[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES, THE UNIVERSITY OF FLORIDA]

Some β-Hydroxypropyl Sulfides and their Derivatives[1]

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The present work is an extension of this Laboratory's program of preparation of physiologically active compounds.[3] The compounds herein described were prepared according to the following schematic representation; their analyses and properties are shown in Tables I and II.

TABLE I

PROPERTIES AND ANALYSES OF THE SULFIDES

	Yield, %	B. p. °C.	Mm.	$n^{25}D$	d^{25}_4	MD Calcd.	MD Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
				(I) Chlorohydroxypropyl Sulfides, $RSCH_2CHOHCH_2Cl$							
Methyl	40	55	1.4	1.5094	1.2250	35.03	34.30	34.16	34.28	6.45	6.25
Ethyl	74	69	1.5	1.5047	1.1651	39.66	39.36	38.83	38.80	7.17	7.53
n-Propyl	73	80	1.4	1.4986	1.1268	44.28	43.92	42.79	42.46	7.76	7.76
n-Butyl	64	77	0.5	1.4939	1.0883	48.90	48.86	46.01	45.74	8.28	8.35
n-Amyl	46	86	0.5	1.4900	1.0664	53.51	53.34	48.84	48.82	8.71	8.84
n-Hexyl	74	97	0.5	1.4880	1.0465	58.14	58.02	51.28	50.92	9.09	9.21
				(IV) Epoxypropyl Sulfides, $RSCH_2CH\underset{O}{\triangle}CH_2$							
Methyl	62	85	70	1.4817	1.0583	28.34	28.04	46.12	45.52	7.74	8.07
Ethyl	62	42	3.5	1.4757	1.0170	32.96	32.76	50.81	50.73	8.53	8.77
n-Propyl	57	45	2.0	1.4730	0.9905	37.58	37.44	54.50	54.66	9.15	9.59
n-Butyl	63	132	70	1.4723	0.9716	42.20	42.17	57.49	57.72	9.65	10.14
n-Amyl	50	68	1.6	1.4707	0.9544	46.82	46.90	59.95	59.92	10.06	10.26
n-Hexyl	32	70	0.7	1.4702	0.9471	51.44	51.36	62.01	62.00	10.41	10.64
				(V) Bis-(alkylthio)-propanols, $RSCH_2CHOHCH_2SR$							
Methyl	(17)[a]	161	50	1.5359	1.1256	42.75	42.17	39.46	39.63	7.95	8.30
Ethyl	55	94	1.0	1.5148	1.0528	51.99	51.63	46.62	46.33	8.95	9.24
n-Propyl	64	105	0.7	1.5063	1.0144	61.23	61.06	51.90	51.56	9.68	9.77
n-Butyl	55	133	1.0	1.5007	0.9867	70.46	70.48	55.88	55.84	10.23	10.53
n-Amyl	67	148	0.8	1.4960	0.9692	79.70	79.71	59.03	58.98	10.67	10.89
n-Hexyl	63	184	1.5	1.4927	0.9547	88.94	89.00	61.58	61.21	11.03	10.54

[a] Obtained as a by-product in formation of $CH_3SCH_2\underset{\llcorner\!\!\lrcorner}{CHCH_2}O$.

As indicated, most of the compounds of this paper were derived directly or indirectly from (I), the addition product of epichlorohydrin and a mercaptan. Until recently, this reaction, while well-known, had not been extensively investigated. Nenitzescu and Scarlatescu[4] reported the addition of various alkyl mercaptans to epichlorohydrin and concluded that a secondary alcohol is formed. Gilman and Fullhart,[5] while observing that Nenitzescu and Scarlatescu made arbitrary assumptions in arriving at this conclusion, nevertheless verified that similar reactions resulted in secondary alcohols. The verification rested upon the identity of the methiodide obtained from the reaction product of a mercaptan and styrene oxide with the methiodide obtained from the reduction product of phenacyl methyl sulfide.

Additional supporting evidence that secondary alcohols are formed was presented by Swern, Billen and Knight,[6] who, by means of rate studies of the reaction product, showed that only a secondary alcohol is formed in the reaction of allyl alcohol with epichlorohydrin.

This paper presents additional evidence that a secondary alcohol is formed according to equation (1) below.

(1) $RSH + CH_2\!-\!\underset{\diagdown\,\diagup}{O}\!-\!CHCH_2Cl \longrightarrow RSCH_2CHOHCH_2Cl$

(2) $RSH + CH_2\!-\!\underset{\diagdown\,\diagup}{O}\!-\!CHCH_2Cl \longrightarrow HOCH_2CHCH_2Cl$ (S bonded to R)

First, the chlorohydroxypropyl sulfides obtained by the addition of mercaptans to epichlorohydrin fail to show even slight vesicant action. This is in contrast to the behavior of compounds of the type indicated in equation (2) above, compounds in which chlorine is beta to the sulfide

(1) Presented in part at the Southeastern Regional Meeting of the American Chemical Society, Oak Ridge, Tenn., June 11, 1949.

