[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGY AND BIOCHEMISTRY OF RUTGERS UNIVERSITY]

THE ACTION OF THIONYL CHLORIDE UPON CHOLESTEROL AND CERTAIN OTHER ALCOHOLS[1]

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Halogen derivatives of cholesterol, substituted monosaccharides and certain other alcohols were desired for further synthetic work. The isomerization, polymerization, reduced yields of the halide and sometimes destructive action which may result from the treatment of alcohols with the halogen derivatives of phosphorus has been pointed out by Darzens.[2] The reaction of diacetone-glucose with phosphorus pentachloride yielded 75% of compounds containing phosphorus.[3] Thionyl chloride acts as a milder reagent and does not cause the Walden inversion of certain optically active alcohols.[4] Darzens[2] offers a general method for the preparation of halogen derivatives of the aliphatic alcohols with good yields by the use of thionyl chloride or thionyl bromide in the presence of an organic base such as pyridine.

However, while attempting to prepare fenchyl chloride by the treatment of fenchyl alcohol with thionyl chloride in the presence of pyridine, Ruzicka and Liebl[5] obtained difenchyl sulfite. There was no chlorination. Richter[6] and Badische[7] have prepared a series of aryl sulfites in a similar manner. A study of the reaction indicated that an alcohol treated with the theoretical amount of thionyl chloride in the presence of pyridine would yield the organic ester of sulfurous acid. By this method the sulfurous acid esters of cholesterol, diacetone-glucose, ethyl alcohol, butyl alcohol and phenol have been prepared. There was no chlorination. These esters were also prepared by treating their sodium salts in petroleum ether or ethyl ether with the theoretical amount of thionyl chloride. This method was described in a previous paper for the preparation of *bis*-(diacetone-glucose)-sulfite.[3]

If a large excess of thionyl chloride is used on the alcohol in the presence of a small amount of pyridine, the reaction evidently goes according to Equation I. When refluxed, sulfur dioxide is eliminated according to Equation II.

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[1] The investigations upon which this article is based were supported by a grant from the firm of Johnson and Johnson of New Brunswick, N. J.

[2] Darzens, *Compt. rend.*, **152**, 1314 (1911).

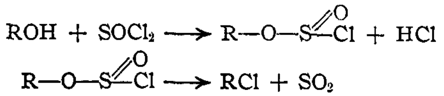
[3] Allison with Hixon, THIS JOURNAL, **48**, 406 (1926).

[4] McKenzie and Clough, *J. Chem. Soc.*, **103**, 687 (1913).

[5] Ruzicka and Liebl, *Helv. Chim. Acta*, **6**, 278 (1923).

[6] Richter, *Ber.*, **49**, 2339 (1916).

[7] Badische Anilin und Sodafabrik, *C. A.*, **13**, 324 (1919).



$$\mathrm{ROH} + \mathrm{SOCl_2} \longrightarrow \mathrm{R{-}O{-}\overset{O}{\overset{/\!/}{S}}{-}Cl} + \mathrm{HCl} \tag{I}$$

$$\mathrm{R{-}O{-}\overset{O}{\overset{/\!/}{S}}{-}Cl} \longrightarrow \mathrm{RCl} + \mathrm{SO_2} \tag{II}$$

McKenzie and Clough[4] obtained an intermediate product, *d*-amyl chlorosulfinate, from which sulfur dioxide was eliminated according to Equation II. An excess of thionyl chloride was used in this reaction. Cholesterol, in the presence of an excess of thionyl chloride, with or without the addition of a small amount of pyridine, yielded cholesteryl chloride almost quantitatively. When an excess of pyridine was used and the reaction was carried out in ether, a small amount of *bis*-cholesteryl sulfite was also formed. When an excess of thionyl chloride is added to diacetone-glucose in ether and in the presence of an excess of pyridine, little or no sulfur dioxide is eliminated upon refluxing the reaction mixture. When poured into water which is kept slightly alkaline with sodium carbonate, the compound which is formed is hydrolyzed and diacetone-glucose is immediately regenerated. Green[8] has isolated a reactive intermediate product, dichlorothionyl quinol, from which sulfur dioxide was not eliminated by heat under the conditions of the reaction.

Experimental Part

Bis-cholesteryl Sulfite.—Two grams of anhydrous cholesterol was dissolved in 50 cc. of dry pyridine. A little in excess of the theoretical amount of thionyl chloride was then added. This mixture was allowed to stand for twenty-four hours at room temperature. At the end of this period water was slowly added until no more precipitate settled out. The impure neutral sulfite ester was filtered off and extracted with a small quantity of hot alcohol to remove any unchanged cholesterol. The ester was purified by several recrystallizations from ethyl acetate; m. p. 186.5–187°. The yield was almost quantitative. Acknowledgment is made for the assistance of two senior students, Karl S. Hecht and Meyer H. Zuravin.

