Summary

Ethyl β-phenyl-β-hydroxypropionate has been dehydrated in the presence of either sodium triphenylmethyl or sodium ethoxide at room temperature.

It has been shown that phenylbenzylcarbinol is not dehydrated by sodium amide at room temperature.

The mechanism of elimination of water from organic compounds by means of bases is discussed.

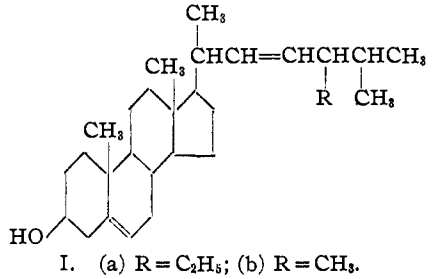
DURHAM, NORTH CAROLINA RECEIVED JULY 26, 1940

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

Preparation of 22,23-Dihydrostigmasterol and 22,23-Dihydrobrassicasterol

BY ERHARD FERNHOLZ AND WILLIAM L. RUIGH

Bernstein and Wallis[1] showed that the double bond in the side-chain of stigmasterol (Ia) could

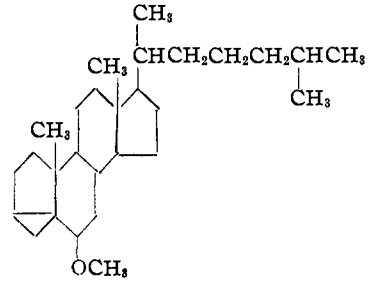


I. (a) R = C_2H_5; (b) R = CH_3.

be selectively reduced by means of palladium and hydrogen. Evidence was brought by the same authors to show the identity of 22,23-dihydrostigmasterol with β-sitosterol from cottonseed oil.

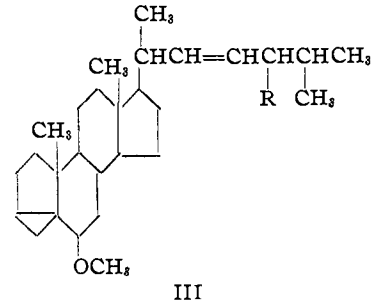
After the elucidation of the structure of brassicasterol,[2] we were interested in the application of such a partial hydrogenation to this sterol so that the properties of 22,23-dihydrobrassicasterol might become known and its isolation from natural sources thus be facilitated. In the attempt to reproduce the experiments of Bernstein and Wallis, however, it became apparent that the selectivity of our palladium catalyst was not great enough, and in following the directions closely we obtained a 22-23-dihydrostigmasterol undoubtedly contaminated with a certain amount of stigmasterol.

It occurred to us at this point that our objective might be reached with much greater ease and certainty if the 5,6-double bond could be blocked by conversion into the *i*-ether prior to hydrogenation. In a noteworthy series of articles Wallis and his school[3,4,5,6] demonstrated that the abnormal cholesteryl ether of Stoll,[7] which is formed when cholesteryl *p*-toluenesulfonate is boiled in methanol in presence of potassium acetate, has structure II.



II

The *i*-cholesteryl ether is without a double bond. If stigmasterol and brassicasterol underwent the same type of abnormal ether formation, it would leave the double bond in the side chain free for hydrogenation. The conversion of stigmasterol and brassicasterol into the *i*-ethers (III) was readily accomplished. When a weak palladium

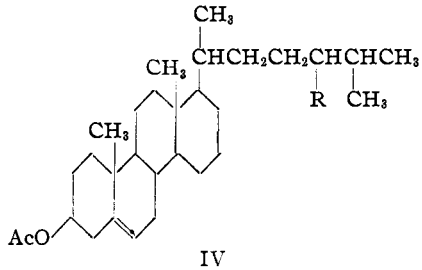


III

catalyst was used, the reaction stopped sharply after one mole of hydrogen was absorbed, giving the reduced ethers in good yields. Treatment with zinc acetate in boiling acetic acid[8] led to rearrangement with the formation of the normal

(1) Bernstein and Wallis, *J. Org. Chem.*, **2**, 341 (1937).
(2) Fernholz and Stavely, THIS JOURNAL, **62**, 1875 (1940).
(3) Wallis, Fernholz and Gephart, *ibid.*, **59**, 137 (1937).
(4) Ford and Wallis, *ibid.*, **59**, 1415 (1937).
(5) Ford, Chakravorty and Wallis, *ibid.*, **60**, 413 (1938).
(6) Ladenburg, Chakravorty and Wallis, *ibid.*, **61**, 3483 (1939).
(7) W. Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).
(8) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 406 (1937).

acetates IV, from which the sterols and other derivatives were prepared. The constants of these



IV

carefully purified substances are recorded in Table I.

