel, and reflux condenser, cooled to 0 °C, was slowly added 133.5 g (1.0 mol) of aluminum chloride with continued cooling. After stirring for 2 h, 9.5 g (0.25 mol) of $LiAlH_4$ was added in small portions over 15 min. After stirring for an additional 2 h, 20 g (0.15 mol) of 2-methylthiotetrahydropyran,[18] bp 60–61 °C (15 Torr) [lit.[19] 47–48 °C (5 Torr)], dissolved in 25 ml of dry ether was added dropwise over 1 h. The solution was heated to reflux for 3 h and cooled and 50% aqueous NaOH was added slowly until a fine white precipitate had formed. The precipitate was filtered and extracted in a Soxhlet extractor with ether for 12 h. The extract was combined with the remaining ether layer, dried over sodium sulfate, and concentrated and the residue distilled, bp 67–69 °C (0.5 Torr) [lit.[20] 121 °C (16 Torr)], yield 16 g (79%).

1-Azido-6-thiaheptane. To 10.0 g (0.075 mol) of the above alcohol in 200 ml of dry pyridine cooled to 0 °C (ice–salt bath) was added 29.0 g (0.15 mol) of *p*-toluenesulfonyl chloride. After standing for 12 h in the refrigerator the solution was poured onto 500 g of ice and stirred for 1 h. The oily tosylate was extracted with three 100-ml portions of ether and the combined ether extracts washed with two 50-ml portions of water, dried over sodium sulfate, and concentrated at reduced pressure. The residue weighed ca. 20 g. It was dissolved in 100 ml of DMF, 16.25 g (0.25 mol) of sodium azide was added, and the mixture was boiled at reflux with magnetic stirring for 24 h. The solution was poured into 500 ml of ice water and the oil which separated taken up in 50 ml of ether. The water layer was extracted two times and taken up in 50-ml portions of ether. The ether extracts were combined, dried over sodium sulfate, and concentrated. The residual yellow liquid was distilled through a short Vigreux column to yield 9.2 g (77%) of product, bp 97–99 °C (15 Torr).

Anal. Calcd for $C_6H_{13}N_3S$: C, 45.25; H, 8.23. Found: C, 44.98; H, 8.17.

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Registry No.—I, 28608-92-6; II, 57774-87-5; III, 38131-89-4; IV, 57774-88-6; V, 57774-89-7; VI, 57774-90-0; VII, 42883-76-1; VIII, 57774-91-1; IX, 53585-64-1; X, 57819-13-3; XI, 57819-14-4; XII, 2506-33-4; XIII, 5161-13-7; XIV, 57774-92-2; 2,5-hexanediol, 2935-44-6; *p*-toluenesulfonyl chloride, 98-59-9; *meso*-2,5-dibromohexane, 54462-67-8; hexaethylphosphorous triamide, 2283-11-6; *meso*-2,5-hexanedithiol, 53585-65-2; *dl*-2,5-hexanedithiol, 53585-66-3; *meso*-2,5-bismethylthiohexane, 57774-93-3; *dl*-2,5-bismethylthiohexane, 57774-94-4; *N*-methylpyrrolidine, 120-94-5; methyl *p*-toluenesulfonate, 80-48-8; *N*-methylpiperidine, 626-67-5; sodium methylmercaptide, 5188-07-8; sodium thiophenolate, 930-69-8; thiophenol, 108-98-5; 2-phenylthiotetrahydropyran, 20965-36-0; dihydropyran, 25512-65-6; 5-phenylthio-1-pentanol, 57774-95-5; 5-phenylthio-1-bromopentane, 21782-59-2; 7-methyl-1-phenyl-7-aza-1-thiaoctane, 57774-96-6; sodium azide, 26628-22-8; 1-amino-4-methyl-5-thiohexane, 57774-97-7; 2-amino-6-thiaheptane, 57774-98-8; 6-thiaheptanol, 57774-99-9; 1-azido-6-thiaheptane, 57775-00-5; 2-methylthiotetrahydropyran, 31053-11-9; 1-azido-5-thiahexane, 57775-01-6.

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