[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XXVI. Sitosteryl Chloride, Stigmasteryl Chloride and Related Compounds

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The Walden inversion involved in the preparation and potassium acetate treatment of the cholestyl chlorides from the isomeric cholestanols has been discussed by Marker and co-workers.[1] Although these facts are the basis for a useful method for preparing *epi* compounds, no systematic study of the preparation and hydrolysis of chlorides related to other sterols has been made.

Sitosteryl chloride has been prepared by Vanghelovici and Angelescu,[2] but neither its mode of preparation nor its physical properties are recorded in any of the four leading abstract journals. Vanghelovici and Angelescu[2] found that sitosteryl chloride gave, when treated with nitric acid and sodium nitrite, "nitrodehydrositosteryl chloride." This substance, which is 6-nitrositosteryl chloride, can be reduced by zinc and acetic acid to 3-chloro-6-sitostanone, and the latter, upon Clemmensen reduction, gives "isositosteryl chloride," m. p. 108°, a substance which very probably is identical with α-sitostyl chloride[3] which we have now prepared. Furthermore, "isocholesteryl chloride," m. p. 110°, which Vanghelovici and Angelescu prepared in an analogous manner from cholesterol, is probably identical with α-cholestyl chloride, m. p. 112°, prepared by Marker and co-workers.[1] Bonstedt[4] has prepared two unrelated chlorides, sitostene hydrochloride (5-chlorositostane), and γ-sitosteryl chloride, which probably differ from sitosteryl chloride in the same manner as sitosterol differs from γ-sitosterol, namely, in the asymmetry of the side-chain.[5]

The accompanying chart shows the interrelationships between the compounds studied in the present investigation. Sitosterol (I) and stigmasterol (II), when treated with phosphorus pentachloride, give sitosteryl chloride (III) and stigmasteryl chloride (IV), respectively. When these are boiled with potassium acetate in acetic acid, the corresponding acetates are formed, and these may be hydrolyzed to sitosterol (I) and stigmasterol (II), respectively. The catalytic hydrogenation of either stigmasteryl chloride (IV) or sitosteryl chloride (III) yields α-sitostyl chloride (V). The latter may also be prepared by the action of thionyl chloride on stigmastanol (VI) or by the action of phosphorus pentachloride on *epi*-stigmastanol (IX). The reduction of α-stigmastyl chloride (V) with sodium and amyl alcohol yields stigmastane (VII), a substance which has been prepared previously by the Clemmensen reduction of stigmastanone.[6-9] When α-stigmastyl chloride (V) is refluxed with potassium acetate in acetic acid, the acetate of *epi*-stigmastanol (IX), is formed. *epi*-Stigmastanol has been prepared previously by the hydrogenation of stigmastanone or sitostanone in acetic acid containing hydrobromic acid,[10] by the hydrogenation of dihydrocinchone in butyl ether containing some hydrobromic acid,[11] by the epimerization of dihydrocinchol (stigmastanol) with sodium ethylate,[11] and by the reduction of fucosterol[12] with sodium and amyl alcohol and subsequent catalytic hydrogenation. *epi*-Stigmastanol (IX), when treated with thionyl chloride, yields β-stigmastyl chloride (X). The latter, when refluxed with potassium acetate, yields the acetate of stigmastanol (VI). Stigmastanol (VI) gives β-stigmastyl chloride (X), when treated with phosphorus pentachloride.

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Experimental

Sitosteryl Chloride.—A mixture of 30 g. of sitosterol and 30 g. of phosphorus pentachloride was ground in a mortar

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(1) Marker, THIS JOURNAL, **57**, 1755 (1935); Marker, Whitmore and Kamm, *ibid.*, **57**, 2358 (1935).

(2) Vanghelovici and Angelescu, *Bul. soc. chim. romània*, **17**, 177 (1935); *C. A.*, **30**, 1064 (1936).

