

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, UNIVERSITY OF WISCONSIN]

The Dehydration of Cholesterol in Liquid Sulfur Dioxide<sup>1</sup>BY ROBERT H. LEVIN<sup>2</sup>

In recent years there has been an increasing utilization of liquid sulfur dioxide as a medium for organic reactions.<sup>3</sup> Attempting to use it as a solvent, we found that cholesterol is dehydrated by liquid sulfur dioxide at elevated temperatures with the formation of dicholesteryl ether. Since dicholesteryl ether is of interest in connection with the reported chemical antirachitic activation of sterols,<sup>4</sup> this reaction was investigated further.

A variety of reagents have been used to produce dicholesteryl ether.<sup>5</sup> Usually the yield is poor and there is much formation of cholesterolenes and tarry material. Bills and McDonald<sup>6</sup> have obtained dicholesteryl ether in 40% yield by refluxing a carbon tetrachloride solution of cholesterol over floridin.

In the present investigation the dehydration was carried out in a steel reaction vessel of 80 cc. capacity, using the type of heating and shaking apparatus described by Adkins.<sup>7</sup> A typical experiment is described in detail.

**Treatment of Cholesterol with Sulfur Dioxide and Anhydrous Copper Sulfate.**—Fifteen grams (0.039 mole) of cholesterol (Wilson) and 7.5 g. of anhydrous copper sulfate were placed in the bomb which was then cooled in an ice-salt-bath. Liquid sulfur dioxide (30 cc., 43 g.) was poured from a tank into a previously cooled graduate and added to the reaction mixture. After closing the bomb as tightly as possible by hand, it was removed from the bath for the final sealing operation. The bomb was heated on the shaker at 100° for seventeen hours, cooled to room temperature, chilled, and opened. It was placed in the hood while it gradually warmed up, and residual sulfur dioxide was removed by heating the bomb on the steam-bath for five minutes. The contents were washed out with 200 cc. of warm chloroform and the copper sulfate removed by filtration. Concentration of the clear light brown solution gave a flocculent white precipitate which was collected on a Büchner funnel, washed with chloroform, and dried; wt. 4.3 g., m. p. 203–205°.<sup>8</sup>

The filtrate was heated almost to boiling and ethanol (*ca.* 30 cc.) was added in portions until the precipitate which formed just redissolved. After slow cooling, a precipitate of cottony needles deposited and was separated; wt. 3.1 g., m. p. 198–201°. A third crop of crystals was obtained by adding more ethanol to the filtrate; wt. 0.6 g., m. p. 198–201°. The total yield of dicholesteryl ether was 8.0 g. or 54% of the theoretical.

*Anal.* Calcd. for C<sub>34</sub>H<sub>50</sub>O: C, 85.9; H, 12.0. Found: C, 85.6; H, 12.0.

The reaction product gave no test for sulfur and failed to react with benzoyl chloride. It was characterized by the preparation of a tetrabromide.<sup>9</sup>

**Dicholesteryl Ether Tetrabromide.**—A solution of 0.50 g. of dicholesteryl ether in 50 cc. of chloroform was treated with a slight excess of bromine in chloroform. After standing an hour at room temperature, the solvent and excess reagent were removed *in vacuo*. The residue was crystallized from chloroform-methanol, m. p. 164–166° (dec.).

*Anal.* Calcd. for C<sub>34</sub>H<sub>50</sub>OBr<sub>4</sub>: Br, 29.90. Found: Br, 30.08.

Unchanged cholesterol (6.2 g.) was easily recovered from the filtrate of the cholesteryl ether precipitations. It is noteworthy that in this run the yield of pure dicholesteryl ether and the amount of pure cholesterol recovered account for 95% of the starting material, indicating a complete lack of side reactions. On the basis of 8.8 g. of cholesterol actually reacting, the yield of dicholesteryl ether (8.0 g.) is 93% of the theoretical.

In earlier experiments, using just cholesterol and liquid sulfur dioxide at temperatures of 100 to 140° for periods of three to twenty-four hours, the yield of dicholesteryl ether varied from 9 to 33%, depending on temperature and reaction time. However, the dicholesteryl ether and recovered cholesterol accounted for 78–95% of the starting material.

Since the formation of dicholesteryl ether is reported to be an equilibrium reaction,<sup>10</sup> it was thought possible that the addition of water absorbing reagents would shift the equilibrium toward the side of the dicholesteryl ether. It was found that anhydrous copper sulfate does affect the reaction, but plaster of Paris inhibits the reaction completely. These results led to the study of other catalysts. With copper, Raney nickel, ferrous sulfate, and a mixture of sodium carbonate and copper phosphate there was no reaction. When the experiment described above was repeated at a temperature of 135° the yield of dicholesteryl ether (based on cholesterol used) was only 40%. The use of hydrated copper sulfate (instead of the anhydrous variety) increased the extent of side reactions. Thus shaking at 100° for twenty hours resulted in a 76% yield of the ether (based on cholesterol used). When the experiment was repeated at 135°, all the cholesterol was resinified and no crystalline material was isolable. Powdered soft

(1) Abstracted from a thesis presented to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1941.

(2) Present address, The Upjohn Company, Kalamazoo, Michigan.

(3) For a review on the use of liquid sulfur dioxide in organic chemistry see Ross and co-workers, *Ind. Eng. Chem.*, **34**, 924 (1942).

