Reductions with Metal Hydrides. XV. Reduction of 2-Tetrahydropyranyl and 2-Tetrahydrofuranyl Thioethers with Lithium Aluminum Hydride–Aluminum Chloride

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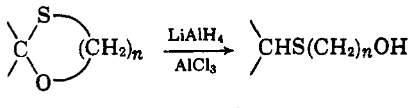
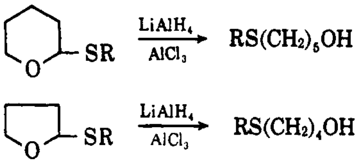
The reduction of 2-tetrahydropyranyl alkyl thioethers and 2-tetrahydrofuranyl alkyl thioethers with lithium aluminum hydride–aluminum chloride to the corresponding 5-hydroxypentyl alkyl thioethers and 4-hydroxybutyl alkyl thioethers is described.

In a previous publication[2] we described the reduction of a number of cyclic monothioacetals and monothioketals to hydroxy thioethers by means of lithium aluminum hydride–aluminum chloride ("mixed hydride").

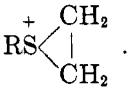


$n = 2$ or 3

We have now applied this reduction to 2-tetrahydropryanyl and 2-tetrahydrofuranyl thioethers which are readily synthesized by the addition of mercaptans to 2,3-dihydropyran and 2,3-dihydrofuran, respectively, and which, being monothioacetals, are subject to the cleavage reaction by "mixed hydride."[3] Unlike the oxygen analogs described in the preceding paper,[4] the sulfur compounds underwent selective cleavage of the ring carbon–oxygen bonds to hydroxy thioethers.



The method is a convenient one for synthesizing hydroxyalkyl thioethers with four or five methylene groups between the oxygen and sulfur atoms and thus complements the previously described[2] method which yields the corresponding compounds with two or three methylene groups between oxygen and sulfur.

In the previous work[2] we observed that β-hydroxyethyl alkyl thioethers, $RSCH_2CH_2OH$, are easily overreduced by "mixed hydride" to ethyl alkyl thioethers, $RSCH_2CH_3$, *via* intermediate cyclic sulfonium ions,  $\overset{+}{\mathrm{RS}}\!<\!\begin{matrix}CH_2\\|\\CH_2\end{matrix}$. No such overreduction occurs with γ-hydroxypropyl alkyl thioethers, $RS(CH_2)_3OH$,[5] because of absence of sulfur participation requiring a four-membered ring. In the present work, it was found that δ-hydroxybutyl alkyl thioethers also have no tendency to undergo overreduction even though twice the theoretical amount of hydride was employed in the cleavage of the tetrahydrofuranyl thioether. This suggests, contrary to previous indications,[6] that there is no ready sulfur participation through a five-membered ring either. Similarly, we found no strikingly high reactivity of the halogen in 4-chlorobutyl cyclohexyl thioether, $C_6H_{11}S(CH_2)_4Cl$. These observations are qualitative and do not completely rule out formation of a five-membered cyclic sulfonium ion intermediate, but they do indicate that such participation, if it occurs, is much less prominent than participation involving a three-membered ring.

The 2-tetrahydropyranyl- and 2-tetrahydrofuranyl thioether starting materials for this work are listed in Tables I and II, and the reduction products in Tables III and IV.

2-Cyclohexylthiotetrahydropyran was also reduced with lithium aluminum hydride–boron trifluoride, a reagent previously used in the reduction of acetals[7] and monothioketals.[8] The yield of product in this case was only 33%, however, compared with 75% with lithium aluminum hydride–aluminum chloride.

To confirm the structure of the compounds obtained in this work, an authentic sample of 4-hydroxybutyl cyclohexyl thioether was prepared from cyclohexyl mercaptan and γ-butyrolactone to give γ-cyclohexylthiobutyric acid which was then reduced with lithium aluminum hydride. The product was found to be identical with the product of hydrogenolysis of 2-cyclohexylthiotetrahydrofuran. Similarly, a sample of 5-benzylthio-1-pentanol prepared from pentamethylene chlorohydrin and sodium benzyl mercaptide was identical with the cleavage product of 2-tetrahydropyranyl benzyl thioether.