(3) Considerable confusion arises out of the naming of various phytosterols as α_1-, α_2-, β-, and γ-sitosterols. We prefer to designate β-sitosterol simply as sitosterol [Marker and Wittle, THIS JOURNAL **59**, 2704 (1937)], and to use the prefixes α and β to distinguish between isomers such as the isomeric sitostyl chlorides. This usage is in harmony with the analogous nomenclature of the cholestyl chlorides,[5] and of the pregnandiols and pregnanolones [Marker, Kamm, Wittle, Oakwood, Lawson and Laucius, *ibid.*, **57**, 2291 (1937)] and is that first advocated by Fieser ("Chemistry of Natural Products Related to Phenanthrene," Reinhold Pub. Corp., New York, 1937, 2d ed., pp. 398 ff.).

(4) Bonstedt, *Z. physiol. Chem.*, **176**, 269 (1928).

(5) Ruzicka and Eichenberger, *Helv. Chim. Acta*, **18**, 430 (1935).

(6) Windaus and Rahlen, *Z. physiol. Chem.*, **101**, 223 (1918).

(7) Windaus and Brunken, *ibid.*, **140**, 47 (1924).

(8) Kuwada and Morimoto, *J. Pharm. Soc. Japan*, **57**, 246 (1937).

(9) Bengtsson, *Z. physiol. Chem.*, **237**, 46 (1935).

(10) Dalmer, v. Werder, Honigmann and Heyns, *Ber.*, **68**, 1814 (1935).

(11) Dirscherl, *Z. physiol. Chem.*, **237**, 52 (1935).

(12) Coffey, Heilbron, Spring and Wright, *J. Chem. Soc.*, 1205 (1935); Coffey Heilbron and Spring, *ibid.*, 738 (1936).

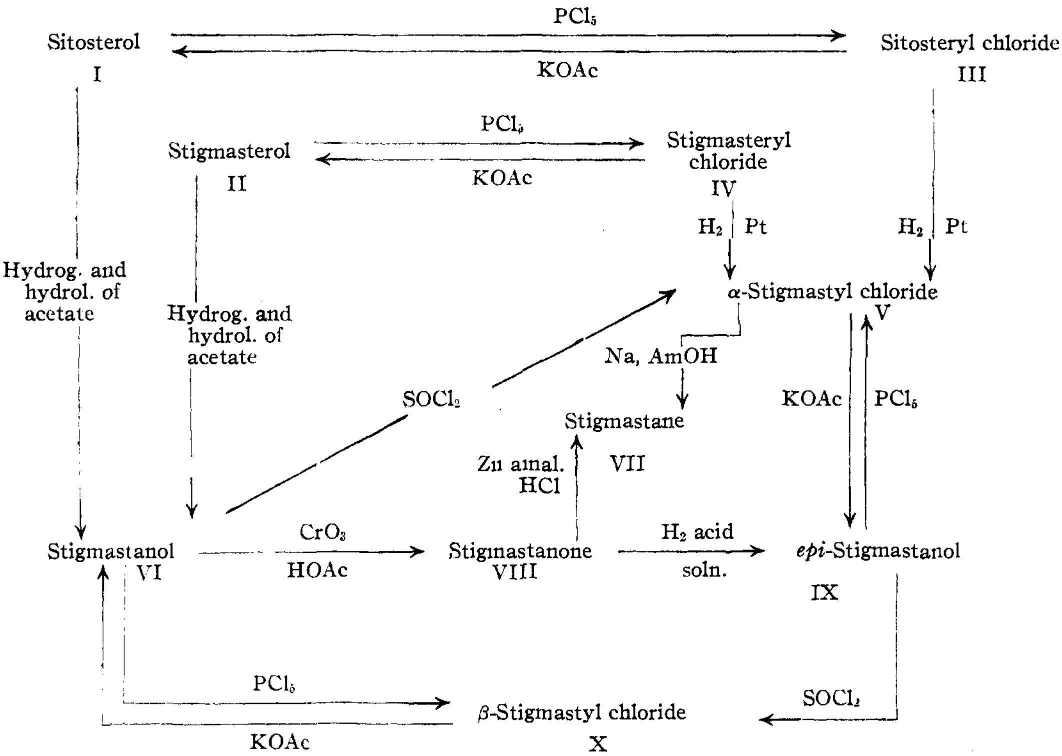

Fig. 1.

