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The Reaction of Thiols with Propylene Oxide in the Presence of Free Radical Sources[1]

By Matsuji TAKEBAYASHI, Tadao SHINGAKI and Takakimi MIHARA

Department of Chemistry, College of General Education, Osaka University, Toyonaka, Osaka

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The effect of free radical sources on the reaction of thiols with propylene oxide has been studied. In the presence of free radical sources, such as benzoyl peroxide, tetraphenylhydrazine and tetramethylthiuram disulfide, the reaction gives a single addition product, 1-aryl(or aralkyl)thio-2-propanol, in the same manner as when alkaline catalysts are employed. When *l*(+)-propylene oxide is used, an optically-active 1-thio-2-propanol is obtained. However, azobisisobutyronitrile manifests no catalytic influence on the reaction. Mercury-vapor light also has no effect on the interaction of thiols and propylene oxide, while the light leads to the decomposition of thiols. The mechanism of the reaction has been discussed in terms of a thiyl anion intermediate.

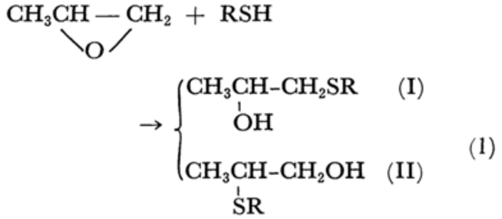
It has been reported that the reactions of thiols with cyclic ethers to give hydroxysulfides are promoted by alkaline catalysts.[2] Searles,[3] investigating the reaction of thiophenol with trimethylene oxide, obtained a good yield of 3-phenylthio-1-propanol with an alkaline catalyst, but a very poor yield of the product with an acid catalyst. The observation of Schuetz[4] has shown that the interaction of thiophenol and propylene oxide in the presence of an alkaline catalyst gives a single product, 1-phenylthio-2-propanol, in an excellent yield, while in the presence of an acid catalyst a mixture of the two possible isomers, 1-phenylthio-2-propanol and 2-phenylthio-1-propanol, is obtained in a poor yield. In these reactions, thiophenol reacts ionically on cyclic ethers, and the position of the ring opening of the cyclic ethers depends on the nature of the catalysts employed and also on the polarity or the steric effect of substituents on the carbon atom of the oxide ring.[5]

On the other hand, it has been recognized that benzoyl peroxide[6] and azobisisobutyronitrile[7] are effective catalysts in the homolytic addition of thiophenol to unsaturated compounds, and that tetraphenylhydrazine, triphenylmethyl peroxide and hexaphenylethane also accelerate the radical decomposition of aromatic azides in thiols.[8] In the light of such experimients, we investigated the reaction of thiols with propylene oxide in the presence of such free radical sources as benzoyl peroxide, tetraphenylhydrazine, tetramethylthiuram disulfide and azobisisobutyronitrile.

Results and Discussion

The reaction of thiols (0.3 mol.) with propylene oxide (0.2 mol.) has been carried out with a small amount (0.01 mol.) of free radical sources at 80°C in an atmosphere of nitrogen. The results are shown in Table I.

Two kinds of reaction products, I and II, may be expected.



$$\underset{\diagdown O \diagup}{\mathrm{CH_3CH - CH_2}} + \mathrm{RSH} \rightarrow \begin{cases} \mathrm{CH_3\underset{OH}{C}H\text{-}CH_2SR} & \text{(I)} \\ \mathrm{CH_3\underset{SR}{C}H\text{-}CH_2OH} & \text{(II)} \end{cases} \qquad (1)$$

However, the reaction gave a single product (I) in the same manner as when alkaline catalysts were employed. No reaction took place in the absence of free radical sources.

Among the free radical sources employed, tetraphenylhydrazine and tatramethylthiuram disulfide act as the most effective catalysts on the reaction. Benzoyl peroxide promotes the reaction to some extent, though without any conspicuous evolution of carbon dioxide. On the other hand, azobisisobutyronitrile manifests practically no catalytic influence on the reaction.

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[1] Presented in part at the Symposium of Organic Reaction Mechanism, Fukuoka, October, 1963.

[2] R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 737 (1959).

[3] S. Searles, *J. Am. Chem. Soc.*, **73**, 4515 (1951).