Experimental

2,3-Dihydrofuran was prepared as previously described.[4] 2,3-Dihydropyran was kindly donated by Dr. David Scheiber, Electrochemicals Department, E. I. du Pont de Nemours and Co. The preparation of 2-isopropylthiotetrahydropyran and 2-cyclohexylthiotetrahydrofuran and the reduction of 2-*t*-butylthiotetrahydrofuran are described as being typical of the examples reported in Tables I–IV.

2-Isopropylthiotetrahydropyran.[9]—Isopropyl mercaptan (19 g., 0.25 mole), 42 g. (0.50 mole) of 2,3-dihydropyran, and a few crystals of *p*-toluenesulfonic acid were placed in a 300-ml. round-bottom flask equipped with a reflux condenser, heated on the steam bath for 0.5 hr., and then cooled and neutralized with methanolic sodium methoxide. The reaction mixture was distilled to give, after a forerun, 29.4 g. (75.3%) of 2-isopropylthiotetrahydropyran, b.p. 80.5° (15 mm.), n^{20}_{D} 1.4806 (see Table I).

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[1] From the Ph.D. Dissertation of R. A. Daignault. We gratefully acknowledge support of this work under National Institutes of Health Grant GM-08848 and National Science Foundation Grant G-14251.

[2] E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Am. Chem. Soc.*, **84**, 2377 (1962).

[3] E. L. Eliel, *Record Chem. Prog.* (Kresge-Hooker Sci. Lib.), **22**, 129 (1961).

[4] Paper XIV: E. L. Eliel, B. E. Nowak, R. A. Daignault, and V. G. Badding, *J. Org. Chem.*, **30**, 2441 (1965).

[5] E. L. Eliel, E. W. Della, and M. Rogić, *J. Org. Chem.*, **30**, 855 (1965).

[6] E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 116.

[7] A. R. Abdum-Nur and C. H. Issidorides, *J. Org. Chem.*, **27**, 67 (1962).

[8] B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **41**, 2671 (1963).

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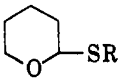
TABLE I

2-TETRAHYDROPYRANYL ALKYL THIOETHERS

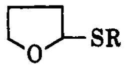


R	B.p., °C. (mm.)	$n^{20}D$	Yield, %	Calcd., %		Found, %	
				C	H	C	H
$(CH_3)_2CH$[a]	80–80.5 (15)	1.4806	75	59.93	10.08	60.20 60.39	10.43 10.27
$(CH_3)_3C$	86.5 (15)	1.4788	85	62.00	10.43	62.83	10.41
n-C_5H_{11}	82 (2)	1.4800	78	63.78	10.73	63.87	10.74
Cyclohexyl	89 (0.75)		78	65.95	10.06	65.65	10.02
n-C_7H_{15}	117 (12)	1.4799	85	66.59	11.20	66.78	11.29
$C_6H_5CH_2$	122 (1)[b]	1.5582 (25°)	61				

[a] Lit.[9] b.p. 48° (2.5 mm.). [b] Lit.[9] b.p. 86–87° (2 mm.).

TABLE II

2-TETRAHYDROFURANYL ALKYL THIOETHERS



R	B.p., °C. (mm.)	Yield, %	Calcd., %		Found, %	
			C	H	C	H
$(CH_3)_3C$	86–88 (20)	62	59.95	10.06	60.07	10.19
Cyclohexyl	125 (9)	60	64.47	9.74	64.53	9.63
n-C_6H_{13}	121 (11)	68	63.77	10.71	63.66	10.67
$C_6H_5CH_2$	125 (2.5)[a]	61	68.00	7.26	68.04	7.15

[a] Also 15% starting material recovered.

TABLE III

5-HYDROXYPENTYL ALKYL THIOETHERS

$RS(CH_2)_5OH$

R	B.p., °C. (mm.)	Yield, %	Calcd., %		Found, %	
			C	H	C	H
$(CH_3)_2CH$	120–122 (22)	82	59.20	11.18	59.48	11.31
$(CH_3)_3C$	130–132 (16)	80	61.30	11.43	60.94	11.59
n-C_5H_{11}	147–148 (17)	80	63.09	11.65	63.26	11.76
Cyclohexyl	174–176 (7)	75	65.29	10.96	65.28	10.95
n-C_7H_{13}	132–134 (3.5)	74	65.99	12.00	66.11	12.02
$C_6H_5CH_2$[a]	136–140 (0.5)	58		b		

[a] Result of E. L. Eliel and V. G. Badding [*J. Am. Chem. Soc.*, **81**, 6087 (1959)]. [b] $n^{25}D$ 1.5507. See Experimental for analysis of authentic sample.

