

Reductions with Metal-Ammonia Combinations. II. Monothioacetals and Monothioketals. A Synthesis of Alkoxy Mercaptans^{1a}

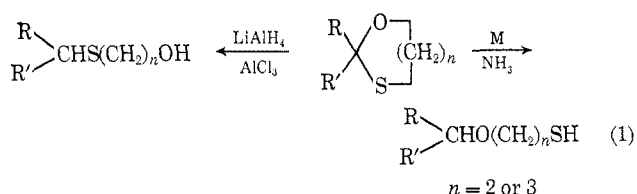
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The reduction of oxathiolanes and oxathianes with metal-liquid ammonia combinations gives rise to β - and γ -alkoxy mercaptans. Twenty-six cases have been studied; yields are good for all oxathianes and most oxathiolanes (except those with very simple 2-alkyl groups) when the metal is calcium.

In previous papers² the hydrogenolysis of monothioacetals and monothioketals by "mixed hydride"³ (lithium aluminum hydride-aluminum chloride in a 1:4 ratio) in ether solution was described.⁴ Reduction of 1,3-oxathiolanes and 1,3-oxathianes leads to β -hydroxyethyl and γ -hydroxypropyl sulfides, respectively^{2a} (eq 1), while 2-tetrahydrofuranyl and 2-tetrahydropy-



ranyl thioethers yield δ -hydroxybutyl and ϵ -hydroxypentyl sulfides, respectively.^{2b} The reaction involves selective cleavage of the C-O bond.

It is evident that selective cleavage of the C-S bond of 1,3-oxathiolanes and 1,3-oxathianes (eq 1) would provide a convenient route to β -alkoxyethyl and γ -alkoxypropyl mercaptans, respectively. The use of metal-ammonia solutions to cleave C-S bonds seemed promising in this regard, since it has long been known in the literature⁵ as being of great importance in the removal of S-protective groups, especially in peptide synthesis.⁶

There are several reports in the literature regarding treatment of dithiolanes with metal-ammonia solutions. For the most part such treatment leads to complete desulfurization⁷ or to more complicated reactions.⁸ Miles and Owen, however, have reported the selective cleavage of 2,2-dimethyl-4-hydroxymethyl-1,3-dithio-

lane to 2-isopropylthio-3-hydroxypropyl mercaptan.⁹ While this work was in progress,¹⁰ Brown, Iqbal, and Owen¹¹ reported the selective reduction of a number of other 1,3-dithiolanes to β -mercaptoethyl sulfides and the selective reduction of 2,2-dimethyl-*trans*-4,5-cyclohexano-1,3-oxathiolane to *trans*-2-isopropoxycyclohexanethiol. In contrast, Pinder and Smith have found the reduction of 2-phenyl-2-methyl-1,3-oxathiolane with sodium in liquid ammonia to give ethylbenzene.¹²

Scope

We have found that metal-ammonia reduction of 1,3-oxathiolanes and 1,3-oxathianes (ethylene and trimethylene monothioketals and -acetals) is a fairly general preparative method for β - and γ -alkoxy mercaptans as it involves selective cleavage of the acetal C-S bond (eq 1). The 1,3-oxathiolanes were reduced both with calcium and sodium in liquid ammonia; the compounds reduced and the yields of reduction products obtained are shown in Tables I and II, respectively. Table I also includes the properties of the products. The data for the reduction of 1,3-oxathianes are summarized in Table III; this reduction proceeds more slowly than that of the oxathiolanes.

The starting materials used in this study were prepared from the corresponding aldehydes and ketones and appropriate hydroxy mercaptan in the presence of an acid catalyst.^{2a,13} 3-Hydroxypropyl mercaptan was prepared by the method of Clinton and coworkers.¹⁴ In Table V (see Experimental Section) are listed all new starting materials prepared in the present investigation. Configurational assignments to the diastereoisomeric monothioketals obtained in this work have been discussed elsewhere,^{2a,15,16} as have the nmr spectra of a number of the oxathiolanes listed in Table V.¹⁷ Reduction products were characterized by ir and nmr spectra; some of them (Table I) were known compounds.¹⁸

In accord with the report of Pinder and Smith,¹² we have found that 1,3-oxathiolanes carrying 2-phenyl

(1) (a) E. L. Eliel and T. E. Hoover, *J. Org. Chem.*, **24**, 938 (1959), is considered paper I in this series; (b) from the Ph.D. Dissertation of T. W. Doyle, University of Notre Dame, 1966; (c) Charles Bernard McCanna Fellow, 1964-1966.

(2) (a) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, **84**, 2377 (1962); (b) E. L. Eliel, B. E. Nowak, and R. A. Daignault, *J. Org. Chem.*, **30**, 2448 (1965).

(3) E. L. Eliel, *Rec. Chem. Progr.*, **22**, 129 (1961); M. N. Rerick in "Reduction," R. L. Augustine, Ed., Marcel Dekker, Inc., New York, N. Y., 1968, Chapter 1.

(4) See also B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **41**, 2671 (1963).

(5) F. E. Williams and E. Gebauer-Fuelnegg, *J. Amer. Chem. Soc.*, **53**, 352 (1931); R. C. Krug and S. Tocker, *J. Org. Chem.*, **20**, 1 (1955); W. E. Truce, D. P. Tate, and D. N. Burdge, *J. Amer. Chem. Soc.*, **82**, 2872 (1960); W. E. Truce and J. J. Breiter, *ibid.*, **84**, 1621 (1962).

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(9) L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 2938 (1950).

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(11) E. D. Brown, S. M. Iqbal, and L. N. Owen, *J. Chem. Soc. C*, 415 (1966).

(12) A. R. Pinder and H. Smith, *ibid.*, 113 (1954).

(13) E. J. Salmi, *Ber.*, **71B**, 1803 (1938).

(14) R. O. Clinton, C. M. Suter, S. C. Laskowski, M. Jackman, and W. Huber, *J. Amer. Chem. Soc.*, **67**, 594 (1945).

