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.

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An Addition Reaction to a Hindered Ketone

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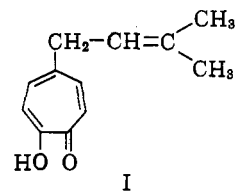
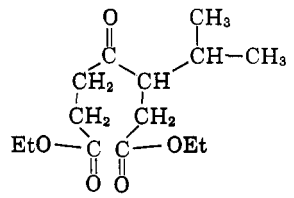
In the course of investigating a proposed synthesis of nootkatin, I, it became necessary to carry out an addition reaction to the ketone function of diethyl β-isopropyl-γ-ketopimelate, II. The keto diester, II, was

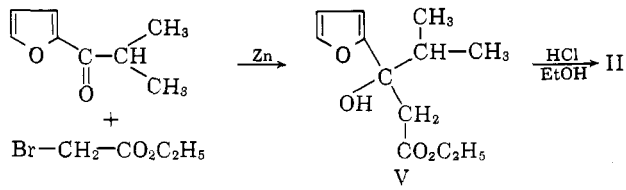


I



II

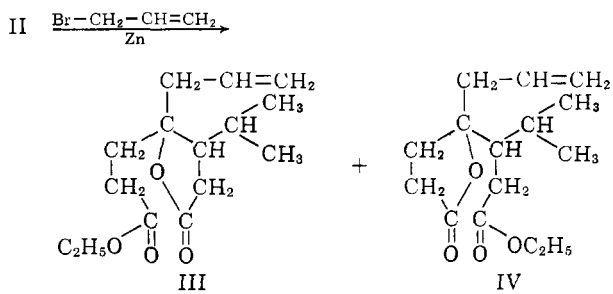
synthesized *via* a modification of the procedure of Marckwald[1] for the preparation of γ-keto pimelic esters and is outlined below:



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

yields (40%) of addition to the ketone affording an intermediate suitable for use in elaborating the "isopentenyl" side chain of nootkatin. This reaction involved treating the ketone, II, with allyl bromide and zinc in a mixture of benzene and ether as solvent, to afford a mixture of the lactones III and IV.

This procedure and result is unique and we are reporting it because of its striking success in contrast to the more usual procedures tried for effecting addition to this particularly hindered ketone.

Experimental[3]

Reformatsky Addition to Isopropyl 2-Furyl ketone.—To 50 g. of zinc (previously washed with dilute hydrochloric acid, water, acetone, and dried) and a few crystals of iodine in 200 ml. of dry benzene and 200 ml. of dry ether were added 13.8 g. of isopropyl 2-furyl ketone[4] and 13.5 ml. of ethyl bromoacetate. The mixture was heated to reflux and five additions of 50 g. of zinc with a crystal of iodine were made at 4–5-min. intervals. The reaction was stirred throughout the additions.

The reaction was cooled, made homogeneous by adding glacial acetic acid and then decanted from the zinc into water. This mixture was acidified with acetic acid, the benzene layer separated, and the aqueous layer back extracted with ether. The combined organic layers were washed with dilute ammonia, water, dried over sodium sulfate, and distilled. This gave 21.2 g. (95%) of the Reformatsky product, V, b.p. 75–80°/.15 mm.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 64.07; H, 8.20.

Diethyl β-Isopropyl-γ-keto Pimelate, II.—Ten grams of ethyl 3-furyl-3-isopropyl-3-hydroxypropionate, V, was dissolved in 50 ml. of 95% ethanol. Anhydrous hydrogen chloride from a compressed gas cylinder was passed into the reaction mixture until the reaction mixture heated to boiling. It was allowed to boil 15 min. with continued introduction of hydrogen chloride. This was repeated and the reaction mixture then allowed to stand overnight.

The reaction mixture was concentrated *in vacuo*, the residue taken up in chloroform, washed with dilute sodium carbonate solution, water, dried over sodium sulfate, and distilled. This gave 9.9 g. (82%) of II, b.p. 120°/0.40 mm.

Anal. Calcd. for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 62.05; H, 8.91.

Preparation of III and IV. Diethyl β-isopropyl-p-ketopimelate 11, (5.0 g.) was mixed with 4 ml. of allyl bromide, 30 ml. of dry ether, and 20 ml. of dry benzene. The reaction mixture was refluxed 18 hr. and catalyzed by periodic additions of iodine. In one run, a small magnesium shaving was found to aid initiating the reaction. At the end of this time, all the zinc had reacted and the solution was yellow in color.

The reaction mixture was hydrolyzed using ice and dilute sulfuric acid. The organic layer was separated and the aqueous layer extracted successively with three 25-ml. portions of ether. The combined extracts were dried over sodium sulfate and distillled giving 2.0 g. (40%) of a mixture of the lactones III and IV, b.p. 92–100°/1 mm. The infrared spectrum of this material showed among other absorptions bands at 5.60 μ (1785 cm.$^{-1}$) for the lactone carbonyl and 5.75 μ (1740 cm.$^{-1}$) for the ester carbonyl. The n.m.r. spectrum of this material showed a typical vinyl group multiplet and the relative area of the vinyl protons to the $-CH_2-$ protons of the ethoxy grouping was 3:2.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.25; H, 8.95. Found: C, 67.40; H, 9.01.

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Lactam Complexes of Bromine–Hydrogen Bromide

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Tafel and Wassmuth discovered that a chloroform solution of pyrrolidone-2 yielded a brick red solid on treatment with bromine.[2] This solid had the over-all elemental composition $C_4H_7NO{\cdot}Br$, corresponding to an addition complex of one atom of bromine to one molecule of pyrrolidone-2. Evidence was presented that the material was actually a mixture of the addition compound A, $(C_4H_7NO)_2{\cdot}Br_2$, and the hydrobromide B, $C_4H_7NO{\cdot}HBr$, the hydrogen bromide arising by substitution to form N-bromopyrrolidone-2 and hydrogen bromide.

Products A and B were proposed to co-crystallize from solution as the red solid, while N-bromopyrrolidone-2 remained in solution.

Their complex was unstable, decreasing in available bromine content on recrystallization from 35 to 38% until, after many recrystallizations from chloroform, a stable product was obtained with an available bromine content of between 31 and 32.5%.

Repetition of the above work yielded a product which was in full agreement with the published data. The complex had poor shelf stability, however, constantly decreasing in available bromine content until a level of 30–32% was reached, at which point no further decrease was noticed. This behavior prompted further work on our part to see whether the stable complex could be directly obtained.

It was thought that stability might be due to the formation of Br_3^- complexes, as is likely in many other complexes of halogens and hydrohalides with organic compounds.[3-7]

In accordance with this, the preparation was carried out at higher temperatures in order to promote the substitution to the point where products A and B would be formed in equal molar quantities. At 60–65° the reaction of bromine and pyrrolidone-2 in chloroform yielded beautiful orange crystals containing 30.9% free bromine. This material showed no decrease in free bromine titer over a five-month storage test at ambient temperatures. A carefully purified sample on analysis contained 31.60% available bromine, 14.18% bromine, and corresponded to the empirical formula $(C_4H_7NO)_3{\cdot}HBr{\cdot}Br_2$ (C). The purified sample melted at 88.5–90.5°.

We then attempted to form C from the compounds pyrrolidone-2, hydrogen bromide, and bromine in the respective molar ratios 3:1:1. This succeeded in

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