(2) Abstracted from a portion of the dissertation submitted by Thomas K. Todsen to the Graduate School of the University of Florida in partial fulfillment of requirements for the degree of Doctor of Philosophy.

(3) Flores-Gallardo and Pollard, *J. Org. Chem.*, **12**, 831 (1947).

(4) Nenitzescu and Scarlatescu, *Ber.*, **68**, 589 (1936).

(5) Gilman and Fullhart, THIS JOURNAL, **71**, 1478 (1949).

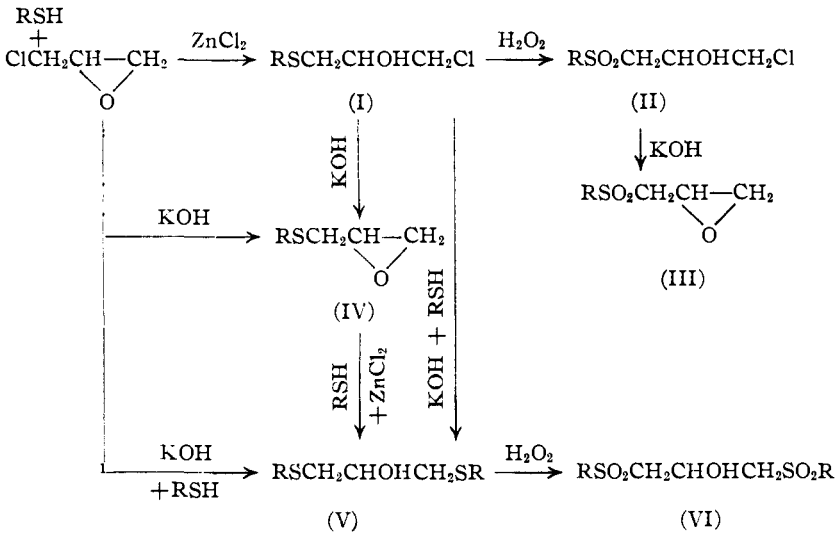
(6) Swern, Billen and Knight, *ibid.*, **71**, 1152 (1949).

TABLE II

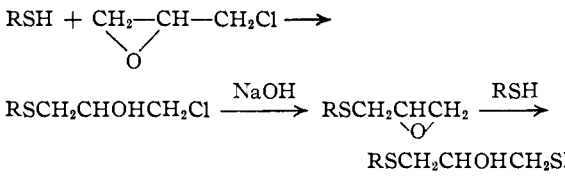
PROPERTIES AND ANALYSES OF THE SULFONES

Sulfone	Yield, %	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
(II) Chlorohydroxypropyl Sulfones, $RSO_2CH_2CHOHCH_2Cl$						
Methyl	76.5	57	27.83	27.42	5.25	5.16
Ethyl	83	47	32.17	31.78	5.94	6.02
n-Propyl	90	49	35.91	35.92	6.53	6.55
n-Butyl	85	57.0–57.3	39.16	38.98	7.04	7.28
n-Amyl	90	58.4–58.7	42.00	42.02	7.49	7.69
n-Hexyl	40	59.5–59.8	44.52	44.19	7.89	8.22
(III) Epoxypropyl Sulfones, $RSO_2CH_2C(O)CH$						
Methyl	75	261(d)	35.28	35.54	5.92	6.32
Ethyl	30	226	39.98	39.81	6.71	6.96
n-Propyl	61	194	43.88	44.00	7.37	7.42
n-Butyl	90	170	47.17	47.45	7.93	8.35
n-Amyl	65	161	49.97	49.92	8.39	8.71
n-Hexyl	88	179	52.39	52.35	8.79	9.04
(VI) Bis-(alkylsulfonyl)-propanols, $RSO_2CH_2CHOHCH_2SO_2R$						
Methyl	93	136	27.77	27.28	5.59	5.92
Ethyl	70	113	34.41	34.45	6.60	6.70
n-Propyl	84	156	39.68	39.99	7.40	7.56
n-Butyl	71	134	43.97	43.92	8.05	8.19
n-Amyl	60	144	47.53	47.69	8.59	9.03
n-Hexyl	53	150	50.52	50.59	9.05	9.29

linkage. The latter compounds generally exhibit some degree of vesicant action.[7,8,9,10]



Second, the disulfones (VI) showed little or no hydrolysis when subjected to conditions under which Stuffer[11] obtained complete hydrolysis of gamma disulfones. This indicates that the following additions are involved in the preparation of the intermediate disulfides: any other mode of addition would lead to intermediates which would result in gamma disulfones on oxidation.