[4] R. D. Schuetz, ibid., **73**, 1881 (1951).

[5] E. L. Eliel, "Substitution at Saturated Carbon Atoms," in "Steric Effects in Organic Chemistry," Ed. by M. S. Newman (1956), p. 106.

[6] M. S. Kharasch, A. T. Read and F. R. Mayo, *Chem. & Ind.*, **57**, 752 (1938).

[7] Cf., for instance, T. Hoshino et al., *J. Chem. Soc. Japan, Pure Chem. Sect.* (*Nippon Kagaku Zassi*), **74**, 510 (1953); ibid., **75**, 1086 (1954); This Bulletin, **29**, 447 (1956).

[8] M. Takebayashi and T. Shingaki, *J. Chem. Soc. Japan, Ind. Chem. Sect.* (*Kogyo Kagaku Zasshi*), **64**, 469 (1961); M. Takebayashi, T. Shingaki and T. Mitsuyama, *Science Reports, Osaka Univ.*, **10**, 35 (1961).

TABLE I. REACTION OF THIOLS WITH PROPYLENE OXIDE AT 80° C FOR SIX HOURS
Propylene oxide 0.2 mol., Thiol 0.3 mol., Free radical source 0.01 mol.

Thiol (RSH)	Free Radical Source (R′-R′)	Yields of Products $CH_3\text{-}\underset{OH}{CH}\text{-}CH_2SR$ %a)	RS-SR %b)	R′H %b)
C_6H_5SH	None	0	0	0
	$(C_6H_5)_2N\text{-}N(C_6H_5)_2$	92	96	93
	$C_6H_5\underset{O}{\overset{\|}{C}}O\text{-}O\underset{O}{\overset{\|}{C}}\text{-}C_6H_5$	9.3	96	93
	$(CH_3)_2N\underset{S}{C}S\text{-}S\underset{S}{C}N(CH_3)_2$	75	90	
	$(CH_3)_2\underset{CN}{C}N{=}N\underset{CN}{C}(CH_3)_2$	0	99	
$C_6H_5CH_2SH$	None	0	0	0
	$(C_6H_5)_2N\text{-}N(C_6H_5)_2$	99	98	98
	$C_6H_5\underset{O}{C}O\text{-}O\underset{O}{C}C_6H_5$	18	66	c)
	$(CH_3)_2N\underset{S}{C}S\text{-}S\underset{S}{C}N(CH_3)_2$	85	99	
	$(CH_3)_2\underset{CN}{C}N{=}N\underset{CN}{C}(CH_3)_2$	0	90	

a) Mole % based on the amount of propylene oxide.
b) Mole % based on the amount of free radical source added.
c) Syrupy oil (2.36 g.) containing sulfur atom.

In these experiments, the disulfides corresponding to the thiols used were obtained nearly quantitatively; diphenylamine and benzoic acid were also produced in good yields during the reactions with tetraphenylhydrazine and benzoyl peroxide respectively.

Another experiment investigated the reaction using L(+)-propylene oxide. The L(+)-propylene oxide shows practically no change in its optical activity ($[\alpha]_D^{15}$: +16.51° in ether) during the course of being heated with benzylmercaptan at 80°C for six hours in an atmosphere of nitrogen. Therefore, the reaction of L(+)-propylene oxide with benzylmercaptan has been carried out in the presence of tetramethylthiuram disulfide under the conditions described above. (−)-Benzylthio-2-propanol ($[\alpha]_D^{15}$: −17.73° in ether) was obtained in a good yield (78%). This suggests that no bonds at the asymmetric carbon atom of propylene oxide are made or broken during the reaction.

When quinone or hydroquinone was added as a free radical scavenger in the reaction mixture, the reaction was slightly suppressed. Therefore, a mixture of propylene oxide (0.30 mol.) and thiophenol (0.45 mol.) was exposed to a mercury-vapor light of 2537 and 3500 Å at 10°C for 24 hr. in an atmosphere of nitrogen. Diphenyl disulfide, hydrogen sulfide and hydrogen were thus obtained, without any reaction product corresponding to I or II; most of the propylene oxide was also recovered.