TABLE I

Compound	M. p.	$[\alpha]_D$
22,23-Dihydrostigmasterol	136	−34
Acetate	119.5	−37
m-Dinitrobenzoate	202	−11
22,23-Dihydrobrassicasterol	158	−46
Acetate	145	−46
Benzoate	162	−19
p-Nitrobenzoate	172	−11
m-Dinitrobenzoate	197.5	−17

A natural sterol similar in properties to our 22,23-dihydrobrassicasterol does not seem to have been described as yet. 22,23-Dihydrostigmasterol is considered to be identical with β-sitosterol. Bernstein and Wallis[1] compared their 22,23-dihydrostigmasterol, benzoate and *m*-dinitrobenzoate with β-sitosterol derived from cottonseed oil and observed excellent agreement of melting points and rotations. So far as the free sterol and the *m*-dinitrobenzoates are concerned our constants also agree quite well with their data. However, while the m. p. of β-sitosterol from cottonseed oil is reported to be at 125–126°,[9] we have not been able to raise the m. p. of our 22,23-dihydrostigmasteryl acetate above 119.5°.

Experimental

Stigmasteryl *p*-Toluenesulfonate.—The ester, prepared by the method applied by Freudenberg and Hess[10] to cholesterol, formed stout rods from dry acetone; m. p. 148–150° $[\alpha]_D$ −47.1° (22.1 mg. in 2 cc. of chloroform, $\alpha^{24}D$ −0.52°, *l* 1 dm.).

Anal. Calcd. for $C_{36}H_{54}O_3S$: C, 76.27; H, 9.60. Found: C, 76.53; H, 9.92.

***i*-Stigmasteryl Methyl Ether.**—Stigmasteryl *p*-toluenesulfonate (3.5 g.) was refluxed in a solution of 3.5 g. of fused potassium acetate in 175 cc. of dry methanol for three hours. The methanol was evaporated and the residue taken up with ether, and washed with water, dilute sodium hydroxide, and water, dried over potassium carbonate and the ether evaporated. A benzene–hexane solution of the crude product was passed through a column of alumina and washed through with hexane to remove the stigmasterol, which is strongly adsorbed. The *i*-ether forms prisms from acetone, m. p. 54–55° $[\alpha]^{24}D$ +34.7° (21.9 mg. in 2 cc. of chloroform, α_D +0.38°, *l* 1 dm.).

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.63; H, 12.07.

22,23-Dihydrostigmasterol.—One gram of *i*-stigmasteryl methyl ether in 25 cc. of pure ethyl acetate and 0.3 g. of palladium black saturated with hydrogen were shaken in an atmosphere of hydrogen. One mole of hydrogen was taken up within 40 minutes, and in the course of another hour no detectable amount of hydrogen was absorbed. The oily 22,23-dihydro-*i*-stigmasteryl methyl ether was not purified but refluxed for six hours with 50 cc. of acetic acid and 2 g. of zinc acetate. The mixture was then diluted with water, extracted with ether and the ether solution washed with alkali. The ether residue was crystallized from alcohol and gave 0.72 g. of shining plates, m. p. 117.5–119.5°. This slightly impure acetate was hydrolyzed with alcoholic potassium hydroxide. The free sterol was treated with charcoal in ether solution and recrystallized from benzene–alcohol it forms leaflets melting at 135–136°. From acetone solution it crystallizes in needles, m. p. 135.5–136°; $[\alpha]^{24}D$ −34.3° (23.9 mg. in 2 cc. of chloroform, α_D 0.41°, *l* 1 dm.).

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 83.77; H, 12.08.