(15) E. L. Eliel, E. W. Della, and M. Rogic, *J. Org. Chem.*, **30**, 855 (1965).

(16) M. P. Mertes, *ibid.*, **28**, 2320 (1963); M. P. Mertes, H. K. Lee, and R. L. Schowen, *ibid.*, **34**, 2080 (1969).

(17) D. J. Pasto, F. M. Klein, and T. W. Doyle, *J. Amer. Chem. Soc.*, **89**, 4368 (1967).

(18) M. F. Shostakovskiy, E. N. Prilezhaeva, and E. S. Shapiro, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 325 (1953); 235, 245 (1954).

TABLE I
REDUCTION OF 1,3-OXATHIOLANES WITH CALCIUM IN AMMONIA

Starting material, ethylene monothioacetal or monothioacetal of	Product, R'R'CHOCH ₂ CH ₂ SH R	Registry no.	Yield, % ^a		Bp, °C (mm)	n _D ^b	Carbon, %		Hydrogen, %	
			Anal	Isold			Calcd	Found	Calcd	Found
Acetaldehyde ^c	CH ₃		9	...						
Isobutyraldehyde ^d	(CH ₃) ₂ CH		21	7	51-53 (11)	1.4482				
Trimethylacetaldehyde	(CH ₃) ₃ C	24699-65-8	40	22	75 (34)	1.4401	56.73	57.03	10.88	10.85
Benzaldehyde ^e	C ₆ H ₅		0	0 ^g						
n-Heptanal ^f	n-C ₆ H ₁₃	24699-66-9	24	3	61 (0.5)	1.4550	61.33	61.53	11.44	11.50
Phenylacetaldehyde	C ₆ H ₅ CH ₂	10160-69-7	76	73	100-101 (1.3)	1.5363	65.92	66.00	7.74	7.62
Acetone ^g	CH ₃		24	16	63-67 (43)	1.4460		...		
3-Methyl-2-butanone	(CH ₃) ₂ CH	10160-71-1	78	72	63.5-63.8 (11)	1.4470	56.73	56.37	10.88	10.91
4-Methyl-2-pentanone	(CH ₃) ₂ CHCH ₂	10160-72-2	62	54	79 (15)	1.4465	59.23	59.19	11.18	11.06
Pinacolone	(CH ₃) ₃ C	10160-73-3	90	82	70-71.5 (11)	1.4472	59.23	59.26	11.18	11.05
2,4-Dimethyl-3-pentanone	(CH ₃) ₂ CH	10160-75-5	76	69	57-58.2 (2.2)	1.4532	61.33	61.26	11.44	11.42
Acetophenone ^h	C ₆ H ₅		0	0 ^f						
2-Octanone ⁱ	n-C ₆ H ₁₃	10160-74-4	55	41	62 (0.3)	1.4534	63.12	63.38	11.65	11.56
Phenylacetone	C ₆ H ₅ CH ₂	10160-76-6	91	88	97 (0.9)	1.5239	67.32	67.63	8.22	7.80
4-Phenyl-2-butanone	C ₆ H ₅ CH ₂ CH ₂	10160-77-7	59	47	108.5-109.5 (0.9)	1.5228	68.55	68.82	8.63	8.52
Cyclopentanone	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -	10160-78-8	37	25	54 (2.2)	1.4856 ^j	57.51	57.61	9.65	9.61
Cyclohexanone ^k	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -		68	49	84-86 (5)	1.4860		...		
3,3,5-Trimethylcyclohexanone ^l	β-mercaptoethyl ether ^m	24691-50-7	80 ⁿ	61	78-78.5 (0.8)	1.4772	65.31	65.56	10.96	10.87
3,3,5-Trimethylcyclohexanone ^l	β-mercaptoethyl ether		92 ^o	...						
4-t-Butylcyclohexanone ^l	β-mercaptoethyl ether ^p	24691-51-8	86 ⁿ	80	100-102 (0.98)	1.4892	66.60	66.66	11.18	11.24
4-t-Butylcyclohexanone ^l	β-mercaptoethyl ether		61 ^o	...						

^a First column gives analytical yields determined by iodine titration. Second column gives yield of compound isolated. ^b K. K. Georgiuff and A. Dupré, *Can. J. Chem.*, **37**, 1104 (1959).
^c No attempt made to isolate compound. ^d F. Kipnis and J. Ormfelt, *J. Amer. Chem. Soc.*, **71**, 3555 (1949). ^e Lit. ¹³ bp 45.2-45.5° (9 mm), n_D²⁰ 1.4444. ^f Reference 2a. ^g Toluene obtained in 75% yield. ^h Lit. ¹³ bp 56.1-56.4° (44 mm), n_D²⁰ 1.4424. ⁱ Ethylbenzene obtained in 75% yield. ^j At 22°. ^k Lit. ¹³ bp 73-73.5° (4.5 mm), n_D²⁰ 1.4864. ^l Reference 16. ^m Stereochemistry *cis*. ⁿ From S-axial isomer. ^o From O-axial isomer. ^p Stereochemistry *trans*.

TABLE II
REDUCTION OF 1,3-OXATHIOLANES WITH SODIUM IN AMMONIA

Starting material, ethylene monothioacetal of	Product, R'RCHOCH ₂ CH ₂ SH		Yield, % ^a	
	R'	R	Anal	Isold
2,4-Dimethyl-3-pentanone	(CH ₃) ₂ CH	(CH ₃) ₂ CH	62	51
2-Octanone ^b	<i>n</i> -C ₆ H ₁₃	CH ₃	49	41
Cyclopentanone	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -		25	17
Cyclohexanone ^b	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -		55	43
3,3,5-Trimethylcyclohexanone ^c	3,3,5-Trimethylcyclohexyl β-mercaptoethyl ether ^f		64 ^d	36
4- <i>t</i> -Butylcyclohexanone ^b	4- <i>t</i> -Butylcyclohexyl β-mercaptoethyl ether ^g		82 ^d	70
4- <i>t</i> -Butylcyclohexanone ^b	4- <i>t</i> -Butylcyclohexyl β-mercaptoethyl ether ^g		44 ^e	35

^a First column gives analytical yields determined by iodine titration. Second column gives yield of compound isolated. ^b Reference 2a. ^c Reference 16. ^d From S-axial isomer. ^e From O-axial isomer. ^f *cis* isomer. ^g *trans* isomer.

