[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

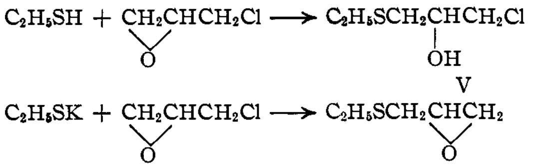
Some Substituted β-Hydroxyethyl Sulfides

BY HENRY GILMAN AND LAWRENCE FULLHART

In connection with a study on the preparation of physiologically active sulfides and sulfones, some sulfur analogs of the pharmacologically important alkaloid, ephedrine, have been prepared. There have also been prepared related compounds in which the phenyl radical has been replaced by the vinyl group. This paper is being presented now in view of the publication of Prelog[1] and co-workers on similar compounds.

The compounds were prepared by the reaction of the mercaptan with the appropriate epoxy compound in a basic medium or by the reaction of the sodium mercaptide with the epoxide. It is obvious in a reaction of this type that two isomeric products are possible.

The reaction of mercaptans with unsymmetrical epoxides has not been extensively studied. Nenitzescu and Scarlatescu[2] have reported the addition of various alkyl mercaptans to epichlorohydrin. They report the following reactions between ethyl mercaptan and epichlorohydrin.

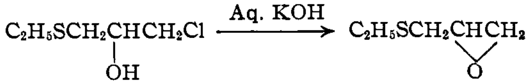


$$C_2H_5SH + \underset{\diagdown O \diagup}{CH_2CH}CH_2Cl \longrightarrow C_2H_5SCH_2\underset{\overset{|}{OH}}{CH}CH_2Cl \quad \text{V}$$

$$C_2H_5SK + \underset{\diagdown O \diagup}{CH_2CH}CH_2Cl \longrightarrow C_2H_5SCH_2\underset{\diagdown O \diagup}{CHCH_2}$$

VI

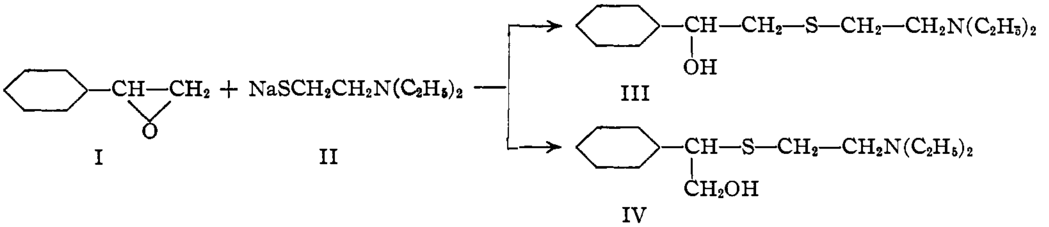
The proof of the structure of compound (V) was based on the fact that treatment of (V) with aqueous potassium hydroxide gave compound (VI), their identity being established by boiling point, refractive index and density.



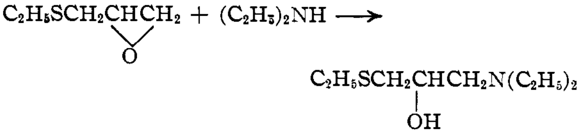
$$C_2H_5SCH_2\underset{\overset{|}{OH}}{CH}CH_2Cl \xrightarrow{\text{Aq. KOH}} C_2H_5SCH_2\underset{\diagdown O \diagup}{CHCH_2}$$

V VI

Compound (VI) was then converted into 2-hydroxy-3-diethylaminopropyl ethyl sulfide (VII) by treating it with diethylamine.