A sample of the sterol (232 mg.) dissolved in 90% alcohol (20 cc.) added to a 1% solution of digitonin in 90% alcohol (100 cc.) gave 893 mg. of digitonide (96%). The properties of the sterol recovered by splitting this digitonide were unchanged.

22,23-Dihydrostigmasteryl Acetate.—The acetate was prepared by refluxing a sample of the above described sterol with acetic anhydride for thirty minutes. It was purified by crystallization from alcohol. The acetate comes in two modifications, a labile, cottony material, and in the form of stable plates; m. p. 118.5–119.5°; $[\alpha]_D$ −37° (16.2 mg. in 2 cc. of chloroform, α_D −0.30°, *l* 1 dm.).

Anal. Calcd. for $C_{31}H_{52}O_2$: C, 81.52; H, 11.48. Found: C, 81.53; H, 11.41.

22,23-Dihydrostigmasteryl *m*-Dinitrobenzoate.—One hundred mg. of the sterol was warmed on the steam-bath for forty-five minutes with a solution of 500 mg. of *m*-dinitrobenzoyl chloride in 7.5 cc. of pyridine (dried over calcium hydride). On cooling, the solution was diluted with water and crude product filtered off. After a Norit treatment in benzene the material crystallized from benzene–alcohol in shining white leaflets, m. p. 201–202°, $[\alpha]^{24}D$ −10.6° (18.9 mg. in 2 cc. of chloroform, α_D −0.10°, *l* 1 dm.).

Anal. Calcd. for $C_{36}H_{52}O_6N_2$: C, 71.02; H, 8.61. Found: C, 71.21; H, 8.80.

Stigmasteryl *m*-Dinitrobenzoate.—The compound prepared as in the previous example crystallized from benzene–alcohol in shining white leaflets; m. p. 226–228° $[\alpha]^{24}D$ −21.5° (22.4 mg. in 2 cc. of chloroform, α_D −0.23°, *l* 1 dm.).

(9) Wallis and Chakravorty, *J. Org. Chem.*, **2**, 335 (1937).

(10) Freudenberg and Hess, *Ann.*, **448**, 128 (1926).

Anal. Calcd. for $C_{36}H_{50}O_6N_2$: C, 71.26; H, 8.31. Found: C, 71.00; H, 8.44.

Brassicasteryl *p*-Toluenesulfonate.—One gram of brassicasteryl acetate, m. p. 153–155°, $[\alpha]^{24}D$ −69°, was hydrolyzed to the free sterol as usual and the product treated overnight with 1 g. of *p*-toluenesulfonyl chloride in 10 cc. of dry pyridine. The solution was poured into cold sodium bicarbonate solution, the precipitate filtered off, washed and the solid dissolved in ether. The ether solution was washed successively with ice cold water, dilute hydrochloric acid, sodium carbonate, water and dried with potassium carbonate. The product crystallized from acetone gave 964 mg. of needles, m. p. 139.5–140.5°; $[\alpha]^{24}D$ −61.6° (20.8 mg. in 2 cc. of chloroform gave αD −0.64, *l* 1 dm.).

Anal. Calcd. for $C_{35}H_{52}O_3S$: C, 76.04; H, 9.48; S, 5.80. Found: C, 76.02; H, 9.45; S, 5.67.

***i*-Brassicasteryl Methyl Ether.**—One gram of brassicasteryl *p*-toluenesulfonate was refluxed with 1 g. of fused potassium acetate in 59 cc. dry methanol for four hours and the product worked up as in the case of *i*-stigmasteryl methyl ether. In the purification over alumina 2 mg. of an impurity in the foreruns was discarded, the *i*-ether forming the main mid-fraction. The substance formed narrow plates from acetone and methanol, m. p. 70–71°, $[\alpha]^{24}D$ +20.0° (22 mg. in 2 cc. of chloroform, αD +0.22, *l* 1 dm.).

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.50; H, 11.66.