TABLE IV

4-HYDROXYBUTYL ALKYL THIOETHERS

$RS(CH_2)_4OH$

R	B.p., °C. (mm.)	Yield, %	Calcd., %		Found, %	
			C	H	C	H
$(CH_3)_3C$	88–90 (2)	71	59.20	11.18	59.36	11.17
Cyclohexyl	108–110 (0.6)	69	63.75	10.71	63.97	10.69
n-C_6H_{13}	108–110 (0.6)	72	63.07	11.66	63.30	11.66
$C_6H_5CH_2$	136–138 (1.5)	63[a]	67.27	8.22	67.44	8.33

[a] Also 15% starting material recovered.

2-Cyclohexylthiotetrahydrofuran.—2,3-Dihydrofuran (7 g., 0.1 mole),[4] 11.6 g. (0.1 mole) of cyclohexylmercaptan, and a few crystals of *p*-toluenesulfonic acid were dissolved in 50 ml. of tetrahydrofuran and heated cautiously at reflux in a 200-ml. round-bottom flask for 1 hr. (In some instances, the addition of mercaptans to 2,3-dihydrofuran is quite exothermic and heating had to be interrupted temporarily during the exothermic phase of the reaction.) The reaction mixture was cooled, neutralized with methanolic sodium methoxide, and distilled, first to remove solvent and then at reduced pressure. There was obtained 11.1 g. (60%) of 2- cyclohexylthiotetrahydrofuran, b.p. 125° (9 mm.) (see Table II).

Reduction of 2-*t*-Butylthiotetrahydrofuran.—To 50 ml. of cooled ether (ice bath) in a 200-ml. round-bottom, three-necked flask was added 13.72 g. (0.1 mole) of anhydrous aluminum chloride. The mixture was stirred for 0.5 hr. and 20 ml. (0.025 mole) of a 1.29 *M* etheral lithium aluminum hydride solution was then added. Stirring was continued for another 0.5 hr., the ice bath was removed, and 8.0 g. (0.05 mole) of 2-*t*-butylthiotetrahydrofuran in ether solution was added slowly at room temperature. The solution was then boiled for 2 hr., cooled, and decomposed by addition of water (to destroy excess hydride) followed by 10% sulfuric acid. The ether layer was separated and the aqueous layer was extracted with several portions of ether. The combined ether layers were washed with water, dried over anhydrous potassium carbonate, and concentrated, and the residue was distilled at reduced pressure to give 5.7 g. (70%) of 4-*t*-butylthio-1-butanol, b.p. 88–90° (2 mm.), following a small forerun (see Table IV).

4-Cyclohexylthio-1-butanol. A. γ-Cyclohexylthiobutyric Acid.[10]—To 150 ml. of ethanol was added 4.6 g. (0.2 g.-atom) of sodium, followed by 23.5 g. (0.2 mole) of cyclohexyl mercaptan, and 21.5 g. (0.25 mole) of γ-butyrolactone. The solution was boiled at reflux for 1.5 hr. and concentrated, and the residue was dissolved in hot water. Acidification with hydrochloric acid gave a solid precipitate which was collected and recrystallized from hexane to give 18.7 g. (46%) of γ-cyclohexylthiobutyric acid, m.p. 29–30°.

Anal. Calcd. for $C_{10}H_{18}O_2S$: C, 59.37; H, 8.97. Found: C, 59.63; H, 8.98.

B. **4-Cyclohexylthio-1-butanol.**—The above acid (16.2 g., 0.08 mole) in about 100 ml. of ether was added to 48 ml. (0.06 mole) of 1.29 *M* standardized ethereal lithium aluminum hydride in a flask equipped with stirrer, reflux condenser, and dropping funnel. After 0.5 hr., the reaction mixture was decomposed with 10 ml. of water followed by 100 ml. of 10% sulfuric acid. The ether layer was separated, the aqueous layer was extracted with five 50-ml. portions of ether, and the ether layers were cleared with water, dried over magnesium sulfate, and concentrated. Distillation of the residue gave 10.9 g. (73%) of 4-cyclohexylthio-1-butanol, b.p. 108–110° (0.6 mm.), whose infrared spectrum was identical with that of the sample prepared by mixed hydride reduction of 2-cyclohexylthiotetrahydrofuran (Table IV).