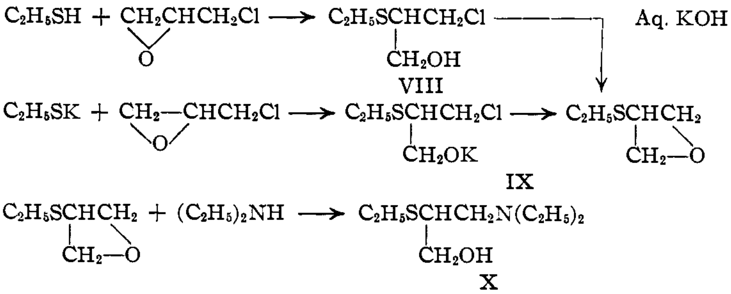
IV



$$C_2H_5SCH_2\underset{\diagdown O \diagup}{CHCH_2} + (C_2H_5)_2NH \longrightarrow C_2H_5SCH_2\underset{\overset{|}{OH}}{CH}CH_2N(C_2H_5)_2$$

VII

However, it is also possible that isomeric compounds could be formed from the same reaction as shown below.



$$C_2H_5SH + \underset{\diagdown O \diagup}{CH_2CH}CH_2Cl \longrightarrow C_2H_5S\underset{\overset{|}{CH_2OH}}{CH}CH_2Cl \xrightarrow{\text{Aq. KOH}}$$

VIII

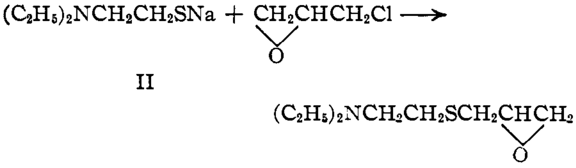
$$C_2H_5SK + \underset{\diagdown O \diagup}{CH_2-CH}CH_2Cl \longrightarrow C_2H_5S\underset{\overset{|}{CH_2OK}}{CH}CH_2Cl \longrightarrow C_2H_5S\begin{array}{l}CHCH_2\\ |\quad\ \diagdown\\ CH_2-O\end{array}$$

IX

$$C_2H_5S\begin{array}{l}CHCH_2\\ |\quad\ \diagdown\\ CH_2-O\end{array} + (C_2H_5)_2NH \longrightarrow C_2H_5S\underset{\overset{|}{CH_2OH}}{CH}CH_2N(C_2H_5)_2$$

X

A reaction similar to the reaction of potassium ethyl mercaptide and epichlorohydrin has already been reported.[3] It was found that when epichlorohydrin is treated with sodium β-diethylaminoethyl mercaptide (II), β-diethylaminoethyl-2,3,-epoxypropyl sulfide (XI) is obtained. The structure of (XI), however, was not definitely established.



$$\underset{\text{II}}{(C_2H_5)_2NCH_2CH_2SNa} + \underset{\diagdown O \diagup}{CH_2CH}CH_2Cl \longrightarrow (C_2H_5)_2NCH_2CH_2SCH_2\underset{\diagdown O \diagup}{CHCH_2}$$

XI

In another case Fromm, Kapeller and Taubmann[4] treated epichlorohydrin with sodium benzyl mercaptide and obtained a product which they assumed was the symmetrical compound, 1,3-dibenzylmercapto-2-propanol (XII). However, the position of the hydroxyl group was not proved.

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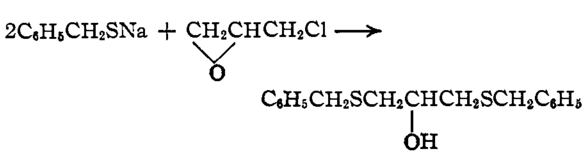
[1] Prelog, Hahn, Brauchli and Beyerman, *Helv. Chim. Acta*, **27**, 1209 (1944).

[2] Nenitzescu and Scarlatescu, *Ber.*, **68**, 587 (1935).

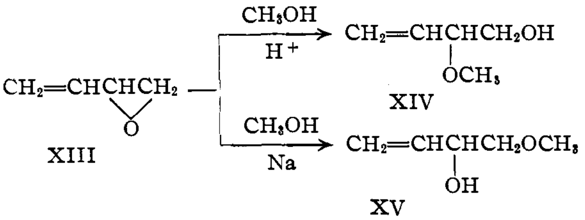
[3] Gilman and Woods, THIS JOURNAL, **67**, 1842 (1945).