Finally, hydrolysis of the ethylthioepoxypropane obtained by dehydrohalogenation of the supposed 1-ethylthio-3-chloropropanol-2 produced a glycol with contiguous hydroxyl groups. This was proved by periodic acid oxidation followed by isolation of methylene bis-methone. Therefore, the original compound was proved to be 1-ethylthio-3-chloropropanol-2 rather than 2-ethylthio-3-chloropropanol-1.

The chlorohydroxypropyl sulfides gave near-quantitative yields of chlorohydroxypropyl sulfones (II) on perhydrol oxidation. Dehydrohalogenation of (II) was accomplished with 50% KOH and the resultant epoxysulfones (III) were obtained in about 50% yield.

The epoxypropyl sulfides, (IV), are obtainable by either of two procedures: treatment of epichlorohydrin with an equimolecular quantity of a mercaptide or by dehydrohalogenation of (I). With the exception of the ethyl epoxypropyl sulfide (which was prepared by both methods), the compounds represented by (IV) were prepared by the latter method. Yields averaged 60%.

The dithio ethers, (V), while obtainable in one step by treatment of epichlorohydrin in the presence of KOH, were prepared by the addition of the mercaptan to the epoxysulfide, (IV). Yields averaged 60%.

Perhydrol oxidation of (V) led to the production of the disulfones, (VI), in average yields of 65%.

Experimental

Detailed directions for the preparation of the compounds herein described are given for only one representative member of each class.

1-Butylthio-3-chloropropanol-2 (I).—A vigorously stirred mixture of 50 g. (0.56 mole) of *n*-butyl mercaptan in 46 g. of epichlorohydrin (0.5 mole) was heated to reflux and 1 g. of zinc chloride was added. After about two minutes, the temperature rose sharply and reached 190° despite cooling. The reaction was allowed to subside until the temperature had been lowered to 100° whereupon the mixture was heated on the steam-bath for one hour. Distillation yielded 57 g. of product (63% of theoretical based upon epichlorohydrin), boiling at 76–77°

(7) Meyer, *Ber.*, **20**, 1729 (1887).

(8) Lynch, Smith and Marshall, *J. Pharm. Exp. Therap.*, **12**, 286 (1918).

(9) Hanzlik and Tarr, *ibid.*, **14**, 226 (1920).

(10) Fromm and Kohn, *Ber.*, **54B**, 320 (1921).

(11) Stuffer, *ibid.*, **23**, 3232 (1890).

under 0.5 mm. This method was modified for the preparation of 1-methylthio-3-chloropropanol-2 in that the mixture was diluted with 150 ml. of dioxane. This was necessitated by the extensive decomposition that resulted when the unmodified procedure was used.

1-Ethylsulfonyl-3-chloropropanol-2 (II).—Five ml. of 30% perhydrol was added slowly to a mixture of 1.0 g. of 1-ethylthio-3-chloropropanol-2 in 10 ml. of glacial acetic acid. After the initial reaction had subsided, the solvent was removed at water-bath temperature, and the residue placed in a refrigerator for recrystallization. The yield of product, m. p. 47° was 1.0 g. or 83%.

1-Butylsulfonyl-2,3-epoxypropane (III).—A 1.0-g. sample of 1-butylsulfonyl-3-chloropropanol-2 was dissolved in 5 ml. of 50% ethanol and 2 g. of sodium hydroxide in 10 ml. of 50% ethanol was slowly added. After an hour, the solid which had formed was removed by filtration and crystallized from acetone. The yield of crystals m. p. 170° was 0.75 g. or 90% of theory (mol. wt. calcd., 176; found, 179 (Rast)). The lower members of this series were prepared similarly except that water, instead of 50% ethanol, was used as a solvent.

1-Ethylthio-2,3-epoxypropane (IV).—This compound was prepared by dehydrohalogenation of 1-ethylthio-3-chloropropanol-2 as well as by the action of potassium ethyl mercaptide on epichlorohydrin. Either procedure was a repetition of the directions of Nenitzescu and Scarlatescu[4] except that the potassium ethyl mercaptide was added to the epichlorohydrin, rather than the reverse.