4-Cyclohexylthio-1-chlorobutane.—To 5.64 g. (0.03 mole) of 4-cyclohexylthio-1-butanol in 100 ml. of chloroform was added, dropwise, 5.35 g. (0.045 mole) of freshly distilled thionyl chloride. Half-way through the addition, the solution was brought to boil on the steam bath. After addition was complete, boiling was continued for 4 hr. Concentration of the chloroform followed by vacuum distillation gave 5.15 g. (83%) of 4-cyclohexylthio-1-chlorobutane, b.p. 111–112° (2.5 mm.), which was free of hydroxylated impurities, according to its infrared spectrum.

Anal. Calcd. for $C_{10}H_{19}ClS$: C, 58.07; H, 9.26; Cl, 17.15; S, 15.39. Found: C, 58.24; H, 9.22; Cl, 17.12; S, 15.39.

The compound underwent negligible solvolysis in 87% ethanol at 25° in 14 days.

5-Benzylthio-1-pentanol.—To a solution of 1.4 g. (0.06 g.-atom) of sodium in 100 ml. of absolute ethanol was added 6.2 g. (0.05 mole) of benzylmercaptan, and the mixture was stirred at reflux. 5-Chloro-1-pentanol (7.35 g., 0.06 mole) in 100 ml. of absolute ethanol was added slowly, and the mixture boiled for 2 hr. more. After cooling, the mixture was poured into 200 ml. of ether and 900 ml. of 1% aqueous sodium hydroxide. The

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[10] Method of W. Reppe, *Ann.*, **596**, 191 (1955).

ether layer was extracted with two 100-ml. portions of 10% sodium hydroxide, dried, and concentrated. Distillation of the residue yielded 7.53 g. (72%) of 5-benzylthio-1-pentanol, b.p. 144° (0.5 mm.), $n^{25}\text{D}$ 1.5488.

Anal. Calcd. for $C_{12}H_{18}OS$: C, 68.52; H, 8.63. Found: C, 68.42; H, 8.50.

The infrared spectrum of the material was identical with that of the cleavage product of 2-benzylthiotetrahydropyran (Table III).

Other Compounds.—Also synthesized in the course of this work was the 2-tetrahydropyranyl derivative of ethyl mercaptoacetate, b.p. 98–99° (2 mm.).

Anal. Calcd. for $C_9H_{16}O_3S$: C, 52.91; H, 7.90. Found: C, 53.01; H, 7.83.

The bis-2-tetrahydropyranyl derivative of mercaptoethanol, b.p. 136–138° (3 mm.), was also synthesized.

Anal. Calcd. for $C_{12}H_{22}O_3S$: C, 58.50; H, 9.00. Found: C, 58.60; H, 8.90.

Notes

Reductions with Metal Hydrides. XVI. Reduction of Some 2-Tetrahydropyranylamines

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Having studied the reduction of 2-tetrahydropyranyl ethers[1] and 2-tetrahydropyranyl thioethers[2] with lithium aluminum hydride–aluminum chloride, we were interested in the reduction of the corresponding 2-tetrahydropyranyl-N,N-dialkylamines. As was to be expected on the basis of the fact[3] that oxazolidines, unlike ketals and monothioketals, are hydrogenolyzed by lithium aluminum hydride alone, without the need for added Lewis acids, 2-piperidinotetrahydropyran, 2-morpholinotetrahydropyran, and 2-benzylaminotetrahydropyran were similarly reduced to substituted 5-aminopentanols. The starting materials (which are

simple models for nucleosides) are readily prepared from 2-chlorotetrahydropyran and the appropriate amine. The reduction product from 2-piperidinotetrahydropyran was identical in infrared spectrum and other physical properties with an authentic sample of 5-piperidino-1-pentanol prepared from pentamethylene chlorohydrin and piperidine.

Hydride reduction of 2-alkylaminotetrahydropyrans provides an alternative to the previously described[4,5] catalytic hydrogenation which also yields 5-alkylamino-1-pentanols.