[4] Fromm, Kapeller and Taubmann, *Ber.*, **61**, 1353 (1928).



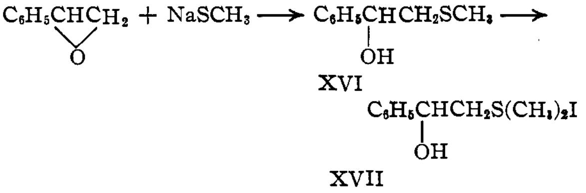
XII

It has been proposed for a number of years that unsymmetrical epoxides cleave in basic media to give secondary alcohols.[5,6,7,8] Recently Castro and Noller[9] have proved this hypothesis in the case of an unsymmetrical epoxide and ammonia. Kadesch[10] has made an extensive examination of the cleavage of 3,4-epoxybutene-1 (XIII). He has given proof for the structure of the compounds obtained and has also advanced a mechanism for the reaction. He found that the reaction of methanol with 3,4-epoxybutene-1 in an acid medium gave 2-methoxy-3-buten-1-ol (XIV) and that when the reaction was carried out in a basic medium 1-methoxy-3-buten-2-ol (XV) was obtained. The cleavage of propylene oxide with alcohols has been studied by Chitwood and Freure.[11] Their results were similar to those of Kadesch.

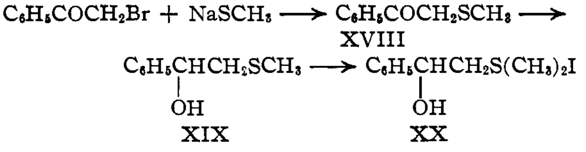


XIII XIV XV

The above evidence would indicate that in the reactions which we have performed the secondary alcohols would be obtained. This has been proved by the reactions



XVI XVII



$$C_6H_5COCH_2Br + NaSCH_3 \longrightarrow \underset{\text{XVIII}}{C_6H_5COCH_2SCH_3} \longrightarrow \underset{\text{XIX}}{\underset{OH}{C_6H_5CHCH_2SCH_3}} \longrightarrow \underset{\text{XX}}{\underset{OH}{C_6H_5CHCH_2S(CH_3)_2I}}$$

The phenacyl methyl sulfide (XVIII) was reduced to β-phenyl-β-hydroxyethyl methyl sulfide by the Meerwein–Ponndorf[12] method using aluminum isopropoxide. Compounds (XVI) and (XIX) were converted to the corresponding methiodide by the method of Bost and Everett.[13]

The fact that the compounds (XVII) and (XX) were identical was shown by the method of mixed melting points.

A similar structure proof was tried earlier using γ-diethylaminopropyl mercaptan instead of methyl mercaptan. The constants of the γ-diethylaminopropyl β′-phenyl-β′-hydroxyethyl sulfide are in fairly close agreement but suitable solid derivatives could not be obtained.

In this connection β-diethylaminoethyl β′-phenyl-β′-hydroxyethyl sulfide was also prepared in two different ways. β-Diethylaminoethyl mercaptan was condensed with styrene oxide in the usual manner to give the proposed β-diethylaminoethyl β′-phenyl-β′-hydroxyethyl sulfide. In the second method phenacyl chloride was reduced to styrene chlorohydrin by the Meerwein–Ponndorf[12] reduction and condensed with sodium β-diethylaminoethyl mercaptide. The constants of these two products are almost identical but the method could not be considered a valid structure proof, as it is possible for the styrene chlorohydrin to be converted to styrene oxide in the basic medium. This could then react with the mercaptan and give rise to possible isomers. An example of this type of reaction has recently been reported by Whitmore[14] and co-workers. From the reaction of 2,3-dibromopropanol with piperidine there was obtained not only the expected 2,3-di-1-piperidyl-1-propanol but also the symmetrical 1,3-di-1-piperidyl-2-propanol. The symmetrical compound can be explained on the basis of the formation of an intermediate epoxide.

