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

Sterols. XXVII. *epi*-Sitosterol and *epi*-Stigmasterol

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Techniques available for the preparation of *epi*-sterols have been developed only recently. Thus, *epi*-cholesterol has been prepared by the oxidation of cholesterylmagnesium chloride,[1] by the Wolff-Kishner reduction of 7-ketocholesteryl acetate,[2] and by the hydrogenation of $\Delta^{5,6}$-cholestenone using the Raney nickel catalyst.[3] *epi*-Ergosterol has been prepared by the aluminum isopropylate reduction of ergostatrienone.[4]

We have now prepared *epi*-sitosterol and *epi*-stigmasterol by the oxidation of the corresponding Grignard reagents prepared from the chlorides. The isomeric β- and *epi*-compounds formed were separated in both cases by the use of digitonin. The structures of these new sterols are proved by their mode of formation, by the fact that they do not precipitate digitonin, by the formation of acetates, and by their reduction to *epi*-stigmastanol. It is interesting that each of the four known *epi*-sterols, as well as the corresponding acetates, melts lower than the corresponding β-compound.

	M.p., °C.	Acetate M.p., °C.		M.p., °C.	Acetate M.p., °C.
Cholesterol	148	115	*epi*-Cholesterol	141	85
Ergosterol	163	172	*epi*-Ergosterol	152	126
Sitosterol	140	122	*epi*-Sitosterol	135	66
Stigmasterol	170	141	*epi*-Stigmasterol	151	98

Both *epi*-sitosterol and *epi*-stigmasterol are readily dehydrated; although in each case the crude sterol mixture was purified by conversion to the half succinic ester, considerable amounts of unsaturated hydrocarbons were found after hydrolysis of these esters. This behavior is similar to that shown by *epi*-allostigmasterol.[5]

Experimental

***epi*-Sitosterol.**—A Grignard reagent was prepared by dropping a solution of 19.8 g. of carefully purified sitosteryl chloride[6] in 200 cc. of dry ether into 2 g. of magnesium with vigorous stirring. The reaction was started by using ethyl bromide. After the addition of the sitosteryl chloride, which required four hours, the mixture was stirred and refluxed for twenty hours. The reaction vessel was surrounded by an ice-bath, and a steady stream of oxygen passed over the surface of the well-stirred mixture for four hours. The reaction mixture was poured into dilute sulfuric acid, extracted with ether, and the ethereal extract washed with sodium carbonate solution and water. The ethereal solution was filtered from some insoluble foreign matter, evaporated and the residue dried by adding 100 cc. of benzene, and distilling the mixture. The dry residue was heated for two hours with 10 g. of succinic anhydride and 20 cc. of dry pyridine. The resulting solution was diluted with ether and water and washed with dilute sulfuric acid. The ether layer was shaken with sodium carbonate. The sodium carbonate layer, after extraction with ether, was acidified, and extracted with ether. The ether was evaporated and the residual ester hydrolyzed with alcoholic potassium hydroxide, cooled, diluted and the precipitated sterol filtered. The crude sitosterol was dissolved in ether, separated from a small amount of water, filtered and evaporated. The residue, a mixture of sitosterol and *epi*-sitosterol, together with some hydrocarbon formed by the facile dehydration of *epi*-sitosterol, weighed 13 g. To 5 g. of this mixture, dissolved in 1.5 liters of alcohol, was added a solution of 10 g. of digitonin in 500 cc. of hot alcohol. The next day the digitonide was filtered, washed well with alcohol and ether, and the filtrate and washings evaporated to dryness. The residue was leached with ether. To remove the remainder of the sterol the residue was dissolved in a small amount of alcohol and shaken with ether and water. The ether layer was added to the ether leachings, and the combined solution evaporated to dryness. The residue was leached with 600 cc. of boiling alcohol and the alcohol concentrated. The dehydration product of *epi*-sitosterol, an unsaturated hydrocarbon, crystallized. The mother liquors were concentrated to yield a crop of crude *epi*-sitosterol. After four crystallizations from methanol, and three from acetone, *epi*-sitosterol, m. p. 135°, was obtained.

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.5; H, 12.2. Found: C, 83.6; H, 12.2.

Fifty milligrams of this substance in 1 cc. of pyridine was acetylated by adding 0.5 cc. of acetic anhydride. After standing overnight, the solution was diluted, and the acetate filtered and crystallized from methanol. It melted at 66°.

Anal. Calcd. for $C_{31}H_{52}O_2$: C, 81.5; H, 11.5. Found: C, 81.1; H, 11.8.

Catalytic Hydrogenation of *epi*-Sitosterol.—A solution of 200 mg. of *epi*-sitosterol in 150 cc. of ether and 20 cc. of acetic acid was shaken for one hour with 0.4 g. of platinum oxide catalyst in a hydrogen atmosphere at 45 lb. (3 atm.) pressure. After filtering the reaction mixture, the ether was evaporated. The *epi*-stigmastanol formed, which crystallized from the residual acetic acid, was

(1) Marker, Oakwood and Crooks, THIS JOURNAL, **58**, 481 (1936); Marker, Kamm, Oakwood and Laucius, *ibid.*, **58**, 1948 (1936).

