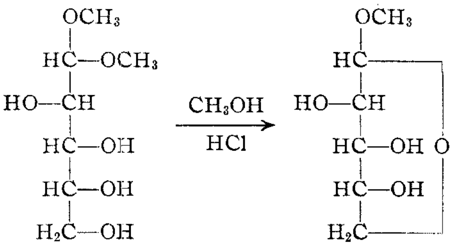
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Cyclization of δ-Hydroxyacetals

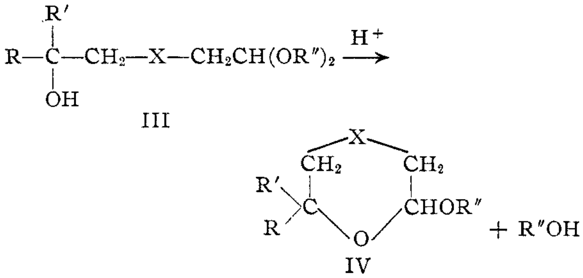
BY WILLIAM E. PARHAM

Although the acid catalyzed alcohol interchange of simple acetals has been examined in some detail,[1] there are few reports in the literature concerning the behavior of substituted hydroxyacetals in acid medium. In this connection Montgomery, Hann and Hudson[2] reported the preparation of a mixture of methyl-*d*-arabinosides (II) by the action of methanolic hydrogen chloride upon *d*-arabinose dimethyl acetal (I).



I II

In order to explore further such intramolecular interchange of acetals, a study has been made of the properties of some simple δ-hydroxyacetals, such as III, to determine whether they would behave in an analogous manner and so lead to cyclic acetals such as IV.



where X = O, S, CH_2

Since it is also known that alcohol interchange in the case of simple acetals leads to poor yields when the entering alcohol is tertiary, some compounds of type III in which the alcohol was secondary and tertiary were included in this study.

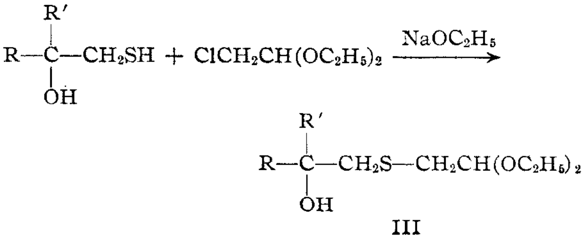
Four compounds of type III were prepared—three sulfides in which the alcohol was primary, secondary and tertiary, respectively, and one oxide in which the alcohol was primary. All four of these compounds underwent cyclization readily when subjected to the action of catalytic amounts of ethanolic hydrogen chloride; the cyclic acetals (IV) were produced in good yields. Thus diethyl (2-hydroxyethyloxy)-acetal (IIIa) was converted into 2-ethoxy-1,4-dioxane (IVa) in 76% yield; diethyl (2-hydroxyethylthio)-acetal (IIIb) gave 2-ethoxy-*p*-oxathiane (IVb) in 90% yield; diethyl (2-hydroxypropylthio)-acetal (IIIc) gave 2-ethoxy-6-methyl-*p*-oxathiane (IVc) in nearly quantitative yield; and diethyl (2-hydroxyisobutylthio)-acetal (IIId) gave 2-ethoxy-6,6-dimethyl-*p*-oxathiane (IVd) in 90% yield.

		III		
Compound	R	R′	R″	X
IIIa	H	H	C_2H_5	O
IIIb	H	H	C_2H_5	S
IIIc	H	CH_3	C_2H_5	S
IIId	CH_3	CH_3	C_2H_5	S

		IV		
Compound	R	R′	R″	X
IVa	H	H	C_2H_5	O
IVb	H	H	C_2H_5	S
IVc	H	CH_3	C_2H_5	S
IVd	CH_3	CH_3	C_2H_5	S

It was not possible to reverse the ring closure and to convert, for example, 2-ethoxy-*p*-oxathiane (IVb) into diethyl (2-hydroxyethylthio)-acetal (IIIb) by the action of ethanolic hydrogen chloride; however, when *n*-butyl alcohol was used, the product was 2-*n*-butoxy-*p*-oxathiane resulting from a simple interchange of the ethoxy and butoxy groups. The exchange of the ethoxy group by other primary alkoxy radicals appears to be general for compounds of type IV. 2-*n*-Butoxy-6,6-dimethyl-*p*-oxathiane was prepared in good yield from 2-ethoxy-6,6-dimethyl-*p*-oxathiane by treatment with *n*-butyl alcohol containing a catalytic amount of ethanolic hydrogen chloride. When the entering alcohol was tertiary, however, the reaction failed. With *t*-butyl alcohol only unchanged starting material was recovered. The failure of *t*-butyl alcohol to enter into an exchange reaction with 2-ethoxy-*p*-oxathiane is in sharp contrast to the rapid cyclization of diethyl (2-hydroxyisobutylthio)-acetal and indicates that tertiary alcohols, under conditions normally employed, undergo appreciable acetal interchange only in intramolecular reactions.

