round-bottomed flask fitted with a condenser. A rubber connecting tube was led from the top of the condenser into a gas washing bottle which was fitted with a sintered glass disk. To the washing bottle was added 150 ml. of anhydrous ether. While heating the reaction flask at reflux temperature, a gas was evolved which dissolved in the ether. After 4 hr. the apparatus was disassembled and dry hydrogen chloride gas was bubbled through the ethereal solution. The precipitate which formed was isolated by rapid filtration and dried *in vacuo*. A yield of 3.2 g. (48.4%) of dimethylamine hydrochloride, m.p. 168–171°, was obtained.

Addition of Dry Ice to the reaction mixture resulted in the formation of a pink organic layer which when separated yielded 7.5 g. (83%) of *o*-cresol. The *p*-bromobenzenesulfonate derivative melted at 78°. A mixture melting point determination with an authentic sample showed no depression. The dibromo derivative (m.p. 56°) likewise showed no depression in melting point when mixed with an equal portion of authentic material.

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The Solvolysis of Stigmasteryl Tosylate

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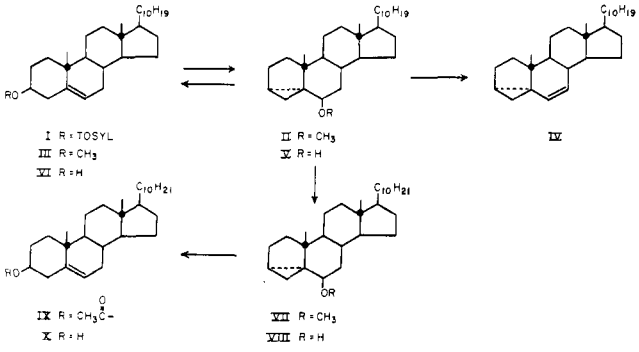
In connection with studies on the identification of an unknown house-fly sterol,[2a] a sample of high purity β-sitosterol was required. All commercial samples of the sterol showed, by gas chromatography, a major impurity[2b] varying, in content, from 10–30%. We therefore converted stigmasterol to β-sitosterol according to published procedures[3] but, again, could not obtain a preparation of satisfactory purity.



In repeating the solvolysis of stigmasteryl tosylate (I) in methanol and chromatography on alumina,[3b] the product obtained could be resolved further by rechromatography on Florisil into *i*-stigmasteryl methyl ether (II) and, as minor components, stigmasteryl methyl ether (III), stigmasterol and a hydrocarbon (IV). Riegel and co-workers[4] described a similar hydrocarbon in the *i*-cholesterol series to which they assigned the Δ^6-*i*-cholestene structure on the basis of its physical and chemical behavior. The structure 3,5-cyclo-6,22-sitostadiene has been assigned to hydrocarbon IV by analogy.[5] Since chromatography of the reaction mixture on Florisil directly gave only *i*-stigmasteryl methyl ether, stigmasteryl methyl ether, and stigmasterol, it would appear that the hydrocarbon IX is an artifact resulting from contact of II with an alumina column. Hydrogenation of *i*-stigmasteryl methyl ether followed by rearrangement with zinc acetate in boiling acetic acid gave, after one recrystallization, 22,23-dihydrostigmasteryl acetate. Hydrolysis of acetate IX gave pure 22,23-dihydrostigmasterol.

The solvolysis of stigmasteryl tosylate in acetone–water was carried out with slight modification of the procedure described for the preparation of *i*-ergosterol and *i*-dehydroergosterol.[6] Chromatography of the mixture on Florisil gave *i*-stigmasterol V and stigmasterol VI. Hydrogenation of *i*-stigmasterol V afforded i-22,23-dihydrostigmasterol (*i*-β-sitosterol) VIII. Rearrangement of this product with zinc acetate in boiling acetic acid gave 22,23-dihydrostigmasteryl acetate IX.