TABLE III
REDUCTION OF 1,3-OXATHIANES WITH CALCIUM IN AMMONIA

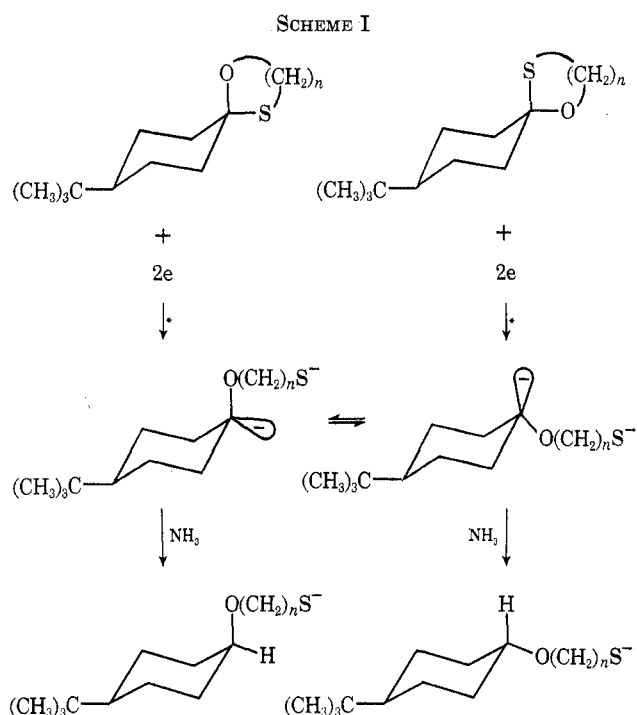
Starting materials, trimethylene mono- thioacetal or mono- thioacetal of	Product, R'RCHOCH ₂ CH ₂ CH ₂ SH		Registry no.	Yield, % ^a		Bp ₁ , °C (mm)	<i>n</i> _D ²⁰	Carbon, %		Hydrogen, %	
	R'	R		Anal	Isold			Calcd	Found	Calcd	Found
Isobutyraldehyde	(CH ₃) ₂ CH	H	24699-76-1	69	66	78 (21)	1.4505	56.73	56.90	10.88	11.18
Pinacolone	(CH ₃) ₂ C	CH ₃	24699-77-2	96	89	60 (2.7)	1.4505	61.33	61.12	11.44	11.18
Cyclopentanone	-CH ₂ CH ₂ CH ₂ CH ₂ -		24699-78-3	98	85	98-99 (14)	1.4833	59.98	60.21	10.07	10.14
Cyclohexanone ^b	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -		24699-79-4	90	70	72.5 (0.85)	1.4869	62.04	62.10	10.41	10.34
4- <i>t</i> -Butylcyclohexanone ^c	4- <i>t</i> -Butylcyclohexyl- O(CH ₂) ₃ SH			84-90 ^d	...						
4- <i>t</i> -Butylcyclohexanone ^c	4- <i>t</i> -Butylcyclohexyl- O(CH ₂) ₃ SH			24-52 ^e	...						
4- <i>t</i> -Butylcyclohexanone ^c	4- <i>t</i> -Butylcyclohexyl- O(CH ₂) ₃ SH		24699-80-7	78 ^f	61	98-100 (0.3)	1.4859	67.77	67.80	11.37	11.33

^a First column gives analytical yields determined by iodine titration. Second column gives yield of compounds isolated. ^b Reference 2a. ^c Reference 15. ^d from S-axial isomer. ^e From O-axial isomer. ^f Compound not isolated. ^g From synthetic mixture (55% O-axial isomer, 45% S-axial isomer) using sodium as the metal.

substituents are cleaved completely to the corresponding alkylbenzenes. The reduction of allyl and benzyl ethers with metal-ammonia solutions has long been known in the literature,¹⁹ thus any β-mercaptoethyl benzyl ethers, C₆H₅CHROCH₂CH₂S⁻, initially produced by the reduction might well be expected to be cleaved further to the hydrocarbon and β-mercaptoethanol.

While the reduction of monosubstituted 1,3-oxathiolanes generally leads to poor yields of mercaptan, 2-benzyl-1,3-oxathiolane is an exception. Similarly, 2-benzyl-2-methyl-1,3-oxathiolane gives mercaptan in better yield than might be expected on purely steric grounds. This may be ascribed to an inductive electron withdrawal by the benzyl group which enhances the electron affinity of the oxathiolane and thus facilitates its reduction.

Stereochemistry and Reaction Mechanism.—The reduction of oxathiolanes and oxathianes presumably proceeds by the transfer of two electrons, probably stagewise, and addition of a proton from ammonia at the carbon²⁰ (*cf.* Scheme I). There may be an intermediate radical anion with the anionic center either at the sulfur or at the carbon, and protonation of this anion radical may precede transfer of the second electron.²⁰ In this connection it is of interest that reduction of the diastereoisomeric oxathiolanes and oxathianes derived from 4-*t*-butylcyclohexanone¹⁵ is strongly though not completely stereoconvergent (Table IV) with the more stable equatorial β- or γ-hy-



* This reaction probably proceeds via R₂C-O(CH₂)_nS^{•-} or R₂CO(CH₂)_nS^{•-}. Protonation (and interconversion of stereoisomers) may, alternatively, occur at the radical-anion stage.

droxyethyl sulfide being by far the predominant product, regardless of the configuration of the starting material. This suggests that the rate of interconversion of the intermediate dianions or anion radicals (Scheme I) is somewhat more rapid than protonation;

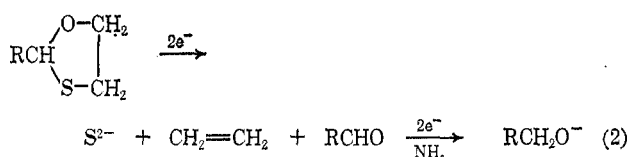
(19) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, New York, 1963, p 151-285.