Incidental to the preparation of some of these compounds we prepared some of the thiols by treating sulfur with organolithium compounds. The reactions were smooth, giving yields averaging 60%. There was evidence of some disulfide formation. The reaction of Grignard reagents with sulfur has been reported several times in the literature,[15] but the reaction with organolithium compounds apparently had not been tried. The complementary nature of the Grignard reagent and the organometallic compounds of lithium should make this reaction a useful tool in obtaining heretofore unobtainable thiols.

Experimental

β-Diethylaminoethyl β′-Phenyl-β′-acetoxyethyl Ether.—β-Diethylaminoethyl β′-phenyl-β′-hydroxyethyl ether (10 g., 0.042 mole) was acetylated at 100° with acetic anhydride (40 ml.) and sodium acetate (3 g.). The solution was treated with ammonium hydroxide and extracted with benzene, and the benzene solution was dried over sodium sulfate. The benzene was removed and the residue distilled at 138–141° (0.5 mm.) to give 9.2 g. (78%) of

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(5) Tiffeneau and Fourneau, *Compt. rend.*, **146**, 697 (1908).

(6) Kitchen and Pollard, *J. Org. Chem.*, **8**, 338 (1943).

(7) Petrov, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 131 (1938).

(8) Emerson, THIS JOURNAL, **67**, 516 (1945).

(9) Castro and Noller, *ibid.*, **68**, 203 (1946).

(10) Kadesch, *ibid.*, **68**, 41 (1946); see, also, Bartlett and Ross, *ibid.*, **70**, 926 (1948).

(11) Chitwood and Freure, *ibid.*, **68**, 680 (1946).

(12) Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. II, 1944, p. 178.

(13) Bost and Everett, THIS JOURNAL, **62**, 1752 (1940).

(14) Whitmore and co-workers, *ibid.*, **68**, 531 (1946).

(15) Runge, "Organometallverbindungen. I Teil. Organomagnesiumverbindungen," Wissenschaftliche Verlagsgesellschaft, m. b. h., Stuttgart, 1932.

TABLE I

COMPOUNDS PREPARED FROM STYRENE OXIDE AND ALKALI MERCAPTIDES

Mercaptan	Product, sulfide	B. p., °C.	Mm.	d^{20}_{20}	$n^{20}\text{D}$	*MR* Obs.	*MR* Calcd.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl[a]	β-Phenyl-β-hydroxyethyl methyl[b]	127	0.8	1.1082	1.5690	49.67	49.38	22	..	..
γ-Diethylaminopropyl[a]	γ-Diethylaminopropyl β′-phenyl-β′-hydroxyethyl[c]	149–152	.5	1.0122	1.5363	82.24	81.49	50.5	5.24	5.44
β-Diethylaminoethyl[a,d]	β-Diethylaminoethyl β′-phenyl-β′-hydroxyethyl	132	.5	1.0175	1.5423	78.18	76.87	20	5.54	5.56
p-Aminothiophenol[e]	β-Phenyl-β-hydroxyethyl *p*-aminophenyl	185	.001	....	....	...	...	68	5.72	5.60

[a] The potassium salt was prepared from equivalent quantities of solid potassium hydroxide and the mercaptan. The epoxide was added to this salt. [b] The reaction proceeded spontaneously when the ice-bath was removed. The product was cooled and diluted with water. [c] The reaction mixture was heated for twenty minutes. [d] This preparation was made from 0.18 mole of styrene oxide and 0.2 mole of the mercaptide. The reaction mixture was heated for fifteen minutes. [e] The sodium salt was prepared in toluene from equivalent quantities of the metal and the thiol.

product; $n^{20}\text{D}$ 1.4910; d^{20}_{20} 1.0096; *MR* 79.61 (calcd.); 80.21 (obs.).