Anal. Calcd. for $C_{54}H_{90}O_3S$: S, 3.91. Found: S, 4.02.

Bis-cholesteryl sulfite is soluble in cold petroleum ether, carbon tetrachloride, chloroform and ethyl ether. It is only slightly soluble in boiling methyl or ethyl alcohol and acetone. It is only slightly soluble in cold ethyl acetate but very soluble at the boiling temperature. The ester is quite stable to aqueous acid or alkaline saponification. It can be quickly hydrolyzed by boiling in 30% alcoholic potassium hydroxide with a quantitative yield of cholesterol.

This sulfite ester is partially converted into cholesteryl chloride when heated with phosphorus pentachloride in carbon tetrachloride. A small quantity of cholesterol and some unchanged sulfite were also isolated from the reaction mixture. The end-products would indicate that the reaction had gone in the same way that Michaelis[9] found for the action of phosphorus pentachloride upon diethyl sulfite. The sulfurous acid esters of ethyl alcohol, butyl alcohol and phenol were prepared in a similar manner.

Bis-(diacetone-glucose)-sulfite.—Five grams of diacetone-glucose and 100 cc. of pyridine were dissolved in 50 cc. of dry ethyl ether; 0.72 cc. of thionyl chloride was added a drop at a time. The mixture was permitted to stand for three hours. The pyridine

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[8] Green, *J. Chem. Soc.*, 500 (1927).

[9] Michaelis, *Ber.*, **7**, 1074 (1874).

hydrochloride which had separated was removed by decantation. The reaction mixture was poured into three volumes of water which was kept faintly alkaline with sodium carbonate. After complete neutralization the ether-soluble portion was separated from the water-soluble constituents. The ether solution was dried over anhydrous sodium carbonate. When the ether was removed under reduced pressure, a yellow transparent syrup remained which had all of the properties of *bis*-(diacetone-glucose)-sulfite. Tests showed the presence of sulfur but no chlorine. The product was identified by hydrolysis with 0.1 *N* alcoholic potassium hydroxide. Potassium sulfite and diacetone-glucose resulted.

Cholesteryl Chloride.—To 5 g. of cholesterol and 1 cc. of pyridine, 10 cc. of thionyl chloride was added rapidly. The reaction mixture was kept cool with running water and was refluxed for one hour. Sulfur dioxide was liberated. The mixture was cooled, poured into water and then extracted with ether. The ethereal solution was dried over anhydrous sodium carbonate. When the solvent was removed under reduced pressure a semi-crystalline product remained. This was recrystallized from alcohol and identified as cholesteryl chloride; m. p. 95–96°. The yield was almost quantitative. The reaction was repeated without the addition of pyridine with identical results.

Ethyl chloride, and butyl chloride were prepared in a similar manner. Attempts to prepare chlorobenzene from phenol by this method were unsuccessful.

Reaction of Diacetone-glucose with Excess Thionyl Chloride.—Five grams of diacetone-glucose and 10 cc. of dry pyridine were dissolved in 30 cc. of dry ethyl ether; 10 cc. of thionyl chloride was added rapidly and the reaction mixture was kept cool by immersion in ice water. It was refluxed for one hour. The pyridine hydrochloride which separated was removed by decantation and the solution poured into ice water. The ether-soluble portion was separated and dried over anhydrous sodium carbonate. When the solvent was removed under reduced pressure a semi-crystalline mass remained which contained sulfur and a trace of chlorine. Upon recrystallization from high-boiling petroleum ether about 3 g. of diacetone-glucose separated; m. p. 102°. Hydrolysis of the remaining sirup with alcoholic potassium hydroxide yielded diacetone-glucose, potassium sulfate and potassium sulfite. It is hoped that a further study of this reaction will result in the production of the chloride.

A similar reaction with cholesterol yielded about 80% of cholesteryl chloride and about 20% of *bis*-cholesteryl sulfite.

Summary

1. The synthesis of *bis*-cholesteryl sulfite is reported and some of its properties are described.

2. The action of thionyl chloride, in the theoretical amount, upon cholesterol and certain other alcohols in the presence of an excess of pyridine yields the sulfurous acid ester of the alcohol. No chlorination takes place.

3. The action of thionyl chloride, in large excess of the theoretical amount, upon cholesterol and certain other alcohols in the presence of an theoretical amount of pyridine, yields the chloride of the alcohol. Evidence is presented to indicate that an intermediate compound is formed which upon heating may break down to form sulfur dioxide and the alkyl chloride.

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