(20) *E.g.*, R. Gerdil and E. A. C. Lucken, *J. Chem. Soc.*, 2857, 5444 (1963); 3916 (1964), and references there cited.

however, the fact that stereoconvergence is not complete, *i.e.*, that a slightly larger proportion of equatorial (*trans*) ether is obtained from the S-axial monothioacetals than from the S-equatorial ones (Table IV) shows that the rates of equilibration and protonation must be of similar magnitude. It is also noteworthy (Table IV) that product yields are consistently lower when the starting material is O axial, which suggests that development of the initially axial carbanion (dicarbanion or anion radical) is less facile than formation of the initially equatorial ion. Predominant formation of the equatorial products from the largely equilibrated carbanion intermediates is in keeping with what is observed in other reactions involving six-membered rings;²¹⁻²³ the reasons are probably kinetic (*i.e.*, dependent on rate of proton approach) rather than thermodynamic.²³

The configuration of the starting materials I-IV had been previously assigned¹⁵ and rests on firm grounds (nmr data, oxidation rates) for I and II and on somewhat less firm ones (nmr data only) for III and IV. Similarly the stereochemistry of the products V and VI was unequivocally established by Raney nickel hydrogenolysis to the known²⁴ *cis*- and *trans*-4-*t*-butylcyclohexyl ethyl ethers, whereas the assignment for VII and VIII rests on analogy only.

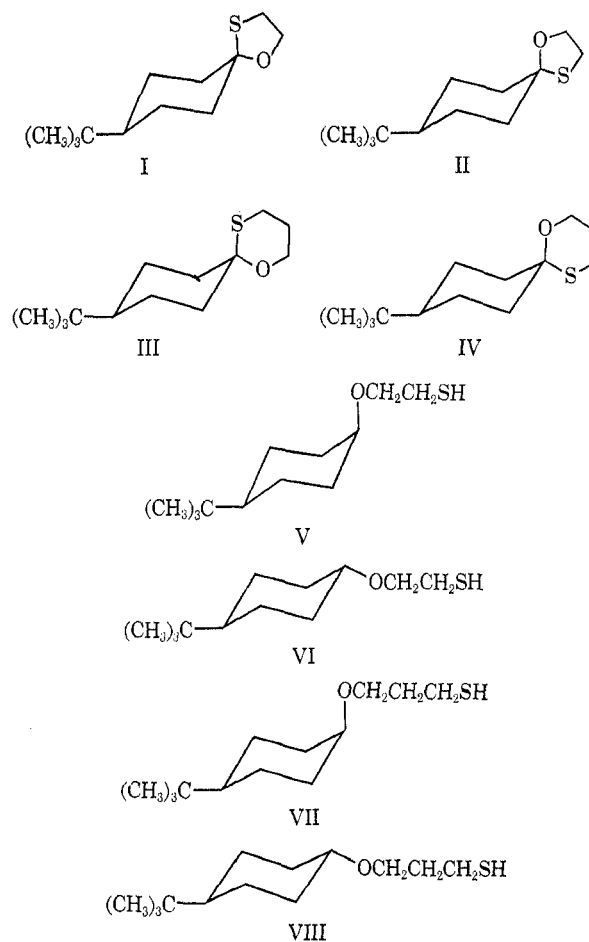
The low yield of β -alkoxy mercaptans from aldehydes and the less branched ketones (Table I) was found to be due, at least in part, to a side reaction leading to alcohol, hydrogen sulfide, and ethylene. Formation of alcohol (and sometimes also a small amount of ketone) was evident from the infrared spectrum. The side reaction was studied in some detail for the ethylene monothioacetal derived from heptaldehyde; *n*-heptyl alcohol (identified by boiling point, refractive index, and infrared spectrum), ethylene (identified mass spectrometrically as constituting 90+% of the off-gas), and hydrogen sulfide (identified by odor and by formation of lead sulfide) were found to be present. A reasonable reaction course is shown in eq 2. The



alcohol product presumably results from further reduction of aldehyde; it was shown independently that a carbonyl compound (4-*t*-butylcyclohexanone) is reduced under the conditions of the reaction (see ref 23). The products shown in eq 2 are derived directly from the monothioacetal rather than from the alkoxy mercaptan, $\text{RCH}_2\text{OCH}_2\text{CH}_2\text{SH}$, formed from it, for β -cyclohexyloxyethyl mercaptan was unaffected by sodium in liquid ammonia. Our proposed mechanism for the side reaction as well as the mercaptan forming reaction is shown in Scheme II.

Although attack of organolithium compounds both at the 2 position^{25,26} and at the 4 position²⁷ of dioxo-

TABLE IV
STEREOCHEMISTRY OF REDUCTION OF
1-OXA-4-THIA-8-*t*-BUTYLSPIRO[4.5]DECANES (I, II) AND
1-OXA-4-THIA-9-*t*-BUTYLSPIRO[5.5]UNDECANES (III, IV)
WITH CALCIUM OR SODIUM IN LIQUID AMMONIA



Substrate used	Yield, % RO(CH ₂) _n SH	Metal used	Isomer distribution ^a	
			% <i>cis</i> (V or VII)	% <i>trans</i> (VI or VIII)
I ^b	83-89	Ca	1.9-3.0	97.0-98.1
I	75-82	Na	2.5	97.5
II ^c	47-61	Ca	3.5-10.4	89.6-96.5
II ^d	44-46	Na	3.8-4.8	95.2-96.2
III ^e	84-90	Ca	0.5	99.5
IV ^e	24-52	Ca	6.8-15.6	84.4-93.2
III, IV ^f	80	Ca	6.5	93.5

^a By gas chromatography of the products or, in the case of I and II, the ethyl ethers derived from V and VI by desulfurization. ^b Average of six runs. ^c Average of five runs. ^d Average of two runs. ^e Average of three runs. ^f 1:1 mixture.

lanes, leading to cleavage of the ring, has been reported, it was found that 2-*n*-hexyloxathiolane is unaffected by calcium amide; thus the cleavage reaction in our case must be associated with reduction and cannot be due just to the presence of base.