Anal. Calcd. for $C_{16}H_{25}O_3N$: N, 5.02. Found: N, 4.74, 4.88.

β-Phenyl-β-hydroxyethyl Methyl Sulfide Methiodide.—Prelog and co-workers[1] reported the methiodide as melting with decomposition at 132.5–133.5°, but we found the melting point to be 138–139° (dec.). A mixed m. p. with the similarly prepared methiodide of the compound prepared from styrene oxide and potassium methyl mercaptide was not depressed.

Anal. Calcd. for $C_{10}H_{15}OIS$: I, 40.92; S, 10.30. Found: I, 41.15; S, 10.47.

Phenacyl Methyl Sulfide 2,4-Dinitrophenylhydrazone.—This derivative was prepared by the method of Shriner and Fuson[16] incidental to the synthesis of β-phenyl-β-hydroxyethyl methyl sulfide from phenacyl methyl sulfide,[1] and melted at 164–165.5°.

Anal. Calcd. for $C_{15}H_{14}O_4N_4S$: N, 16.17. Found: N, 16.40.

γ-Diethylaminopropyl Phenacyl Sulfide.—To 0.1 mole of sodium ethoxide in absolute ethanol was added 14.7 g. (0.1 mole) of γ-diethylaminopropyl mercaptan in absolute ethanol. To this solution was added 19.9 g. (0.1 mole) of phenacyl bromide in absolute ethanol. The reaction mixture was refluxed under nitrogen for two hours and cooled. The suspended salt was filtered and the filtrate was concentrated under reduced pressure and extracted with ether. The ether extract was dried and distilled to give 16 g. (62%) of product distilling at 158–160° (0.8 mm.); $n^{20}\text{D}$ 1.5240; d^{20}_{20} 1.0027; *MR* 79.79 (calcd.); 81.02 (obs.). In another preparation the following constants were obtained: b. p. 157-161° (1 mm.); $n^{20}\text{D}$ 1.5226.

Anal. Calcd. for $C_{15}H_{23}ONS$: N, 5.28. Found: N, 5.62.

The 2,4-dinitrophenylhydrazone was prepared by the usual method; its melting point was 183–184° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{21}H_{30}O_8N_5S$: N, 14.90. Found: N, 14.80.

β′-Diethylaminoethyl β′-Phenyl-β′-hydroxyethyl Sulfide.—To sodium ethoxide (0.1 mole) in absolute ethanol was added 13.3 g. (0.1 mole) of β-diethylaminoethyl mercaptan in 25 ml. of absolute ethanol. To this solution was then added 15.6 g. (0.1 mole) of styrene chlorohydrin (prepared in 86% yield from phenacyl chloride and aluminum isopropoxide) in 25 ml. of absolute ethanol. The solution was cooled and the precipitated salt filtered. The filtrate was distilled to give 19.5 g. (78%) of product distilling at 152–155° (1.5 mm.); $n^{20}\text{D}$ 1.5425.

γ-(β-Diethylaminoethylmercapto)propyl β′-Phenyl-β′-hydroxyethyl Ether.—To a solution of 43 g. (0.225 mole) of β-diethylaminoethyl γ-hydroxypropyl sulfide and 11.2 g. (0.2 mole) of potassium hydroxide was added 21.6 g. (0.18 mole) of styrene oxide. The solution was refluxed for one hour and poured into water. The solution was acidified with 12 g. (0.2 mole) of glacial acetic acid and extracted with benzene. The benzene was dried and distilled to give 10 g. (15%) of product distilling at 160–174° (0.6 mm.). Redistillation gave the pure compound distilling at 180–182° (1.5 mm.); $n^{20}\text{D}$ 1.5448. The compound has a tendency to superheat.

Anal. Calcd. for $C_{17}H_{29}O_2NS$: N, 4.50. Found: N, 4.35.