(2) Marker, Kamm, Fleming, Popkin and Wittle, *ibid.*, **59**, 619 (1937).

(3) Ruzicka and Goldberg, *Helv. Chim. Acta*, **19**, 1407 (1936).

(4) Marker, Kamm, Laucius and Oakwood, THIS JOURNAL, **59**, 1840 (1937).

(5) Marker and Oakwood, *ibid.*, **59**, 2708 (1937).

(6) Marker and Lawson, *ibid.*, **59**, 2711 (1937).

recrystallized from alcohol. It melted at 204°, and showed no depression in melting point when mixed with *epi*-stigmastanol prepared by the hydrogenation of stigmastanone.

Anal. Calcd. for $C_{29}H_{52}O$: C, 83.4; H, 12.4. Found: C, 83.4; H, 12.6.

It formed an acetate, m. p. 84°, which showed no depression in melting point when mixed with authentic *epi*-stigmastyl acetate.

epi-Stigmasterol.—A Grignard reagent was prepared by adding a solution of 22 g. of carefully purified stigmasteryl chloride[6] in 200 cc. of dry ether over a period of four hours to a well-stirred mixture of 2 g. of magnesium, 10 drops of ethyl bromide and 10 cc. of ether. The mixture was stirred and refluxed for twenty hours. The resulting Grignard solution was oxidized, and treated as described for the preparation of *epi*-sitosterol. Seven grams of a mixture of stigmasterol and *epi*-stigmasterol was isolated. Five grams of this mixture was treated with digitonin in the same manner as described for the previous preparation. In this manner the filtrate from the digitonide, which weighed 10 g., yielded a first crop which was apparently an unsaturated hydrocarbon. The mother liquors were concentrated to give a crude product, m. p. 122–140°. After seven crystallizations from alcohol, *epi*-stigmasterol, m. p. 151°, was obtained.

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.4; H, 11.7. Found: C, 84.4; H, 11.8.

Fifty milligrams of this sterol was acetylated as described for the preparation of *epi*-sitosteryl acetate. The product, after crystallization from methanol, melted at 98°.

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

Catalytic Hydrogenation of *epi*-**Stigmasterol.**—A solution of 200 mg. of *epi*-stigmasterol in 150 cc. of ether and 20 cc. of acetic acid was shaken for one hour with 0.4 g. of platinum oxide catalyst in a hydrogen atmosphere at 45 lb. (3 atm.) pressure. The catalyst was filtered, the ether evaporated and the residual acetic acid solution cooled. The crude *epi*-stigmastanol was filtered and crystallized from alcohol. The purified product, melting at 203°, showed no depression in melting point when mixed with *epi*-stigmastanol prepared by the reduction of stigmastanone in acid solution.

Anal. Calcd. for $C_{29}H_{52}O$: C, 83.4; H, 12.4. Found: C, 83.4; H, 12.6.

It formed an acetate, m. p. 83°, which did not depress the melting point of authentic *epi*-stigmastyl acetate.

Anal. Calcd. for $C_{31}H_{54}O_2$: C, 81.2; H, 11.8. Found: C, 81.0; H, 11.8.

Summary

epi-Sitosterol and *epi*-stigmasterol have been prepared by oxidation of the Grignard reagents from the corresponding chlorides. Both *epi*-sitosterol and *epi*-stigmasterol are very readily dehydrated. Upon hydrogenation, they yield *epi*-stigmasterol.

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Alkylation with a Hydrogenating Catalyst

BY V. I. KOMAREWSKY

Recently[1] it was found that aromatic and naphthene hydrocarbons can undergo a destructive alkylation under the action of a specially prepared nickel–alumina catalyst.[2] In this article a direct alkylation of aromatic (benzene) and naphthene (cyclohexane) hydrocarbons with an olefin (ethylene) in the presence of the same catalyst will be described.

Ethylene and benzene passed over nickel–alumina catalyst at 350° produced a liquid boiling at 79–110°. This product was completely free from unsaturated hydrocarbons (stable toward permanganate). By fractionation it was possible to isolate and identify toluene (5% of the benzene charged). The bottoms after distillation contained crystals (2% of the benzene charged) which were identified as a mixture of naphthalene and diphenyl. The gas produced by the reaction contained hydrogen, methane and ethane.

Benzene alone under the same conditions remained practically unchanged. Diphenyl crystals were found in the bottoms after distillation of the liquid product; traces of hydrogen were found in the gas. These results show that a direct alkylation of benzene with ethylene takes place, but according to the previous observation[1] the ethylbenzene formed decomposes in contact with nickel–alumina to toluene and methane. Hydrogen was produced along with the formation of naphthalene.

Ethylene and cyclohexane passed over the same catalyst at 300° produced a liquid boiling at 78–100°, free from unsaturated hydrocarbons (permanganate test). By fractionation of this liquid,

(1) Ipatieff and Komarewsky, THIS JOURNAL, **58**, 922 (1936).
(2) Zelinsky and Komarewsky, *Ber.*, **57**, 667 (1924).