While we do not have a complete understanding of the counterplay of reduction and cleavage mech-

(25) P. S. Wharton, G. A. Hiegel, and S. Ramaswami, *ibid.*, **29**, 2441 (1964); K. D. Berlin, B. S. Rathore, and M. Peterson, *ibid.*, **30**, 228 (1965); T. L. V. Ulbricht, *J. Chem. Soc.*, 6649 (1965).

(26) 1,3-Oxathiolanes are also reported to undergo such a reaction: personal communication from D. Seebach.

(27) C. H. Heathcock, J. E. Ellis, and R. A. Badger, *J. Heterocycl. Chem.*, **6**, 139 (1969).

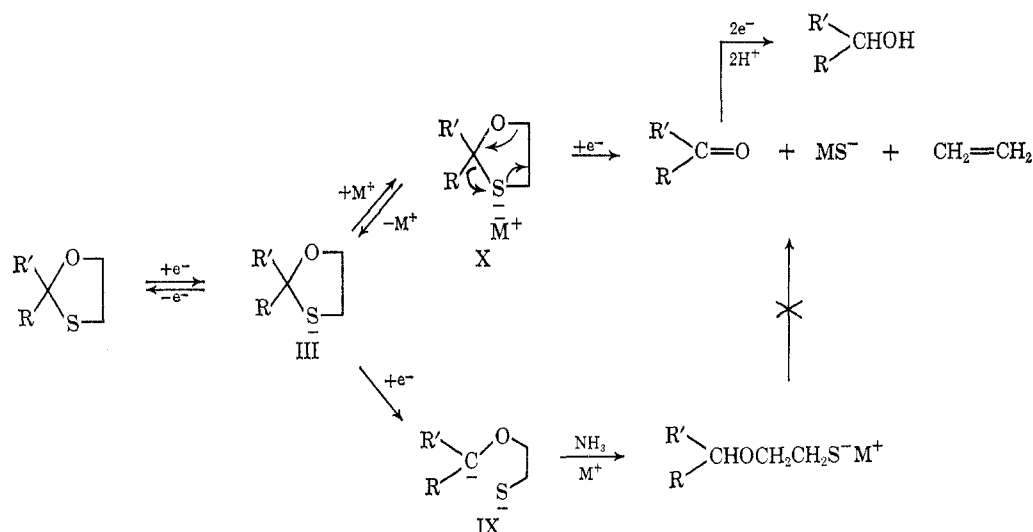
(21) E. L. Eliel and Y. Senda, *Tetrahedron*, in press.

(22) J. C. Rieher, *J. Org. Chem.*, **30**, 324 (1965).

(23) Cf. J. W. Huffmann and J. T. Charles, *J. Amer. Chem. Soc.*, **90**, 6486 (1968); D. A. H. Taylor, *Chem. Commun.*, 476 (1969).

(24) E. L. Eliel and S. Krishnamurthy, *J. Org. Chem.*, **30**, 848 (1965).

SCHEME II



anisms (Scheme II), the following additional findings are of interest.

(1) The effectiveness of metals in reduction is $\text{Ca} > \text{Li} > \text{Na} > \text{K}$. The consistently lesser yields obtained by sodium compared with calcium are seen by comparison of Table II with Table I; more extensive studies with cyclohexanone ethylene monoethioketal showed a drop in analytical yield from $69 \pm 3\%$ (Ca) to $62 \pm 1\%$ (Li) to $48 \pm 7\%$ (Na) to $38 \pm 2\%$ (K). Addition of CaCl_2 in reduction with Na does not effect the yield, but addition of KBr in reduction with Ca lowers the yield by about 25%.

(2) Optimum concentration of metal is about 0.35 *N*. Increase to 0.70 *N* with Ca had little effect on mercaptan yield but increasing $[\text{Na}]$ above 1 *N* or below 0.1 *N* led to a 10–15% drop.

(3) The addition of proton-donor (*t*-BuOH, EtOH) cosolvents is not helpful; if anything, it tends to lower the yield slightly. Added ether lowers the yield considerably.

(4) Use of MeNH_2 and EtNH_2 with Li gave lower yields than NH_3 .

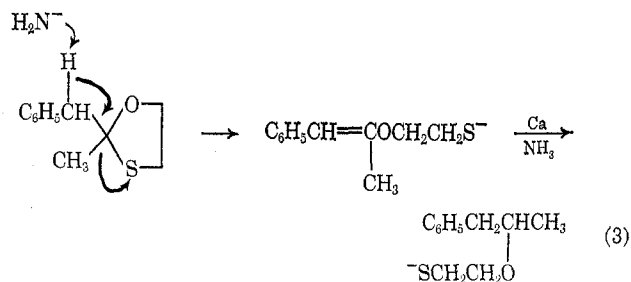
(5) The yields are much better for oxathianes (which cannot undergo the cleavage shown in eq 2) than for oxathiolanes, suggesting that the cleavage is responsible for the low yield of mercaptans in some of the cases shown in Table I.

(6) More branched structures (Table I, bottom half) give better yields of mercaptan than less branched ones (Table I, top entries).

We tentatively suggest that formation of a radical ion pair (X, Scheme II) is responsible for the competing cleavage reaction. It would appear^{28,29} that the ease of ion-pair formation is $\text{K}^+ > \text{Na}^+ > \text{Li}^+$ which explains why K favors cleavage most. Lowering the dielectric constant of the solvent (NH_3 -ether *vs.* NH_3 alone, MeNH_2 , or EtNH_2 *vs.* NH_3) favors cleavage, as is required by this explanation; so does the addition of the strongly pairing K^+ in reduction with Ca. Branching may interfere sterically with ion-pair formation, thus favoring reduction over cleavage. An alternative explanation of one-electron transfer, leading

to cleavage, *vs.* two-electron transfer, producing reduction,²⁰ *without* invoking ion-pair formation cannot readily account for the effects of variation in metal, solvent, and substrate structure on mercaptan yields which we have observed.