Thiophenol has strong absorption bands in the regions of 2350 Å (ε_{max} 8500) and 2690 Å (ε_{max} 720),[9] and the ArS–H and Ar–SH bond dissociation energies of thiophenol are close to 86 and 74 kcal./mol. respectively. The absorption of light of 2537 Å in one mole of a substance corresponds to that of an energy ($E = N_A h\nu$) of 112 kcal. per mol. Therefore, thiophenol may be dissociated in two ways by the absorption of the light:

$$C_6H_5SH \xrightarrow{h\nu} \cdot C_6H_5 + \cdot SH \qquad (2)^{10)}$$

$$C_6H_5SH \xrightarrow{h\nu} C_6H_5S\cdot + H\cdot \qquad (3)^{11)}$$

The free radicals, $\cdot C_6H_5$, $\cdot SH$ and H, produced by the reactions 2 and 3 react on thiophenol to give the thiyl radical, $C_6H_5S\cdot$:

$$C_6H_5SH + \cdot C_6H_5 \rightarrow C_6H_5S\cdot + C_6H_6 \qquad (4)$$

$$C_6H_5SH + \cdot SH \rightarrow C_6H_5S\cdot + H_2S \qquad (5)$$

$$C_6H_5SH + H\cdot \rightarrow C_6H_5S\cdot + H_2 \qquad (6)$$

If the thiyl radical attacks propylene oxide, the reaction products, I and/or II, should be produced. However, the thiyl radical dimerized to give disulfide without any reaction toward propylene oxide.

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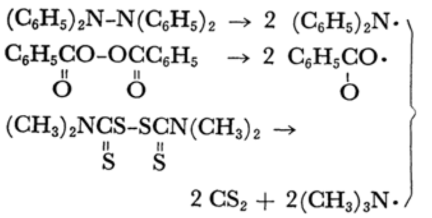
9) K. Browden, E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, **1946**, 948.
10) W. M. Malisoff and E. M. Marks, *Ind. Eng. Chem.*, **23**, 1114 (1931).
11) C. Walling and R. Rabinowitz, *J. Am. Chem. Soc.*, **81**, 1137 (1954).

$$2\ C_6H_5S \rightarrow C_6H_5S\text{-}SC_6H_5 \qquad (7)$$

The results presented above suggest that the reaction is not initiated by thiyl radicals derived from the reactions of thiols with free radical sources. The reaction may, then, reasonably explained as follows.

In the first place, the thermal decomposition of free radical sources occurs, giving rise to the corresponding free radicals:



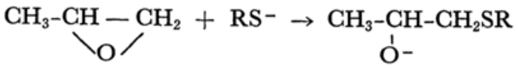
$$\left.\begin{array}{l} (C_6H_5)_2N\text{-}N(C_6H_5)_2 \rightarrow 2\ (C_6H_5)_2N\cdot \\ C_6H_5\underset{\underset{O}{\|}}{C}O\text{-}O\underset{\underset{O}{\|}}{C}C_6H_5 \rightarrow 2\ C_6H_5\underset{\underset{O}{|}}{C}O\cdot \\ (CH_3)_2N\underset{\underset{S}{\|}}{C}S\text{-}S\underset{\underset{S}{\|}}{C}N(CH_3)_2 \rightarrow \\ \qquad\qquad 2\,CS_2 + 2(CH_3)_3N\cdot \end{array}\right\} \qquad (8)$$

These free radicals have lone-pair electrons on their free radical atoms. Therefore, a proton-transfer reaction 9 to give thiyl anion must take place in addition to the abstraction of hydrogen (10). For instance:

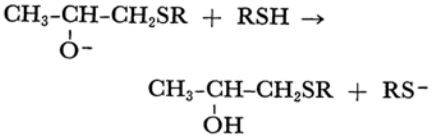
$$(C_6H_5)_2N\cdot + RSH \rightarrow (C_6H_5)_2\overset{+}{\underset{\cdot}{N}}H + RS^- \qquad (9)$$

$$(C_6H_5)_2N\cdot + RSH \rightarrow (C_6H_5)_2NH + RS\cdot \qquad (10)$$

The thiyl anion attacks the primary carbon atom of propylene oxide as a result of the inductive effect of the methyl group, and the reactions 11 and 12 will proceed in a chain mechanism:



$$CH_3\text{-}CH\text{—}CH_2\ (\text{-}O\text{-}) + RS^- \rightarrow CH_3\text{-}\underset{\underset{O^-}{|}}{C}H\text{-}CH_2SR \qquad (11)$$



$$CH_3\text{-}\underset{\underset{O^-}{|}}{C}H\text{-}CH_2SR + RSH \rightarrow CH_3\text{-}\underset{\underset{OH}{|}}{C}H\text{-}CH_2SR + RS^- \qquad (12)$$