The over-all yield of 22,23-dihydrostigmasterol obtained *via* the *i*-sterol (70%) is better than that obtained *via* the *i*-stigmasteryl methyl ether (63%). In addition, the route *via* the *i*-sterol permits the recovery of reusable stigmasterol. The 22,23-dihydrostigmasterol obtained through either procedure gave only one peak in gas–liquid chromatography which differed from that of stigmasterol. Although there have been many examples of β-sitosterol isolated from plant sources, the purity of these materials may be open to question. The conversion of stigmasterol to β-sitosterol *via* the *i*-sterol is a convenient procedure, affording good yields and leading to a product of very high purity.

Experimental[7]

Stigmasteryl Tosylate (I).—To a solution of 15.0 g. of dry stigmasterol in 200 ml. of dry pyridine was added 18.0 g. of *p*-toluenesulfonyl chloride [freshly recrystallized from petroleum ether (b.p. 60–70°). The reaction mixture was allowed to stand overnight in the dark at room temperature and poured into 1 l. of ice-cold 5% aqueous potassium bicarbonate solution. The resulting solid tosylate was collected by filtration, washed with water, and dried in a vacuum oven at 60°. Recrystallization from dry acetone gave (I) as colorless crystals, m.p. 147–148°, $[\alpha]_D$ −49°.

***i*-Stigmasteryl Methyl Ether** (II).—To a refluxing solution of 8.0 g. of fused potassium acetate in 400 ml. of dry methanol was added 8.0 g. of finely pulverized stigmasteryl tosylate. The mixture was refluxed for 3 hr. After removal of the solvent *in vacuo*, the residue was extracted with ether, washed with water, 5% aqueous potassium bicarbonate, water, dried over potassium carbonate, and evaporated *in vacuo* leaving 6.0 g. of oily material. This oily residue was dissolved in petroleum ether, adsorbed on a

(1) Deceased, May 31, 1962.

(2) (a) Dr. William Robbins and staff, Insect Physiology Laboratory, ARS, U. S. Department of Agriculture, Beltsville, Md.; (b) The nature of this impurity is the subject of a forthcoming publication by M. J. Thompson, S. J. Louloudes, W. Robbins, J. A. Waters, J. A. Steele, and E. Mosettig.

(3) (a) S. Bernstein and E. S. Wallis, *J. Org. Chem.*, **2**, 341 (1938); (b) E. Fernholz and W. L. Ruigh, *J. Am. Chem. Soc.*, **62**, 3346 (1940); (c) B. Riegel, E. W. Meyer, and J. Beiswanger, *ibid.*, **65**, 325 (1943).

(4) B. Riegel, G. P. Hager, and B. L. Zenity, *ibid.*, **68**, 2562 (1946).

(5) The ultraviolet spectrum of IX showed only end absorption, thus ruling out a 3,5-diene structure.

(6) W. R. Nes and J. A. Steele, *J. Org. Chem.*, **22**, 1457 (1957).

(7) All melting points were determined on a Kofler block and are uncorrected. Analyses are by the Analytical Service Laboratory of this Institute under the direction of Mr. Harold G. McCann. Rotations were taken in 1% chloroform solutions at 20° by Mrs. E. Peake. The infrared spectra were determined on a Perkin–Elmer double beam spectrophotometer (Model 21) in carbon disulfide by Mr. H. K. Miller with the assistance of Mrs. C. I. Wright. The gas chromatographic analyses were carried out on a Barber–Colman gas chromatograph with SE-30 support. "Woelm" neutral alumina, activity grade I, and Florisil (60–100 mesh) purchased from the Floridin Co., Tallahassee, Fla. were used for chromatography. Solvents were purified, distilled, and dried with the help of Mr. J. Lyons, with the exception of ethanol and chloroform which were the usual commercial grades of reagent material.

column of 150 g. of Florisil and eluted as follows: 1–15, 50-ml. fractions of petroleum ether; 16–25, 125-ml. fractions of petroleum ether; 26–36, 125-ml. fractions of petroleum ether–benzene (10:1); 37–38, 250-ml. fractions of ethanol.