It was earlier noted that oxathiolanes with a 2-benzyl substituent give an unusually high yield of reduction product (Table I), and this was ascribed to the inductive effect of the phenyl group. An alternative explanation, namely that an abstraction of the benzylic hydrogen by base, followed by formation of an enol ether and subsequent reduction of that ether (eq 3), might be involved, could be ruled out on two



counts. First of all, β -ethoxystyrene, $\text{PhCH}=\text{CHOEt}$, chosen as a model for the proposed intermediate enol ether, was found to yield ethylbenzene rather than β -phenethyl ether, $\text{PhCH}_2\text{CH}_2\text{OEt}$, when treated with calcium in liquid ammonia (even though the latter ether is stable to this combination). Secondly, when all the hydrogens on the carbons at C-2 in 2-methyl-2-benzyl-2-oxathiolane (eq 3) were replaced by deuterium by preparing the oxathiolane from $\text{PhCD}_2\text{-COCD}_3$ and reduction was carried out, the product, $\text{PhCD}_2\text{CH}(\text{CD}_3)\text{OCH}_2\text{CH}_2\text{SH}$, had acquired no hydrogen at the benzyl (or methyl) position, as shown by nmr spectroscopy. Equation 3 would require replacement of one of the benzylic deuterium atoms by hydrogen in the reduction.

Several new compounds prepared in conjunction with this study but not heretofore mentioned are listed at the end of the Experimental Section.

(28) T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 318 (1966). We could find no data on Ca.

(29) See also T. S. Das, *Advan. Chem. Phys.*, **4**, 303 (1962).

TABLE V
STARTING MATERIALS^a

Ethylene ketal or monothioacetal of	Registry no.	Yield, %	Bp, °C (mm)	<i>n</i> _D ²⁰	Carbon, %		Hydrogen, %	
					Calcd	Found	Calcd	Found
Isobutyraldehyde ^b	17643-70-8	79	166-168 (745)	1.4783				
Trimethylacetaldehyde	17643-69-5	83	59.5 (13)	1.4754	57.51	57.66	9.65	10.00
Phenylacetaldehyde	24699-49-8	74	111 (1.5)	1.5705	66.65	66.84	6.71	6.63
3-Methyl-2-butanone	16047-98-6	73	64-65 (11)	1.4783	67.61	67.80	9.65	9.65
4-Methyl-2-pentanone	21-87-9	73	51-51.5 (3)	1.4740	59.98	60.11	10.07	10.11
Pinacolone	17642-77-2	75	75-77 (15)	... ^c	59.98	60.13	10.07	9.69
2,4-Dimethyl-3-pentanone	16047-99-7	50	57.1-57.5 (1.9)	1.4822 ^d	62.02	61.88	10.41	10.41
Cyclopentanone	176-38-5	89	29.5 (0.2)	1.5097 ^e	58.31	58.52	8.39	8.43
3,3,5-Trimethylcyclohexanone	24699-55-6	70	64-70 (0.3)	... ^f	... ^g			
Phenylacetone	17642-77-2	72	94 (0.7)	1.5590	68.02	68.12	7.27	6.98
1-Phenylpentadeuteriopropanone ^b	24699-57-8	87	83-85 (0.2)	1.5572				
4-Phenyl-2-butanone	17642-78-3	85	100-102 (0.45)	1.5480	69.21	69.43	7.74	7.93
Trimethylene acetal or monothioacetal of								
Isobutyraldehyde	24699-59-0	49	74-75 (13)	1.4871	57.51	57.74	9.65	9.65
Pinacolone	24699-60-3	20	49-49.5 (0.5)	1.4935	62.04	62.30	10.41	10.71
Cyclopentanone	24699-61-4	54	81.5-82.6 (4)	1.5205	60.74	60.54	8.72	8.73

^a Materials earlier prepared in this laboratory (ref 2a, 15) are not listed. ^b F. Kipnis and J. Ornfelt, *J. Amer. Chem. Soc.*, **71**, 3555 (1949), report bp 29° (2.5 mm). The nmr spectrum confirmed the assigned structure. ^c Solidifies to a glass, softening point 40-42°. ^d *n*_D²⁰. ^e *n*_D²⁰. ^f Separated, by column chromatography on Alcoa F-20 alumina, into an isomer of bp 60-61° (0.25 mm), *n*_D²⁰ 1.4992, and one of bp 84° (10.9 mm), *n*_D²⁰ 1.5004. Nmr spectra were compatible with the assigned structures. ^g Reference 16 reports bp 118-131° (19 mm); both isomers are described. ^h The nmr spectrum of the oxathiolane was identical with that of the derivative from phenylacetone except for the near absence of the methyl and benzyl (CH₂) resonances at 1.45 and 2.98 ppm (downfield from TMS). Extent of deuteration as estimated from nmr spectrum: 90% at CD₂, 92% at CD₃.

Experimental Section

All boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer infracord instrument. Gas chromatograms were obtained on a F & M Scientific Co. Model 810 research chromatograph. Nuclear magnetic resonance spectra were recorded with a Varian Associates Model V-4311 HR-60 spectrometer at 60 Mc by Mr. D. Schifferl. Complete ir and nmr spectra are recorded in the Ph.D. Thesis of T. W. Doyle (1966) available on interlibrary loan from the University of Notre Dame library. Elemental analyses were performed by either Midwest Microlab, Indianapolis, Ind., or Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Starting Materials.—The preparation of the starting materials used in this investigation was carried out according to the method of Eliel, Pilato, and Badding.^{2a} The properties of all new starting materials are listed in Table V. Known starting materials agreed in their physical properties with samples previously prepared and described in the literature.