for thirty minutes. The resulting paste was poured into water and heated on a steam-bath for one hour. The mixture was cooled and extracted with ether. The ethereal solution was washed with sodium carbonate solution, filtered, and then evaporated to a small volume. Alcohol was added and, upon cooling, sitosteryl chloride crystallized. After several recrystallizations from acetone, it melted at 86°.

Anal. Calcd. for $C_{29}H_{49}Cl$: C, 80.4; H, 11.4. Found: C, 80.3; H, 11.4.

With bromine in acetic acid, it gave a dibromide, m. p. 96°.

Anal. Calcd. for $C_{29}H_{49}ClBr_2$: C, 58.8; H, 8.2; Found: C, 59.1; H, 8.3.

Stigmasteryl Chloride.—A mixture of 30 g. of stigmasterol and 30 g. of phosphorus pentachloride was treated as described for the preparation of sitosteryl chloride. The product was crystallized from acetone. It melted at 83°.

Anal. Calcd. for $C_{29}H_{47}Cl$: C, 80.7; H, 11.0. Found: C, 80.5; H, 11.1.

With bromine in acetic acid, it gave a tetrabromide, m. p. 182°.

Anal. Calcd. for $C_{29}H_{47}ClBr$: C, 46.4; H, 6.2. Found: C, 46.5; H, 6.1.

Hydrolysis of Sitosteryl Chloride.—A mixture of 1 g. of sitosteryl chloride, 2 g. of anhydrous potassium acetate and 25 cc. of acetic acid was refluxed for four hours. Water was added and the product was crystallized from acetone, methanol and ethanol. The purified product, m. p. 125°, gave no depression in melting point when mixed with sitosteryl acetate.

Anal. Calcd. for $C_{31}H_{52}O_2$: C, 81.5; H, 11.5. Found: C, 81.4; H, 11.5.

Hydrolysis of Stigmasteryl Chloride.—A mixture of 1 g. of stigmasteryl chloride, 2 g. of anhydrous potassium acetate, and 25 cc. of acetic acid was treated as described for the hydrolysis of sitosteryl chloride. The product, after crystallization from ethanol, melted at 140°. When mixed with stigmasteryl acetate it gave no depression in melting point.

Anal. Calcd. for $C_{31}H_{50}O_2$: C, 81.9; H, 11.1. Found: C, 82.3; H, 11.2.

α-Sitostyl Chloride or α-Stigmastyl Chloride. (a).—To a solution of 1 g. of sitosteryl chloride in 100 cc. of ether was added 200 mg. of platinum oxide catalyst. The mixture was shaken with hydrogen under a pressure of 45 lb. (3 atm.) for two hours. The catalyst was filtered, the ether evaporated, and the residue crystallized from acetone to give a product which melted at 107°.

Anal. Calcd. for $C_{29}H_{51}Cl$: C, 80.0; H, 11.8. Found: C, 80.1; H, 11.7.

(b).—One gram of stigmasteryl chloride was reduced to α-stigmastyl chloride in the same manner as described for the reduction of sitosteryl chloride. It gave a product melting at 108° which gave no depression in melting point when mixed with α-sitostyl chloride.

Anal. Calcd. for $C_{29}H_{51}Cl$: C, 80.0; H, 11.8. Found: C, 80.1; H, 11.7.

(c).—A mixture of 1 g. of *epi*-stigmastanol and 1 g. of phosphorus pentachloride was ground in a mortar. Water was added and the product was extracted with ether and washed with sodium carbonate solution. The ether was evaporated and the residue was crystallized from acetone. The purified α-stigmastyl chloride, m. p. 108°, gave no depression in melting point when mixed with either (a) or (b).