Fractions 5–19 yielded 4.9 g. of II as a colorless oil. Crystallization from acetone–water gave 4.5 g. of i-stigmasteryl methyl ether (II) as colorless prisms, m.p. 58–59°, $[\alpha]_D$ +33.7°; $\lambda_{max}^{CS_2}$ 9.12 μ and 10.34 μ. Fractions 20–25 gave 0.10 g. of oil which was not investigated further. Fractions 28–38 gave 0.60 g. of crystalline III which was recrystallized from acetone giving 0.50 g. of stigmasteryl methyl ether (III), m.p. 121–122°. Three recrystallizations from acetone afforded (III) as colorless crystals, m.p. 123.5–124° (lit.,[8] m.p. 122°), $[\alpha]_D$ −56°; $\lambda_{max}^{CS_2}$ 9.1 μ and 10.3 μ.

In a separate experiment a hydrocarbon (IV) was isolated by chromatography of the reaction mixture on alumina and rechromatography on Florisil. This hydrocarbon had the following properties: m.p. 81.5–82.5°, $[\alpha]_D$ −81°; $\lambda_{max}^{CS_2}$ 3.34 μ, 6.1 μ, and 10.3 μ.

Anal. Calcd. for $C_{29}H_{46}$: C, 88.25; H, 11.75. Found: C, 88.22; H, 11.51.

i-Stigmasteryl methyl ether, stigmasteryl methyl ether, and stigmasterol were also isolated from this chromatography.

i-Stigmasterol (V).—A solution of 5.0 g. of stigmasteryl tosylate and 3.2 g. of potassium bicarbonate in 2 l. of acetone and 200 ml. of water was refluxed for 6 hr., concentrated to volume of 700 ml., diluted with water, and extracted with ether. The ether extract was washed with water, dried over potassium carbonate, and evaporated to dryness under reduced pressure giving 3.9 g. of colorless oil which was placed on a column of 150 g. of Florisil. The following fractions were obtained: 1–5, 250-ml. fractions of petroleum ether–benzene (10:1.5); 6–14, 250-ml. fractions of petroleum ether–benzene (2:3); 15–21, 250-ml. fractions of benzene–chloroform (1:1); 22–23, 250-ml. fractions of chloroform.

Fractions 6–13 gave 3.0 g. of *i*-stigmasterol (V) as a colorless oil. Crystallization from acetone–water gave 2.9 g. of V as colorless crystals melting at 48–50°; analytical sample from acetone–water, m.p. 50–52°, $[\alpha]_D$ +24°; $\lambda_{max}^{CS_2}$ 2.79 μ and 10.3 μ.

Anal. Calcd. for $C_{29}H_{48}O$; C, 84.40; H, 11.72. Found: C, 84.19; H, 11.81.

Fractions 15–21 gave 0.50 g. of crude stigmasterol (VI). Recrystallization from acetone–methanol gave 0.49 g. of stigmasterol (V), m.p. 170–171°.

i-22,23-Dihydrostigmasterol (i-β-Sitosterol) (VIII).—A solution of 2.8 g. of V in 75 ml. of ethyl acetate was shaken in a hydrogen atmosphere with 0.78 g. of palladium black. One mole of hydrogen was absorbed in 42 min., and no further uptake of hydrogen was observed in an additional 30 min. The oily *i*-22,23-dihydrostigmasterol (VIII) was crystallized from acetone–water giving (VIII) as colorless crystals, m.p. 78–79°, $[\alpha]_D$ +47°; $\lambda_{max}^{CS_2}$ 2.79 μ.

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 83.83; H, 12.20.

22,23-Dihydrostigmasteryl Acetate (IX).—*i*-Stigmasteryl methyl ether (II) (4.2 g.) was hydrogenated under conditions given above for the hydrogenation of *i*-stigmasterol (V), giving oily 22,23-dihydro-*i*-stigmasteryl methyl ether (VII). The crude product was refluxed with magnetic stirring for 6 hr. in 210 ml. of acetic acid containing 8.8 g. of freshly fused zinc acetate. The mixture was diluted with water, cooled to 0°, and filtered, giving 4.3 g. of 22,23-dihydro-stigmasteryl acetate (IX) as colorless crystals, m.p. 117–120°. Recrystallization from acetone–methanol gave 4.0 g. of IX as colorless crystals, m.p. 121–122°, $[\alpha]_D$ −37.5°; $\lambda_{max}^{CS_2}$ 5.75 μ.