3-Diethylamino-1,2-epoxypropane.[17]—In a 3-liter, 3-necked flask were placed 556 g. (6.0 moles) of epichlorohydrin, 432 g. (5.9 moles) of diethylamine and 18 g. (1.0 mole) of water. The solution was stirred for six hours at a temperature of 28–30°. The temperature was then lowered to 22° and 280 g. (7.0 moles) of sodium hydroxide in 456 ml. of water was added while the temperature was kept below 25°. The solution was stirred for forty minutes; a yellow layer separated out during this time. The yellow layer was removed and the water layer extracted with ether. The ether extracts and the original layer were combined and dried over potassium hydroxide. The ether solution was decanted and distilled to give 430 g. (56.5%) of product distilling at 69° (32 mm.); $n^{20}\text{D}$ 1.4362.

Thiophenol.—To 0.195 mole of phenyllithium in ether[18] was added cautiously 6.25 g. (0.195 g. atom) of sulfur. The reaction was exothermic. When all the sulfur had been added, color test (I)[19] for the presence of an organometallic compound was negative. The solution was then hydrolyzed with dilute hydrochloric acid and worked up. On distillation there was obtained 13 g. (62%) of thiophenol distilling at 68° (20 mm.); $n^{20}\text{D}$ 1.5885. Approximately 3 g. of material distilled at 115–121° (0.5 mm.); this material, which later solidified, may have been diphenyl disulfide.

***p*-Dimethylaminothiophenol.**—To a solution of *p*-dimethylaminophenyllithium prepared from 40 g. (0.2 mole) *p*-bromodimethylaniline[16] was added portion-wise 6.4 g. (0.2 g. atom) of sulfur. The reaction was exothermic and a precipitate formed. The mixture was hydrolyzed with the theoretical amount of hydrochloric acid. The ether layer was separated and dried. On distillation there was obtained 15 g. (50%) of product distilling at 122° (2 mm.). The reported[20] boiling point is 259–260°.

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(16) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 143.

(17) This compound was prepared by a modification of a procedure submitted in a N. D. R. C. report from the Laboratory of Columbia University, New York, N. Y. The compound has also been prepared by Drozdov and Cherntov, *J. Gen. Chem.* (*U. S. S. R.*), **4**, 969 (1934) [*C. A.*, **29**, 2148 (1935)] and Eisleb, U. S. Patent 1,845,403 (1932) [*C. A.*, **26**, 2199 (1932)].

(18) Gilman, Zoellner and Selby, THIS JOURNAL, **55**, 1252 (1933).

(19) Gilman and Schulze, *ibid.*, **47**, 2002 (1925).

(20) Leuckart, *J. prakt. Chem.*, [2] **41**, 208 (1890).

TABLE II

COMPOUNDS PREPARED FROM 3-DIETHYLAMINO-1,2-EPOXYPROPANE AND ALKALI MERCAPTIDES

Mercaptan	Product, sulfide	B. p., °C.	Mm.	n^{20}_D	%	Nitrogen, % Calcd.	Found
γ-Diethylaminopropyl[a]	γ-Diethylaminopropyl γ'-diethylamino-β'-hydroxypropyl[b]	131–134	0.5	1.4380	54	10.14	10.05
β-Diethylaminoethyl[a]	γ-Diethylamino-β-hydroxypropyl β'-diethylamino[c]	121–122	.8	1.4850	57	10.69	10.50
Thiophenol[d]	γ-Diethylamino-β-hydroxypropyl phenyl	125–128	.5	1.5452	56	5.85	5.88
p-Dimethylaminothiophenol[a]	γ-Diethylamino-β-hydroxypropyl p-dimethylaminophenyl[e]	145–147	.001	1.5680	52	9.93	9.96
p-Thiocresol[a]	γ-Diethylamino-β-hydroxypropyl p-tolyl[c]	137	.8	1.5412	65	5.53	5.65
p-Aminothiophenol[a]	γ-Diethylamino-β-hydroxypropyl p-aminophenyl[f]	153	1	1.5763	53	11.02	11.04
p-Chlorothiophenol[a]	γ-Diethylamino-β-hydroxypropyl p-chlorophenyl[g]	149–152	1.5	1.5517	23	5.13	5.29