Reductions.—The reduction of phenylacetone ethylene monothioacetal has been described previously in detail.³⁰ Other oxathiolane reductions were effected similarly. Yields and properties of reduction products are listed in Tables I and II. Analytical yields of mercaptan were determined by iodine titration.³⁰

Reduction of the Ethylene Monothioacetal of 1-Phenylpentadeuteriopropanone with Calcium in Ammonia.—The reduction of the ethylene monothioacetal of 1-phenylpentadeuteriopropanone (3.88 g, 0.02 mol) with calcium (1 g, 0.025 g-atom) in liquid ammonia (250 ml) was carried out in the usual fashion. The usual work-up procedure gave 3.86 g of an oil. A small aliquot of this oil was removed and titrated for mercaptan content with iodine³⁰; the yield of mercaptan was 98%. The remaining oil (3.30 g) was distilled to yield 3.24 g (94%) of the desired mercaptan, bp 82° (0.2 mm), *n*_D²⁰ 1.5250. The nmr spectrum of the compound showed 1.27 H (compared with 4 in the undeuterated compound) at 0.84-1.52 ppm and 2.18 H (compared with 4) at 2.23-2.90 ppm. If three of the four high-field hydrogens of the undeuterated compound are assigned to the CH₃ group and two of the four low-field ones to the PhCH₂ group, this indicates labeling in the benzylic position to be 91% complete and deuterium labeling in the methyl position to be 91% complete (which is approximately the amount of labeling in the starting material).

Reduction of 2-*t*-Butyl-2-methyl-1,3-oxathiane.—The reduction of 2-*t*-butyl-2-methyl-1,3-oxathiane is described in some detail. Other reductions of oxathianes were effected similarly. Yields and properties of reduction products are listed in Table III.

To 120 ml of liquid ammonia contained in a 300-ml, three-necked flask, fitted in the usual manner, was added 1 g (0.025 g-atom) of calcium turnings. When the metal had dissolved (after ca. 5 min) a solution of 2.08 g (0.012 mol) of 2-*t*-butyl-2-methyl-1,3-oxathiane in 12 ml of ether was added dropwise to the blue solution over a period of 2 min. When addition was complete the blue solution was stirred for 1 hr. At the end of this time the excess calcium was decomposed by the addition of small amounts of solid ammonium chloride. The reaction mixture was then worked up in the usual manner to yield 2.15 g of an oil. A small aliquot of this oil was removed and titrated for mercaptan content with iodine;³⁰ the yield of mercaptan was 96%. The remaining oil (1.95 g) was distilled to yield 1.70 g (89%) of γ -mercaptopropyl 3,3-dimethyl-2-butyl ether, bp 60° (2.7 mm) (see Table III). The infrared and nmr spectra were compatible with the assigned structure.

Stereochemistry.—The reductions of the diastereoisomeric 1,3-oxathiolane and 1,3-oxathianes derived from 4-*t*-butylcyclohexanone were carried out in the usual manner. After work-up the per cent yield of mercaptan was determined iodometrically for each reaction. The isomer composition of the products was determined by glpc analysis.

In the case of the products from the reduction of the diastereoisomeric 1,3-oxathiolanes the analysis was either carried out directly on the β -mercaptoethyl 4-*t*-butylcyclohexyl ethers or the mercaptans were first desulfurized with Raney nickel (see below) to give the corresponding ethyl ethers which were then analyzed by glpc. The mercaptans were analyzed on a 9-ft 20% Carbowax 20M on 42-60 firebrick column at 200° and a flow rate of 75 ml/min. The ethers were analyzed on the same column at 150°. The products from the reduction of the diastereoisomeric 1,3-oxathianes were analyzed directly by glpc on a 9-ft 20% Carbowax 20M on 42-60 firebrick column at 215° and a flow rate of 75 ml/min. The results of these experiments are summarized in Table IV.

Raney Nickel Desulfurization of β -Mercaptoethyl 4-*t*-Butylcyclohexyl Ether.—Raney nickel (5 g, W-2 grade commercial) was washed once with acetone, once with ethanol, and three times with ether (very carefully!). The 0.5 g of the oil recovered from the metal-ammonia reduction of the oxathiolane was dissolved in 25 ml of ether and added to the nickel. The mixture

(30) D. P. Harnish and D. S. Tarbell, *Anal. Chem.*, **21**, 968 (1949).

was refluxed for 20 min, cooled, and decanted from the nickel which was washed with three 10-ml portions of ether. The combined ethereal extracts were dried over magnesium sulfate and concentrated. The oil was then taken up in 2 ml of hexane and chromatographed on alumina (5–10 g, Alcoa F-20) with hexane to remove alcohol and ketone (produced in the metal-ammonia reduction). The eluent was concentrated and analyzed by glpc on a 9-ft 20% Carbowax 20M on firebrick column at 150°.

cis-3,3,5-Trimethylcyclohexyl Ethyl Ether.—*cis*-3,3,5-Trimethylcyclohexanol³¹ (20 g) was converted to its acetate by treatment with acetic anhydride (50 ml) and pyridine (10 g) (4 hr heating on steam bath). The acetate (23 g, 89%) boiled at 72° (3.5 mm), n_D^{20} 1.4392.

Anal. Calcd for C₁₁H₂₀O₂: C, 71.69; H, 10.94. Found: C, 72.07; H, 11.19.

Reduction was carried out by the method of Pettit and co-workers³² starting with 4.92 g of the acetate in 120 ml of boron trifluoride etherate which was added to 2.28 g of LiAlH₄ in 60 ml of ether. Reaction was effected with cooling for 90 min followed by 1-hr reflux. After decomposition with 10% sodium hydroxide the ether layer was concentrated, chromatographed over Alcoa F-20 alumina with hexane and concentrated again to give upon distillation 2.5 g (55%) of *cis*-3,3,5-trimethylcyclohexyl ethyl ether, bp 77–80° (20 mm). Repetition of the chromatography yielded pure material, bp 48–49° (3.5 mm), n_D^{20} 1.4350.