The δ-hydroxyacetals (III) used in this study were prepared by the condensation of diethyl chloroacetal with the appropriate glycol or thioglycol.



III

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[1] Alquier, *Bull. soc. chim.*, **10**, 197–198 (1943).

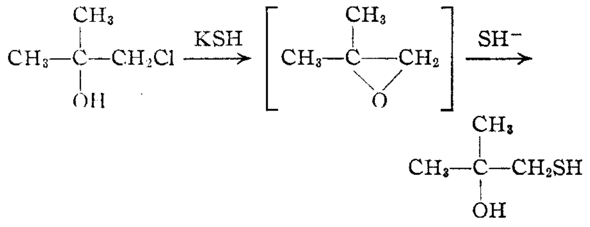
[2] Montgomery, Hann and Hudson, THIS JOURNAL, **59**, 1124 1937).

TABLE I

SUBSTITUTED *p*-OXATHIANES

	Yield, %	B. p. °C.	Mm.	$n^{20}D$	Formula	Mol. wt. (f. p. benzene) Calcd.	Mol. wt. (f. p. benzene) Found	% C Calcd.	% C Found	% H Calcd.	% H Found
2-Methoxy-*p*-oxathiane	90	92	30	1.4922	$C_5H_{10}O_2S$	...	.....	...	...	..	..
IVb	90	81–82	14	1.4850	$C_6H_{12}O_2S$	148.2	142, 149	48.62	48.71	8.16	7.93
IVc	93	88	14	1.4750	$C_7H_{14}O_2S$	162.2	166	51.82	51.78	8.70	8.98
IVd	90	87	12	1.4732	$C_8H_{16}O_2S$	176.3	171	54.51	54.51	9.15	8.96

2-Hydroxyisobutyl mercaptan (V), used in the preparation of IIId is new; it was prepared by the action of potassium hydrosulfide upon isobutylene-α-chlorohydrin. Although this synthesis does not lead to a compound of unequivocal structure, the structure assumed is reasonable, since the only other possibility, 2-mercaptoisobutyl alcohol, would have to be formed by abnormal cleavage of isobutylene oxide. This possibility is not in accord with the evidence so far obtained for the anionic cleavage of oxides.[3,4,5]



V

The ease by which these δ-hydroxyacetals undergo simple acetal interchange suggests that a study of other hydroxyacetals, which cannot form five- or six-membered rings, may prove interesting and may lead to high molecular weight condensation polymers. This possibility is being investigated.

Experimental

Diethyl (2-Hydroxyethyloxy)-acetal (IIIa).—This acetal was prepared from ethylene glycol according to the directions of Palomaa and Aalto[6] using diethyl chloroacetal instead of diethyl bromoacetal. The yield of IIIa was 5% of the theoretical, b. p. 121–123° (17 mm.), $n^{20}D$ 1.4279.

A mixture of 3 ml. of the acetal and 10 ml. of dilute hydrochloric acid was warmed, and a solution of 1.5 g. of 2,4-dinitrophenylhydrazine in 100 ml. of boiling ethanol was added. The solution was shaken for a few minutes, 2 ml. of concentrated hydrochloric acid was added, and the mixture was heated under reflux for five minutes. When the solution was cooled and diluted with water, a large amount of yellow crystals separated. After several recrystallizations from absolute ethanol, the 2,4-dinitrophenylhydrazone of 2-hydroxyethyloxyacetaldehyde melted at 136–138°.

Anal. Calcd. for $C_{10}H_{12}O_6N_4$: C, 42.25; H, 4.26. Found: C, 42.39; H, 4.49.

Cyclization of Diethyl (2-Hydroxyethyloxy)-acetal.—Fifteen grams of (IIIa) was shaken with a few drops of ethanolic hydrogen chloride. The reaction was slightly exothermic. After five minutes of standing the mixture was shaken with 10 ml. of saturated sodium bicarbonate and extracted with ether. The ether extract was dried over anhydrous potassium carbonate and distilled under reduced pressure. There was obtained 8.3 g. (76%) of 2-ethoxy-1,4-dioxane (IVa); b. p. 61° (17 mm.), $n^{20}D$ 1.4260.

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.52; H, 9.15; mol. wt., 132.3. Found: C, 54.24; H, 9.36; mol. wt., 133.1 (f. p. benzene).

