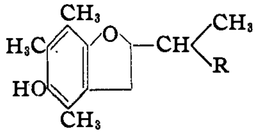
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

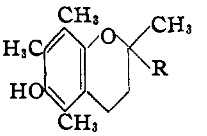
Vitamin E. XLVI.[1] Conversion of 4,6,7-Trimethylcoumaran-3-one into Some Homologs of 2-Isopropyl-4,6,7-trimethyl-5-hydroxycoumaran

BY LEE IRVIN SMITH AND GERALD A. BOYACK[2]

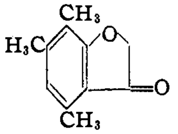
2-(2'-Alkyl)-4,6,7-trimethyl-5-hydroxycoumarans, I, are of interest because these substances are isomeric with, and closely related to, the 2,2-dialkyl-5,7,8-trimethyl-6-hydroxychromans, the structural type of the tocopherols, for example, α-tocopherol, II.



Ia, R = CH_3
b, R = n-C_5H_{11}
c, R = $C_{16}H_{31}$ (4,8,12-trimethyltridecyl)



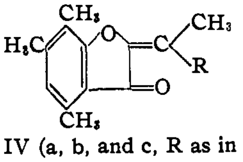
II (R as in Ic)



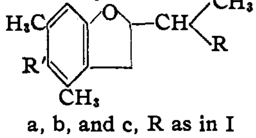
III

In an earlier paper[3] a method for the synthesis of 2-isopropyl-4,6,7-trimethyl-5-hydroxycoumaran (Ia) was described in which the last step involved introduction of the hydroxyl group by replacement of a bromine atom at position 5. Since the steps in this synthesis involved rather accessible intermediates and simple reactions, it was of interest to investigate the generality of the method for synthesis of higher homologs of I, with a view of ultimately synthesizing the coumaran Ic isomeric with α-tocopherol II. The model experiments were successful, and led to the synthesis of Ib but when applied to the synthesis of Ic, the synthesis failed because the last step was unsuccessful.

Methyl n-amyl ketone was condensed with 4,6,7-trimethylcoumaran-3-one, III, to give 2-(2'-heptylidene)-4,6,7-trimethylcoumaran-3-one, IVb, which was catalytically reduced in the presence of Raney nickel to 2-(2'-heptyl)-4,6,7-trimethylcoumaran Vb. The coumaran Vb was converted to the bromo compound VIb by bromination, and the bromo compound was converted into the Grignard reagent VIIb, which was oxidized to the bromomagnesium phenolate VIIIb. The salt, when hydrolyzed, gave the coumaran, Ib. Although the synthesis was successful, serious difficulties were encountered. Thus, neither Vb nor VIb could be obtained in pure form. Hydrogenation of IVb under a variety of conditions did not lead to a product from which pure Vb could be isolated. The crude bromo compound VIb, prepared from impure Vb, contained approximately 4% of halogen which was precipitated by action of alcoholic silver nitrate, and which was not removed by action of activated alumina or of hydrogen in the presence of a palladium catalyst.



IV (a, b, and c, R as in I)



a, b, and c, R as in I
V, R' = H
VI, R' = Br
VII, R' = MgBr
VIII, R' = OMgBr

This route to the coumaran Ib having proved successful, attention was turned to the synthesis of Ic. The coumaranone III condensed with 6,10,14-trimethylpentadecanone-2 in the presence of zinc chloride to produce IVc. Catalytic reduction of IVc failed to yield a product from which pure Vc could be isolated. However bromination of the impure Vc gave a product which when chromatographed on alumina, yielded pure VIc. When the bromo compound VIc was subjected successively to the action of magnesium and oxygen, the product was a red oil from which no Ic could be isolated.

The ultraviolet absorption spectra of several of these compounds are given in Figs. 1, 2 and 3. The spectra of the coumaran-3-ones IVa, b and c (Fig. 1) are very similar; likewise the spectra of the bromocoumarans VIa and c (Fig. 2) are very similar. The spectra of the hydroxycoumarans Ia and b are very similar to that of 2,4,6,7-tetramethyl-5-hydroxycoumaran.[4]

Experimental Part[5]

2,3,5-Trimethylphenoxyacetic Acid.—The following modification of the procedure previously reported[3] was found to give higher yields and more uniform results. A mixture of 2,3,5-trimethylphenol (68 g.), potassium carbonate (69 g.), ethyl bromoacetate (92 g.), and acetone (150 cc.) was refluxed for seventy-two hours—a necessary period of time if good yields are to be obtained. Water (200 cc.) was added, acetone was removed by distillation, and the oily suspension was extracted with ether. The solvent was removed and the oily residue was mixed with a solution of sodium (10 g.) in ethanol (200 cc., 95%—not dry ethanol, as specified in the earlier report). When the vigorous reaction subsided, more ethanol (300 cc., 95%) was added, the mixture was heated for five minutes, and the solid was removed. Hydrochloric acid was added slowly to a stirred suspension of the solid

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[1] XLV, THIS JOURNAL, 66, 1526 (1944).