(4) (a) Bills, *J. Biol. Chem.*, **67**, 753 (1926); (b) Bills and McDonald, *ibid.*, **72**, 3 (1927); (c) Yodor, *Science*, **80**, 385 (1934); (d) Eck, Thomas and Yodor, *J. Biol. Chem.*, **117**, 655 (1937).

(5) Eck and Van Peursem, *Iowa State College J. of Sci.*, **13**, 115 (1939), have recently reviewed this field.

(6) Bills and McDonald, *J. Biol. Chem.*, **68**, 82 (1926).

(7) Adkins, "Reactions of Hydrogen with Organic Compounds over Copper-chromium Oxide and Nickel Catalysts," The University of Wisconsin Press, Madison, Wis., 1937, p. 38.

(8) Sobotka, "Chemistry of the Sterids," Williams and Wilkins Co., Baltimore, Md., 1937, p. 232, lists m. p.'s ranging from 186° on up to 209° for dicholesteryl ether.

(9) Montignie, *Bull. soc. chim.*, **41**, 524 (1937).

(10) Kawasaki, *J. Pharm. Soc. Japan*, **59**, 418 (in Engl. 268) (1939).

glass for fourteen hours at 135° gave 29% of dicholesteryl ether, with the remainder of the sterol resinified. The ether was obtained in 26% yield and 51% of the cholesterol was recovered when copper chloride was used as a catalyst, and a similar experiment using a small amount of sulfur resulted in an 18% yield of dicholesteryl ether and the recovery of 45% of the starting material.

These experiments indicate that in liquid sulfur dioxide at 100° cholesterol is dehydrated to form dicholesteryl ether. There are no side reactions. It is probably an equilibrium reaction and apparently subject to catalysis. Higher temperatures and longer reaction periods produce cholesterilenes and resinous products, either by a competing reaction<sup>11</sup> or by a dismutation of the cholesteryl ether already formed.

(11) For a discussion of the mechanism of dehydration of cholesterol see Bills and McDonald, note 4b; also Kawasaki, note 10.

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### Summary

Cholesterol is dehydrated in liquid sulfur dioxide at elevated temperatures with the formation of dicholesteryl ether. The reaction is subject to catalysis.

A good method for the preparation of dicholesteryl ether has been developed.

KALAMAZOO, MICHIGAN

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

## The Utilization of Aliphatic Nitro Compounds. VIII. Nitrotriols (Nitroglycerols) Prepared from Simple Aldehydes<sup>1</sup>

BY CORNELIUS AUSTIN SPRANG WITH ED. F. DEGERING

In the condensation of nitromethane with formaldehyde to form nitroethanol, a very large excess of nitromethane is required<sup>2</sup> to prevent the formation of 2-nitro-1,3-propanediol and 2-hydroxymethyl-2-nitro-1,3-propanediol. Higher aldehydes are not so readily condensed with nitromethane. Thus it has not been found possible to prepare nitrotriols by condensing three equivalents of such aldehydes with one of nitromethane; but by first condensing the higher aldehyde with one equivalent of nitromethane followed by treatment with a large excess of formaldehyde, a nitrotriol results.<sup>3</sup>

The preparation of the nitrotriols is very much the same as that of the nitrodiols.<sup>4</sup> The reaction is not as sensitive to the alkali concentration, since formaldehyde condenses very readily with nitromethane or with 1-nitro-2-alkanols. The following illustrates the procedure.

**2-Hydroxymethyl-2-nitro-1,3-pentanediol.**—A mixture of 41 g. of 1-nitro-2-butanol, 25 ml. of 95% ethanol, and 3 g. of potassium carbonate is stirred while 62 g. of 40% formalin is added dropwise. The clear solution after standing for four days at room temperature is neutralized with

4 ml. of concentrated hydrochloric acid, then saturated with sodium chloride and extracted with butanol. Part of the butanol is removed by distillation under diminished pressure and the residue is chilled to bring about crystallization. The crystals are recrystallized from dry butanol. Four nitrotriols, as shown in the table, have been prepared by this procedure.

Nitrotriol, 2-hydroxymethyl-2-nitro-	M. p., °C.	% Nitrogen	
		Calcd.	Found <sup>a</sup>
-1,3-pentanediol	141	7.83	7.51
-1,3-hexanediol	154-6	7.26	6.83
-1,3-nonanediol	145-7	5.97	5.82
-5-methyl-1,3-hexanediol	144-6	6.77	6.64

<sup>a</sup> By a modified Kjeldahl method (see Harte, *Ind. Eng. Chem., Anal. Ed.*, 7, 432-3 (1935)).

The nitrotriols are white crystalline substances, very soluble in water, moderately soluble in alcohol, and quite insoluble in ether or in petroleum solvents. Their melting points are somewhat higher than those of the nitrodiols.

### Summary

Nitrotriols are prepared by means of an aldol condensation involving two equivalents of formaldehyde with one equivalent of a higher aldehyde and one of nitromethane. The purification of the nitrotriols is much simpler than that of the nitrodiols which are prepared from aldehydes other than formaldehyde.

LAFAYETTE, INDIANA

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(1) Abstracted from a thesis presented to the Faculty of the Graduate School of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Gorski and Makarov, *Ber.*, 67B, 996-1000 (1934); *C. A.* 28, 5039 (1934). The nitroparaffins used in this work were furnished by The Commercial Solvents Corporation.

(3) Charlton and Kenner, *J. Chem. Soc.*, 750 (1932).

(4) Sprang with Degering, *This Journal*, 64, 1735 (1942).