2-Ethoxy-1,4-dioxane was converted to the same 2,4-dinitrophenylhydrazone derivative as was obtained from IIIa.

The procedure used for the cyclization of diethyl (2-hydroxyethyloxy)-acetal was used as a general procedure for the cyclization of the δ-hydroxyacetals under investigation. The physical properties and analytical data for the additional compounds of type IV, prepared by this procedure, are summarized in Table I.

Preparation of Diethyl (2-Hydroxyethylthio)-acetal (IIIb).—One hundred and fifty-four grams (1.97 moles) of monothioglycol was added in portions to a solution of sodium ethoxide prepared from 45.3 g. (1.97 gram atoms) of sodium and 750 ml. of absolute ethanol. To this solution was added 10 g. of powdered potassium iodide, and, slowly, with stirring, 300 g. (1.97 moles) of diethyl chloroacetal. The mixture was heated overnight at the reflux temperature. After removal of the salt by filtration and evaporation of the ethanol, the residual oil was distilled under reduced pressure. There was obtained 260 g. of diethyl (2-hydroxyethylthio)-acetal, b. p. 112° (1.6 mm.), $n^{20}D$ 1.4710, a yield of 68%.

Anal. Calcd. for $C_8H_{18}O_3S$: C, 49.45; H, 9.34. Found: C, 49.50; H, 9.04.

The 2,4-dinitrophenylhydrazone of 2-hydroxyethylthioacetaldehyde was prepared from IIIb by acid hydrolysis followed by treatment with 2,4-dinitrophenylhydrazine. It showed no depression in melting point with an authentic sample[7,8] (m. p. 74–5°).

Other δ-hydroxyacetals (III) were prepared by the condensation of the appropriate thioglycol and chloroacetal as described for the preparation of diethyl (2-hydroxyethylthio)-acetal. The physical and analytical data for these compounds are summarized in Table II.

2-Hydroxyethylthioacetaldehyde.—A mixture of 60 g. (0.405 mole) of 2-ethoxy-*p*-oxathiane and 200 ml. of dilute hydrochloric acid was heated with stirring for eighty minutes. The resulting solution was cooled to 10°, saturated with sodium chloride and extracted with 5–700-ml. portions of ether. The ether extract was dried and the ether removed at the water pump. The residue, a white semi-solid, was recrystallized from chloroform containing petroleum ether, weight 30.1 g. (62%), m. p. 55–57°. After several recrystallizations from the same solvent the material melted at 56–57°.

Anal. Calcd. for $C_4H_8O_2S$: C, 39.98; H, 6.71. Found: C, 39.77; H, 6.61.

The aldehyde is water soluble. It reacts readily with Schiff reagent and forms a 2,4-dinitrophenylhydrazone, m. p. 74–75°, identical to that obtained directly from IIIb.

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(3) Kadesch, THIS JOURNAL, **68**, 41 (1946).

(4) Glickman and Cope, *ibid.*, **67**, 1012 (1945).

(5) Fraenkel-Conrat and Olcott, *ibid.*, **66**, 1420 (1944).

(6) Palomaa and Aalto, *Ber.*, **66**, 468–472 (1933).

(7) The 2,4-dinitrophenylhydrazone of 2-hydroxyethylthioacetaldehyde was previously prepared by Fuson and Parham from diethyl (2-hydroxyethylthio)-acetal; however, diethyl (2-hydroxyethylthio)-acetal and 2-hydroxyethylthioacetaldehyde were not isolated.

(8) Fuson and Parham, *J. Org. Chem.*, **11**, 482 (1946).

TABLE II

δ-HYDROXYACETALS (III)

Compound	Yield, %	B. p. °C.	B. p. Mm.	n^{20}D	Formula	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found
Dimethyl-(2-hydroxy-ethylthio)-acetal[a]	68–72	90	0.63	1.4810	$C_6H_{14}O_3S$	...	...	..	..
IIIc	72	92–93	0.55	1.4654	$C_9H_{20}O_3S$	51.89	51.25	9.68	9.81
IIId	74	95	0.3	1.4650	$C_{10}H_{22}O_3S$	54.02	53.50	9.97	9.58

[a] The dimethyl chloroacetal was kindly supplied by the General Aniline and Film Corporation.

Preparation of 2-*n*-Butoxy-*p*-oxathiane.—A mixture of 20 g. (0.13 mole) of 2-ethoxy-*p*-oxathiane and 50 g. (0.67 mole) of *n*-butyl alcohol containing 3 drops of ethanolic hydrogen chloride was heated at the reflux temperature for five minutes. The mixture was allowed to cool and treated with 5 g. of anhydrous potassium carbonate. After standing for an hour the mixture was filtered and distilled under reduced pressure. 2-*n*-Butoxy-*p*-oxathiane, 16.6 g. (72%) was collected as a colorless liquid at 109° (13 mm.). This acetal has a sweet odor somewhat similar to butyl ether.