The reaction chain my be terminated by the reactions 13 and 14:

$$(C_6H_5)_2\overset{+}{\underset{\cdot}{N}}H + RS^- \rightarrow (C_6H_5)_2NH + RS\cdot \qquad (13)$$

$$2\ RS\cdot \rightarrow RS\text{-}SR \qquad (14)$$

Experimental

Materials.—*Propylene Oxide (racemic).*—Commercial propylene oxide was refluxed for 2 hr. over pellet potassium hydroxide and fractionated, the fraction boiling at 34.5—35°C being used.[12]

L(+)-Propylene Oxide.—Levene's synthesis was employed.[12] α-Bromoacetone was converted to acetol by treating it with ethyl formate in methanolic potassium hydroxide; the acetol was then reduced to L-propylene glycol by the reductase of yeast. The propylene glycol was converted to L-propylenebromohydrin with dry hydrogen bromide, and the bromohydrin was then cyclized to L(+)-propylene oxide with concentrated aqueous potassium hydroxide. The crude material was purified by refluxing it over potassium hydroxide pellets; b. p. 34.5—35°C, $[\alpha]_D^{15}$: +16.51° (in ether).

Thiophenol.—Benzenesulfonyl chloride was reduced by zinc and sulfuric acid to thiophenol.[13] The crude distillate was fractionated; b. p. 61°C/15 mmHg.

Benzylmercaptan.—A mixture of benzyl alcohol and hydrobromic acid (48%) was refluxed for 12 hr.; the reaction product was then hydrolyzed by an alkaline solution.[14] The benzyl mercaptan produced was purified by fractionation; b. p. 65°C.

Tetraphenylhydrazine.—A solution of diphenylamine in acetone was oxidized by potassium permanganate.[15] The crude material was recrystallized in benzene; m. p. 144°C

Tetramethylthiuram Disulfide.—To a hot solution of commercial material in chloroform, ethanol was added; then the mixture was cooled. The precipitate was dissolved again in hot benzene and cooled after ether had been added.[16] The treatment was repeated twice; the disulfide melting at 146°C was used.

Benzoyl Peroxide was purified by treating it with chloroform and methanol;[17] m. p. 107—107.5°C.

Azobisisobutyronitrile was recrystallized in 95%-alcohol;[18] m. p. 102—103°C.

The Reaction of Thiols with Propylene Oxide in the Presence of Free Radical Sources.—Propylene oxide (0.2 mol., 11.6 g.), thiol (0.3 mol.) and a free radical source (0.01 mol.) were placed in a hard glass reaction tube, which had been cooled in an ice-salt bath, avoiding the entrance of moisture. After it had been flushed with dry nitrogen, the tube was sealed immediately. The sealed tube was then agitated and placed in a constant temperature bath (at 80—0.5°C) for an appropriate time. After the required reaction time, the tube was cooled in ice water and opened. After the unreacted propylene oxide had then been evaporated at room temperature under diminished pressure, the unreacted thiophenol and benzylmercaptan were distilled off at 61—62°C/15 mmHg and 64—65°C/3 mmHg, respectively, and the reaction products were separated by fractionation and column chromatography.

(A) In the reaction of thiophenol with propylene oxide, a fraction boiling at 103—110°C/1 mmHg was collected and redistilled. Nearly all of the fraction was distilled at 103—105°C/1 mmHg, and the liquid product was confirmed to be 1-phenylthio-2-propanol (Found: C, 64.16; H, 7.21; S, 18.90%).[19] The ultraviolet absorption curve (λ_{max} 254 mμ, ε_{max} 8.70×10^3) of this product accorded completely with that of the 1-phenylthio-2-propanol, which had been prepared according

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[12] C. C. Price and M. Osgan, *J. Am. Chem. Soc.*, **78**, 4787 (1956).