Anal. Calcd for C₁₁H₂₂O: C, 77.58; H, 13.02. Found: C, 77.64; H, 13.05.

trans-3,3,5-Trimethylcyclohexyl ethyl ether was synthesized analogously from the *trans* alcohol.³¹ The acetate, bp 60–60.5° (2 mm), n_D^{20} 1.4399, was obtained in 82% yield.

Anal. Calcd for C₁₁H₂₀O₂: C, 71.69; H, 10.94. Found: C, 72.04; H, 11.15.

The ether was obtained in 68% yield, bp 74–75° (20 mm), n_D^{20} 1.4338.

(31) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961).

(32) G. R. Pettit, U. R. Ghatak, B. Green, T. R. Kasturi, and D. M. Piatak, *ibid.*, **26**, 1685 (1961).

Anal. Calcd for C₁₁H₂₂O: C, 77.58; H, 13.02. Found: C, 77.86; H, 13.40.

trans-4-t-Butylcyclohexyl propyl ether was obtained analogously from *trans*-4-t-butylcyclohexanol and propionic anhydride, followed by reduction. The ether boiled at 112–114° (10 mm), n_D^{20} 1.4476.

Anal. Calcd for C₁₃H₂₆O: C, 78.72; H, 13.21. Found: C, 79.13; H, 13.20.

trans,trans-4-t-Butylcyclohexyloxyethyl Disulfide.—*trans*-4-t-Butylcyclohexyloxyethyl mercaptan of 98% stereoisomeric purity (Table IV) (0.95 g, 4.5 mmol) in 8 ml of 5% NaOH solution was treated with 0.5 ml of 30% hydrogen peroxide. Excess peroxide was destroyed with solid sodium metabisulfite and the product was extracted three times with a 20-ml portion of ether. Drying and concentration yielded 0.92 g (97%) white solid, recrystallized from ethanol to give white plates, mp 51.5–52°.

Anal. Calcd for C₂₄H₄₆O₂S₂: C, 66.92; H, 10.77; S, 14.89. Found: C, 67.16; H, 10.76; S, 14.77.

β-Chloroethyl benzyl sulfide was prepared from 40 g (0.25 mol) of β-hydroxyethyl benzyl sulfide³³ and 120 ml of concentrated hydrochloric acid by refluxing (with a gas trap) for 4 hr. The mixture was poured into 200 ml of water, the organic layer separated, and the aqueous layer was twice extracted with 100-ml portions of ether. The combined organic product was washed once with water and once with concentrated aqueous NaCl, dried, and concentrated to give after distillation 33 g (75%) of β-chloroethyl benzyl sulfide, bp 91.5° (0.6 mm), n_D^{20} 1.5682.

Anal. Calcd for C₉H₁₁ClS: C, 57.89; H, 5.93; Cl, 18.99. Found: C, 58.44; H, 6.00; Cl, 18.86.

Registry No.—*cis*-3,3,5-Trimethylcyclohexyl ethyl ether, 24691-15-4; *cis*-3,3,5-trimethylcyclohexanol (acetate), 24691-16-5; *trans*-3,3,5-trimethylcyclohexyl ethyl ether, 24691-17-6; *trans*-3,3,5-trimethylcyclohexanol (acetate), 24691-18-7; *trans*-4-t-butylcyclohexyl propyl ether, 24691-19-8; *trans,trans*-4-t-butylcyclohexyloxyethyl disulfide, 24691-20-1; β-chloroethyl benzyl sulfide, 4332-51-8.

Aromatic Nitration by Silver Nitrate Impregnated Silicic Acid in the Presence of Carbon Tetrachloride

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Carbon tetrachloride reacts rapidly with excess silver nitrate impregnated silicic acid at room temperature to produce carbon dioxide and a nitrating agent. With carbon tetrachloride in excess, phosgene and the nitrating agent are formed. Aromatic compounds are nitrated by this system under column-chromatographic or batch conditions. A reaction sequence involving trichloromethyl nitrate, phosgene, nitryl chloride, carbonyl nitrate, and dinitrogen pentoxide is proposed.

While chromatographing *trans*-stilbene on AgNO₃-silicic acid, we attempted to elute with carbon tetrachloride. The result was complete destruction of the stilbene with formation of some 4,4'-dinitrostilbene.¹ We have observed nitration of several other aromatic compounds under these conditions, but none of these reactions occurs in the absence of carbon tetrachloride.^{1,2} Carbon tetrachloride is generally considered inert to silver nitrate in homogeneous solution.³ Petrenko-Kritschenko and Opotsky⁴ reported 3% reaction with 0.2 N silver nitrate in 95% ethanol at 90° in 12

hr; the products were not examined. We were thus interested to attempt identification of the reactions involved.

Results

Static batch experiments with benzene and anisole are summarized in Table I. The basic experimental results drawn from there and the Experimental Section follow. (1) Neither benzene nor anisole is nitrated by AgNO₃-silicic acid alone (expt 8, 18). Both are nitrated in high yield by AgNO₃-silicic acid in the presence of CCl₄ (expt 16, 17). (2) The nitration reaction involves specifically Ag⁺, NO₃⁻, CCl₄, and the silicic acid surface (expt 6, 8, 9; ref 4). (3) The nitration reaction is independent of illumination and the presence of air (expt 3, 4, 11, 12). (4) Phosgene is formed in quantity. Two independent determinations

(1) J. E. Gordon, *J. Chromatogr.*, **48**, 532 (1970).

(2) E. Wenkert, D. J. Watts, and L. L. Davis [*Chem. Commun.*, 1317 (1969)], have recently reported nitration of phenols by AgNO₃-silicic acid alone. This appears to depend upon the presence of the acidic OH group.

(3) See, *e.g.*, R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 136 ff.

(4) P. Petrenko-Kritschenko and V. Opotsky, *Ber.*, **59**, 2131 (1926).