1,3-Bis-(butylthio)-propanol-2 (V).—A mixture of 13 g. of 1-butylthio-2,3-epoxypropane and 10 g. of *n*-butyl mercaptan was heated to reflux, whereupon 0.2 g. of zinc chloride was added. Heating was continued until a sudden rise to 200° indicated that reaction had occurred. The product was washed with water, dried with Drierite, and distilled at 1 mm. The yield of product boiling at 133° was 11.5 g. or 55%, based upon 1-butylthio-2,3-epoxypropane.

1,3-Bis-(ethylsulfonyl)-propanol-2 (VI).—Ten ml. of 30% perhydrol was added slowly to a mixture of 2 g. of 1,3-bis-(ethylthio)-propanol-2 in 10 ml. of glacial acetic acid. After the initial reaction had subsided, the solvent was removed at water-bath temperature, and the residue crystallized from 95% ethanol. The yield was 1.9 g. of product melting at 113° (70%).

Hydrolysis of Bis-(alkylsulfonyl)-propanols.—About 0.25 g. of the bis-(alkylsulfonyl)-propanol was suspended in 25.00 ml. of 0.1038 *N* NaOH and refluxed for eight hours. The unreacted sodium hydroxide was then determined by titration with 0.1134 *N* hydrochloric acid. Based upon the following equation, the decomposition ranged from 0% (1,3-bis-(hexylsulfonyl)-propanol-2) to 16% (1,3-bis-(ethylsulfonyl)-propanol-2).

$$(RSO_2CH_2)_2CHOH + NaOH \longrightarrow RSO_2Na + CH_2OHCHOHCH_2SO_2R$$

Hydrolysis of 1-Ethylthio-2,3-epoxypropane and Periodic Acid Oxidation of the Glycol.—A 10-g. sample of 1-ethylthio-2,3-epoxypropane was refluxed with 50 ml. of 0.4 *N* sulfuric acid for three hours. The resulting solution was then treated with potassium periodate according to the directions of Hatch and Nesbitt.[12] The filtrate from this treatment gave the usual aldehyde tests and on treatment with methone, gave methylene bis-methone, m. p. 188–189°, in 60% yield.

Acknowledgment.—The authors express their sincere appreciation to Dr. E. Emmet Reid for suggestions concerning this investigation.

Summary

1. Mercaptans react with epichlorohydrin to produce secondary alcohols.

2. Data concerning the first six members of six homologous series are presented. With the following exceptions these are new to the literature: 1,3-bis-(ethylthio)-propanol-2, 1,3-bis-(ethylsulfonyl)-propanol-2, 1-ethylthio-3-chloropropanol-2, 1-propylthio-3-chloropropanol-2, 1-ethylthio-2,3-epoxypropane, and 1-ethylsulfonyl-3-chloropropanol-2.

(12) Hatch and Nesbitt, THIS JOURNAL, **67**, 39 (1945).

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

Steric Hindrance: Some Reactions of Mesitylacetylene

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The steric hindrance to addition reactions provided by two methyl groups ortho to an unsaturated function has been recognized for some time.[2] Kadesch[3] has contributed to the understanding of this phenomenon by making the hypotheses that (1) addition to a carbonyl function must occur by approach of the reagent more or less in a plane perpendicular to the plane defined by the carbonyl group and the two contiguous atoms; and (2) the carbonyl group in acetomesitylene, and similar hindered compounds, cannot be coplanar with the ring because of repulsive interaction between the hydrogens in the methyl group of the acetyl group and the ortho methyls. Thus the two ortho methyl groups prevent reaction by (A) restricting the free rotation of the acetyl group so that it can never be planar with the ring (thus allowing for an unhindered perpendicular approach of any reactants) at reasonable temperatures[4]; and (3) by hindering perpendicular approach of reagents to the non-planar acetyl group.

If these hypotheses are correct, it occurred to us that if a linear function were diortho substituted, addition reactions should occur until an angular function were formed and that this should then be resistant to further addition reactions. Accordingly we prepared mesitylacetylene[5,6] and

(1) The material presented herein was taken from the M.S. thesis of Harry E. Connor, The Ohio State University, 1949.

(2) For a review see A. E. Remick, "Electronic Interpretations of Organic Chemistry," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 318 ff.

(3) R. G. Kadesch, THIS JOURNAL, **66**, 1207 (1944).

(4) Acetomesitylene can react with hydroxylamine at higher temperatures, *e. g.*, E. Feith and S. H. Davies, *Ber.*, **24**, 3546 (1891), and communication from Dr. P. A. S. Smith, Univ. of Michigan.

(5) T. H. Vaughn and J. A. Nieuwland, THIS JOURNAL, **56**, 1207 (1934).

(6) R. C. Fuson and J. S. Meek, *J. Org. Chem.*, **10**, 551 (1945).