22,23-Dihydrobrassicasterol.—A solution of 683 mg. of *i*-brassicasteryl ether in 50 cc. of ethyl acetate rapidly absorbed the calculated amount of hydrogen in the presence of 300 mg. of palladium. The solution, filtered from the catalyst, was evaporated to an oil which was refluxed for eight hours with a solution of 1 g. of zinc acetate in 50 cc. of glacial acetic acid. The product hydrolyzed and worked up as before gave 657 mg. crude sterol which was chromatographed in a mixture of equal parts of benzene and hexane. Elution with the same mixture yielded 11 mg. of an oil and elution with about 15% of methanol added gave 624 mg. of sterol which, crystallized twice from acetone, gave needles, m. p. 157–158°. From ethanol the material formed leaflets having the same m. p. The needles from acetone were employed for analysis and rotations; $[\alpha]^{24}D$ −46.3 (12.0 mg. in 1.01 cc. of chloroform, αD −0.55, *l* 1 dm.).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 83.87; H, 12.05.

22,23-Dihydrobrassicasteryl Acetate.—The acetate prepared by refluxing 100 mg. of sterol with 3 cc. acetic anhydride for half an hour crystallized from ethanol in leaflets, m. p. 144–145°; $[\alpha]^{24}D$ −45.5° (11.1 mg. in 1.01 cc. of chloroform, αD −0.50, *l* 1 dm.).

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.30; H, 11.30.

22,23-Dihydrobrassicasteryl Benzoate.—Seventy-five mg. of sterol, 300 mg. of benzoyl chloride and 5 cc. of pyridine were warmed on the water-bath for half an hour and worked up as usual. The benzoate formed stubby needles from benzene–ethanol; m. p. 161–162°: $[\alpha]^{24}D$ −19° (10.6 mg. in 1.01 cc. of chloroform, αD −0.20, *l* 1 dm.).

Anal. Calcd. for $C_{35}H_{52}O_2$: C, 83.28; H, 10.39. Found: C, 83.46; H, 10.44.

22,23-Dihydrobrassicasteryl *p*-Nitrobenzoate.—Sixty mg. of sterol was warmed on the water-bath with 500 mg. of *p*-nitrobenzoyl chloride in 5 cc. of pyridine. Due to the relative insolubility of *p*-nitrobenzoic acid, the solution diluted with water was taken up in ether and the ether successively washed with dilute hydrochloric acid, sodium carbonate, water and dried with carbonate. The crude product was treated with Norit in benzene, filtered through super-cell and crystallized from a mixture of 2 cc. of benzene and 5 cc. of ethanol, flat needles, m. p. 172° (with rapid heating) and 243–244°. With slow heating the substance sintered at 172°, gave a semi-solid melt at about 178° which gradually became green; at 243° there appeared a sudden flash of red and a clear brown melt formed; $[\alpha]^{24}D$ −11.4° (10.6 mg. in 1.01 cc. of chloroform, αD −0.12, *l* 1 dm.).

Anal. Calcd. for $C_{35}H_{51}O_4N$: C, 76.46; H, 9.35; N, 2.55. Found: C, 76.83; H, 9.36; N, 2.87.

22,23-Dihydrobrassicasteryl *m*-Dinitrobenzoate.—From 60 mg. of sterol, 300 mg. of *m*-dinitrobenzoyl chloride and 4 cc. of pyridine, worked up as in the previous compound, was obtained 49 mg. of the dinitrobenzoate recrystallized from benzene–ethanol in long straight needles, m. p. 196.5–197.5°; $[\alpha]^{24}D$ −17.1° (11.8 mg. in 1.01 cc. of chloroform, αD −0.20, *l* 1 dm.).

Anal. Calcd. for $C_{35}H_{50}O_6N_2$: C, 70.67; H, 8.47. Found: C, 70.75; H, 8.49.

Bromination of 22,23-Dihydrobrassicasterol.—To 100 mg. of 22,23-dihydrobrassicasterol in 2 cc. of ether, 1 cc. of a 10% solution of bromine in acetic acid was added; after standing no precipitate formed. Under similar conditions cholesterol gave a solid cake of the sparingly soluble dibromide.

Summary

i-Stigmasteryl and *i*-brassicasteryl methyl ether have been prepared and catalytically hydrogenated. The hydrogenated ethers have been rearranged, respectively, to 22,23-dihydrostigmasteryl and 22,23-dihydrobrassicasteryl acetate. The properties of these sterols and some of their derivatives are recorded.

NEW BRUNSWICK, N. J. RECEIVED JULY 23, 1940