Treatment of 2.5 g. of *i*-22,23-dihydrostigmasterol (VIII) with 5.0 g. of zinc acetate in boiling acetic acid as described above for VII gave, after one crystallization from acetone–methanol, 2.4 g. of 22,23-dihydrostigmasteryl acetate (IX) as colorless crystals, m.p. 121–122°, $[\alpha]_D$ −36.8°; $\lambda_{max}^{CS_2}$ 5.75 μ.

22,23-Dihydrostigmasterol (β-Sitosterol) (X).—Hydrolysis of 3.5 g. of 22,23-dihydrostigmasteryl acetate (IX) [obtained *via* *i*-stigmasteryl methyl ether (II) with 5% methanolic potassium hydroxide] gave 3.2 g. of 22,23-dihydrostigmasterol (X) as colorless crystals, m.p. 137–137.5°. Recrystallization from acetone–methanol afforded (X) as colorless crystals, m.p. 137.5–138°, $[\alpha]_D$ −33°, $\lambda_{max}^{CS_2}$ 2.79 μ.

22,23-dihydrostigmasteryl acetate (IX) [obtained *via* *i*-β-sitosterol (VIII)] was hydrolyzed with methanolic potassium hydroxide giving 22,23-dihydrostigmasterol (X) as colorless crystals, m.p. 139–140°, $[\alpha]_D$ −33°; $\lambda_{max}^{CS_2}$ 2.79 μ.

Reacetylation of X gave an acetate with physical constants identical with those described above for IX.

(8) W. von Stall, *Z. Physiol. Chem.*, **207**, 147 (1932).

An Addition Reaction to a Hindered Ketone

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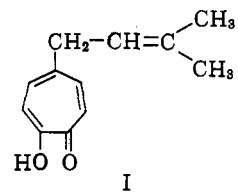
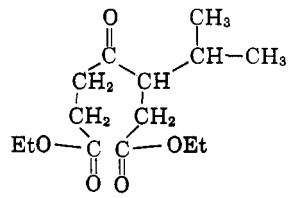
In the course of investigating a proposed synthesis of nootkatin, I, it became necessary to carry out an addition reaction to the ketone function of diethyl β-isopropyl-γ-ketopimelate, II. The keto diester, II, was

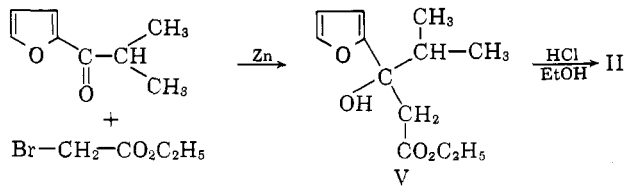


I



II

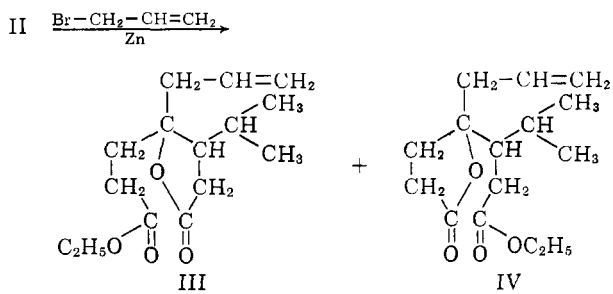
synthesized *via* a modification of the procedure of Marckwald[1] for the preparation of γ-keto pimelic esters and is outlined below:



One interesting feature of this sequence is the Reformatsky reaction which proceeds in 95% yield.

The ketone, II, exhibited particular reluctance to undergo addition reactions. Thus, Grignard addition and reaction with sodium acetylide or lithium acetylide derivatives either do not proceed or can be forced only in poor yield. Surprisingly, even the normally very reactive allylmagnesium bromide adds in poor yield. This low reactivity is not completely unexpected in view of Newman's "Rule of Six."[2]

Finally, a reaction was found that gave acceptable



III IV