[a] The sodium salt, prepared from the metal and the mercaptan in toluene, was used. [b] The reaction mixture was refluxed for sixteen hours. It was then extracted with dilute base before working up. d^{20}_{20} for the compound was 0.9431; *MR:* calcd., 84.57; obs., 83.85. [c] The reaction mixture was refluxed for eight hours, cooled and extracted with dilute base. [d] The epoxide (0.2 mole) was added to an ethereal solution of lithium thiophenolate (0.2 mole) prepared from phenyllithium and sulfur (see text). After refluxing overnight, the reaction mixture was decomposed with water. [e] The reaction mixture was refluxed for five hours, cooled and extracted with dilute base. [f] The reaction mixture was refluxed for twelve hours, cooled and diluted with water. [g] 0.05 molar quantities used. The mixture was refluxed for six hours, cooled and diluted with water.

TABLE III

COMPOUNDS PREPARED FROM 3,4-EPOXYBUTENE-1 AND SODIUM MERCAPTIDE

Mercaptan	Product, sulfide	B. p., °C.	Mm.	d^{20}_{20}	n^{20}_D	*MR* Calcd.	Obs.	Yield, %	N, % Calcd.	Found
p-Aminothiophenol[a]	β-Hydroxy-Δ^3-butenyl p-aminophenyl	165–168	0.8	....	....	...	...	51	7.18	7.20
β-Diethylaminoethyl[b]	β-Hydroxy-Δ^3-butenyl β'-diethylaminoethyl	111	1.5	0.9829	1.5044	61.20	61.35	87	6.90	7.17
γ-Diethylaminopropyl[c]	β-Hydroxy-Δ^3-butenyl γ'-diethylaminopropyl	123	0.8	0.9686	1.5028	66.22	65.97	62	6.45	6.64

[a] The mixture was refluxed for three hours, then diluted with water. [b] Refluxed twelve hours and diluted. [c] Refluxed eight hours and diluted.

γ-Diethylamino-β-hydroxypropyl p-Tolyl Sulfone.—A suspension of 17.9 g. (0.1 mole) of sodium p-toluenesulfinate and 12.9 g. (0.1 mole) of 3-diethylamino-1,2-epoxypropane in toluene was refluxed under a nitrogen atmosphere for twelve hours. The solution was diluted with water and worked up to give 5 g. (17.5%) of product distilling at 217° (1 mm.); m. p. 65–67°.

Anal. Calcd. for $C_{14}H_{23}O_3NS$: N, 4.92. Found: N, 5.12.

Preparation of Substituted Sulfides.—In general, 0.1 mole of the mercaptan was converted to the alkali metal salt either by solid potassium hydroxide or by sodium in benzene or toluene. This salt was then brought into reaction with an equivalent amount of the appropriate epoxide. (For individual times of heating, see footnotes to the Tables.) The reaction mixtures from preparations which used the potassium salt were diluted with water, acidified with glacial acetic acid, extracted with benzene, dried and distilled. The other reaction mixtures were diluted with water (and extracted with dilute base where noted), dried and distilled.

Acknowledgment.—The authors are grateful to the Pittsburgh Plate Glass Company for furnishing the 3,4-epoxybutene-1; to the Dow Chemical Company for furnishing the styrene oxide used in these experiments; and, particularly, to Parke, Davis and Company for arranging for the pharmacological tests, which will be reported elsewhere. They also wish to thank William Meikle and John Morton for assistance.

Summary

A series of substituted β-hydroxyethyl sulfides has been prepared and described. Evidence has been given to indicate that the cleavage of unsymmetrical epoxides by mercaptans in the presence of base results in secondary alcohols.

A method for the preparation of thiols using organolithium compounds has been described.

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