Anal. Calcd. for $C_8H_{16}O_2S$: C, 54.51; H 9.15. Found: C, 54.76; H, 9.44.

2-*n*-Butoxy-6,6-dimethyl-*p*-oxathiane—This compound was obtained from 2-ethoxy-6,6-dimethyl-*p*-oxathiane in 73% yield by the same method used for the preparation of 2-*n*-butoxy-*p*-oxathiane, b. p. 119° (13 mm.), n^{20}D 1.4700. This cyclic acetal possessed a faint fruity odor.

Anal. Calcd. for $C_{10}H_{20}O_3S$: C, 58.78; H, 9.87. Found: C, 58.70; H, 10.03.

2-Hydroxypropylmercaptan.—A cold solution of 135 g. of potassium hydroxide in 750 ml. of 95% ethanol was saturated with hydrogen sulfide and 209 g. (1.5 moles) of propylene bromohydrin was added over a period of one hour. During the entire process the mixture was stirred and a slow stream of hydrogen sulfide was introduced. The mixture was then stirred overnight, heated at the reflux temperature for one hour, cooled and made slightly acid with acetic acid. The salt was removed by filtration and the alcohol at the water-pump. When most of the ethanol was removed the residue set to a light yellow solid. This was diluted with 100 ml. of water and the organic layer was removed. The aqueous layer was saturated with sodium chloride and extracted with ether. The combined organic layer and ether extract was dried and distilled under reduced pressure. There was obtained 64 g. (46%) of 2-hydroxypropylmercaptan, b. p. 58–60° (17 mm.), n^{20}D 1.4805. The product obtained by Sjoberg[9] by the hydrolysis of acetyl-β-oxy-propylmercaptan boiled at 51° (12 mm.), n^{20}D 1.4862.

2-Hydroxyisobutyl Mercaptan (V).—This compound was obtained in 46% yield from isobutylene α-chlorohydrin by the same method described for 2-hydroxypropyl mercaptan, b. p. 64° (26 mm.), n^{20}D 1.4768.

Anal. Calcd. for $C_4H_{10}OS$: C, 45.24; H, 9.49. Found: C, 45.05; H, 9.42.

Summary

It has been shown that simple δ-hydroxyacetals undergo an acid catalyzed cyclization to produce mixed cyclic acetals by the elimination of a mole of alcohol. This reaction has been shown to be general whether the δ-hydroxyl group is primary, secondary or tertiary. 2-Ethoxy-1,4-dioxane and a series of 2-ethoxy-*p*-oxathianes have been prepared by application of this reaction and it has been shown that the ethoxy group of these cyclic acetals can be replaced readily by other primary alkoxy groups, such as *n*-butoxy, by treatment with the corresponding primary alcohol under acidic conditions. Furthermore, evidence is presented which indicates that tertiary alcohols undergo appreciable alcohol exchange with acetals only when the reaction is intramolecular.

MINNEAPOLIS, MINN. RECEIVED APRIL 30, 1947

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(9) Sjoberg, *Ber.*, **75B**, 13–29 (1942).

[CONTRIBUTION FROM THE FLIGHT PROPULSION RESEARCH LABORATORY OF THE NATIONAL ADVISORY COMMITTEE FOR AERONAUTICS]

The Synthesis and Purification of Ethers

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As part of an investigation of possible components of aviation gasoline, this laboratory has prepared a series of 24 ethers of various types. Seven of these ethers are aliphatic in type, both alkyl and alkylene; three are of the methylcycloalkyl type; six of the ethers contain the simple phenoxy radical; and eight are alkyl ethers of alkyl-substituted phenyl radicals. Approximately 2-liter quantities of these ethers were prepared either by purification of commercially available materials or by synthesis and purification. In most cases it was necessary to remove traces of halogen from the crude product by treatment with sodium in liquid ammonia or by azeotropic distillation. After treatment all materials were found to be halogen-free by the Beilstein test. With the exception of the solid, *t*-butyl *p*-*t*-butylphenyl ether, which was successively recrystallized, final purification of each ether was by fractional distillation through helix-packed, glass columns of 80 theoretical plates. All distillations were conducted under nitrogen to prevent oxidation; all but a few were at atmospheric pressure. The ethers were prepared to an estimated purity of 99.5 mole per cent. or better as evidenced by time–temperature freezing and melting curves that were determined