Anal. Calcd. for $C_{29}H_{51}Cl$: C, 80.0; H, 11.8. Found: C, 80.3; H, 11.7.

(d).—A mixture of 1 g. of stigmastanol and 2 cc. of thionyl chloride was allowed to stand at room temperature overnight. Water was added and the product was extracted with ether. The ethereal solution was washed with sodium carbonate solution. The product, α-stigmastyl chloride, after crystallization from acetone, melted at 106° and gave no depression in melting point when mixed with any of the above products.

Anal. Calcd. for $C_{29}H_{51}Cl$: C, 80.0; H, 11.8. Found: C, 80.7; H, 11.8.

β-Sitostyl Chloride or β-Stigmastyl Chloride. (a).—A mixture of 4 g. of stigmastanol and 4 g. of phosphorus pentachloride was ground in a mortar. Hot water was added and the product was extracted with ether. The product, after crystallization from acetone, melted at 118° and gave a depression in melting point when mixed with α-stigmastyl chloride.

Anal. Calcd. for $C_{29}H_{51}Cl$: C, 80.0; H, 11.8. Found: C, 80.2; H, 11.8.

(b).—When sitostanol was treated in the same manner it gave a chloride, m. p. 118°, identical with the above product.

(c).—A mixture of 1 g. of *epi*-stigmastanol and 2 cc. of thionyl chloride was allowed to stand overnight. Water was added and the product was extracted with ether. After crystallization from alcohol-ether, and then acetone, it melted at 116° and gave no depression in melting point when mixed with (a) or (b).

Anal. Calcd. for $C_{29}H_{51}Cl$: C, 80.0; H, 11.8. Found: C, 80.5; H, 11.7.

Hydrolysis of α-Stigmastyl Chloride.—To a solution of 1 g. of α-stigmastyl chloride in 10 cc. of valeric acid was added 2 g. of potassium acetate. After refluxing the mixture overnight, an excess of alcoholic potassium hydroxide solution was added, and the resulting mixture boiled. Water was added and the solid filtered and dried. The carbinol was separated by means of its half succinic ester. The free carbinol was crystallized from alcohol giving a product melting at 202° which gave no depression in melting point when mixed with *epi*-stigmastanol. It gave an acetate melting at 85° which gave no depression in melting point with *epi*-stigmastyl acetate.

Anal. Calcd. for $C_{31}H_{54}O_2$: C, 81.2; H, 11.9. Found: C, 81.3; H, 12.0.

Hydrolysis of β-Stigmastyl Chloride.—One gram of β-stigmastyl chloride was hydrolyzed in the same manner as described for the hydrolysis of α-stigmastyl chloride. The hydrolysis yielded a product melting at 138° which gave no depression in melting point when mixed with stigmastanol. It gave an acetate melting at 134° which gave no depression in melting point when mixed with stigmastyl acetate.

Anal. Calcd. for $C_{31}H_{54}O_2$: C, 81.2; H, 11.9. Found: C, 81.5; H, 12.1.

Stigmastane or Sitostane.—To a solution of 2 g. of α-sitostyl chloride in 100 cc. of dry amyl alcohol was added 5 g. of sodium. When the sodium had dissolved, water was added and the amyl alcohol layer was distilled. The residue was crystallized from alcohol-ether. The sitostane so obtained melted at 84°. The same product was obtained by the reduction of α-stigmastyl chloride.

Anal. Calcd. for $C_{29}H_{52}$: C, 86.9; H, 13.1. Found: C, 87.0; H, 12.7.

Summary

Sitosteryl chloride and stigmasteryl chloride were prepared and reduced to α-stigmastyl chloride. The latter product was also prepared from *epi*-stigmastanol and phosphorus pentachloride and from stigmastanol and thionyl chloride.

β-Stigmastyl chloride was prepared from *epi*-stigmastanol and thionyl chloride and from stigmastanol and phosphorus pentachloride. The halides were hydrolyzed.

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