Experimental

2-Chlorotetrahydropyran.[6]—Hydrogen chloride gas was bubbled into a solution of 33.6 g. (0.4 mole) of dihydropyran and 100 ml. of anhydrous ether at 0° until no more was absorbed. Concentration and distillation at reduced pressure gave 28.8 g. (60%) of 2-chlorotetrahydropyran, b.p. 40–42° (16 mm.), lit.[6] b.p. 40° (15 mm.). The product was stored in a refrigerator over anhydrous potassium carbonate until used.

2-Piperidinotetrahydropyran.—In a 500-ml. three-necked flask equipped with a magnetic stirrer and condenser was placed 27.6 g. (0.2 mole) of anhydrous potassium carbonate, 20.8 g. (0.25 mole) of piperidine, and 100 ml. of anhydrous ether. A solution of 12.7 g. (0.1 mole) of 2-chlorotetrahydropyran in 100 ml. of ether was slowly added from a dropping funnel. After addition was complete, the turbid solution was boiled for 6 hr., cooled, and 100 ml. of water was added to dissolve the salts. The ether layer was separated and the aqueous layer was extracted three times with 100-ml. portions of ether. The combined ethereal extracts were dried over potassium carbonate, decanted, and concentrated. Vacuum distillation of the residue gave 11.9 g. (71%) of 2-piperidinotetrahydropyran, b.p. 93–94° (7 mm.). The infrared spectrum was compatible with the assigned structure.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.93; H, 11.32; N, 8.27. Found: C, 71.00; H, 11.28; N, 8.00.

2-Morpholinotetrahydropyran was similarly prepared from 9.6 g. (0.11 mole) of morpholine in 48% yield (8.2 g.): b.p. 88–89° (7 mm.), $n^{20}\text{D}$ 1.4776; lit.[5] b.p. 111.5° (12 mm.), $n^{20}\text{D}$ 1.4809. The infrared spectrum indicated absence of starting materials.

2-Benzylaminotetrahydropyran was analogously prepared from 11.8 g. (0.11 mole) of benzylamine in 47% yield (9.0 g.) and boiled at 114° (5 mm.). The infrared spectrum indicated substantial absence of benzylamine.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.19; H, 9.27; N, 7.01.

Reduction of 2-Piperidinotetrahydropyran.—Lithium aluminum hydride (0.1 mole) in the form of a clear ethereal solution (*ca.* 1 *M*) was placed in a three-necked flask equipped with a condenser, drying tube, stirrer, and dropping funnel. The solution was diluted with 50 ml. of ether, and 8.5 g. (0.05 mole) of 2-piperidinotetrahydropyran in 100 ml. ether was added dropwise. The solution was boiled for 2 hr., cooled, and decomposed by the addition of 4 ml. of water, 4 ml. of 15% aqueous sodium hydroxide, and again 12 ml. of water. The precipitated solid was removed by suction filtration and washed with several portions of ether, and the combined ether filtrate was dried over potassium carbonate and concentrated. Distillation of the residue at reduced pressure gave 7.0 g. (82%) of 5-piperidino-1-pentanol: b.p. 99–101° (0.75 mm.), $n^{18}\text{D}$ 1.4804; lit.[7] b.p. 140° (13 mm.), $n^{15.5}\text{D}$ 1.4820. The infrared spectrum showed the expected presence of OH and was identical with that of an authentic specimen (see below).

Reduction of 2-Morpholinotetrahydropyran.—From 6.0 g. (0.05 mole) of 2-morpholinotetrahydropyran was obtained 5.5 g. (92%) of 5-morpholino-1-pentanol: b.p. 116–118° (3 mm.), $n^{18}\text{D}$ 1.4750; lit.[5] b.p. 151° (10 mm.), $n^{19}\text{D}$ 1.4780. The infrared spectrum showed a prominent band at 2.95 μ and was different from that of the starting material.

Reduction of 2-Benzylaminotetrahydropyran.—2-Benzylaminotetrahydropyran was reduced on a 0.031 *M* scale (6.0 g.) by proportionally diminishing the amounts of reagents given above.

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(1) E. L. Eliel, B. E. Nowak, R. A. Daignault, and V. G. Badding, *J. Org. Chem.*, **30**, 2441 (1965).

(2) E. L. Eliel, B. E. Nowak, and R. A. Daignault, *ibid.*, **30**, 2448 (1965).

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