[13] H. Gilman, "Organic Syntheses," Coll, Vol. I. John Wiley & Sons, New York (1941), p. 490.

[14] R. L. Frank and P. V. Smith, *J. Am. Chem. Soc.*, **68** 2103 (1946).

[15] L. Gattermann, "Die Praxis des Organischen Chemikers," 36 Aufl., Walter de Gruyler and Co., Berlin (1954), p. 308.

[16] T. E. Ferington and A. V. Tobolsky, *J. Am. Chem. Soc.*, **73**, 1881 (1951); **77**, 4510 (1955).

[17] K. Nozaki and P. D. Bartlett, ibid., **68**, 1686 (1946).

[18] C. G. Overberger, ibid., **71**, 2661 (1949).

[19] The isomer, 2-phenylthio-1-propanol: b. p. 125—126°C/1 mmHg; UV absorption band, λ_{max} 256 mμ, ε_{max} 5.97×10^3.

to the directions of Schuetz,[20] and the 3, 5-dinitrophthalate of this product showed no melting-point depression when mixed with an authentic sample (m. p. 112°C). The residue, a crystalline mass, was treated as follows.

When tetraphenylhydrazine was used as a free radical source, the residue was dissolved in a small amount of alcohol, dried on a water bath after concentrated hydrochloric acid had been added, and treated with benzene. Diphenyl disulfide (2.09 g.) was obtained from the benzene solution, and diphenylamine hydrochloride (3.82 g.) from the residue.

When benzoyl peroxide was used, the residue was dissolved in ether and treated with a 10%-aqueous solution of sodium hydroxide. Diphenyl disulfide (2.18 g.) was obtained from the ether layer, and benzoic acid (2.27 g.) from the aqueous layer, after acidification.

When tetramethylthiuram disulfide was used, the residue was recrystallized from a small amount of alchohol. Diphenyl disufide (2.72 g.) was thus separated from the solution. The solution was then evaporated, and the residue was treated by column chromatography using 50 g. of active alumina. Diphenyl disulfide (1.20 g.) was isolated again by elution with petroleum ether (b. p. 30—40°C); a small amount of a syrupy substance was also obtained by elution with methanol.

When azobisisobutyronitrile was used, no principal product, phenylthiopropanol, was detected in spite of the evolution of nitrogen, while diphenyl disulfide was obtained in a good yield (3.91 g.).

(B) In the reaction of benzyl mercaptan with propylene oxide, the reaction products were treated in the way described above. The fraction boiling at 115—116°C/1 mmHg was identified as 1-benzylthio-2-propanol (Found: C, 65.82; H, 7.80; S, 17.52%).[21] The ultraviolet absorption curve of this product accorded completely with that of 1-benzylthio-2-propanol (λ_{max} 260.3 mμ, ε_{max} 3.40×10^3 and λ_{max} 267.0 mμ, ε_{max} 2.03×10^3).

Dibenzyl disulfide was also obtained nearly quantitatively except when benzoyl peroxide was used as a free radical source. In the latter case, the residue of fractionation was treated by column chromatography using active alumina. Dibenzyl disulfide (1.60 g.) was isolated by elution with petroleum ether, while syrupy products, boiling at 120—123°C/0.5 mmHg (1.0 g.) and 134—145°C/0.5 mmHg (1.36 g.), were obtained by elution with benzene and methanol respectively. The syrupy products gave positive results in tests to detect sulfur.

Summary

The reaction of thiols with propylene oxide leads to the formation of 1-aryl(or aralkyl)-thio-2-propanol in the presence of such free radical sources as tetraphenylhydrazine, tetramethylthiuram disulfide and benzoyl peroxide. In the presence of azobisisobutyronitrile, however, no principal product is obtained.

The reaction of benzylmercaptan with L(+)-propylene oxide in the presence of tetramethylthiuram disulfide gives (−)-benzylthio-2-propanol. When a mixture of thiol and propylene oxide is exposed to a mercury-vapor light, no principal procuct is detected.

It has been suggested that the reaction proceeds not by means of thiyl radicals but by means of thiyl anions in a chain mechanism.

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[20] R. D. Schuetz, *J. Am. Chem. Soc.*, **73**, 1881 (1951).

[21] The isomer, 2-benzylthio-1-propanol: b. p. 124—125°C/1 mmHg.