[2] Abstracted from a thesis by Gerald A. Boyack presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, September, 1947.

[3] Smith, King, Guss and Nichols, THIS JOURNAL, 65, 1594 (1943).

[4] Webb, Smith, Bastedo, Ungnade, Prichard, Hoehn, Wawzonek, Opie and Austin, *J. Org. Chem.*, 4, 389 (1939).

[5] Microanalyses by R. Amidon, Mrs. R. A. Barnes, J. Kerns, P. Morgan and S. Sundet.

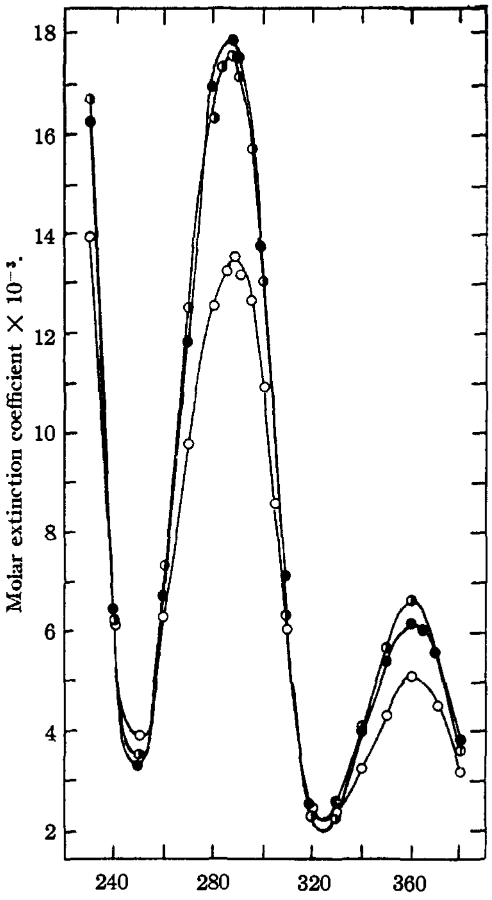

Fig. 1.—Absorption spectra: ○, 2-(6',10',14'-trimethyl-2'-pentadecylidene)-4,6,7-trimethylcoumaran-3-one: ◑, 2-(2'-heptyl)-4,6,7-trimethylcoumaran-3-one: ●, 2-isopropyl-4,6,7-trimethylcoumaran-3-one: solvent, 95% ethanol.[3]

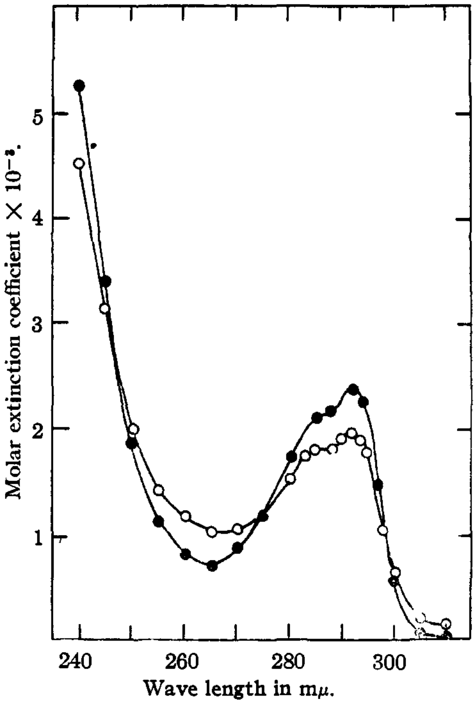

Fig. 2.—Absorption spectra: ○, 2-(6',10',14'-trimethyl-2' - pentadecyl) - 4,6,7 - trimethyl - 5 - bromo - coumaran: ●, 2-isopropyl-4,6,7-trimethyl-5-bromocoumaran[3]; solvent, absolute ethanol.

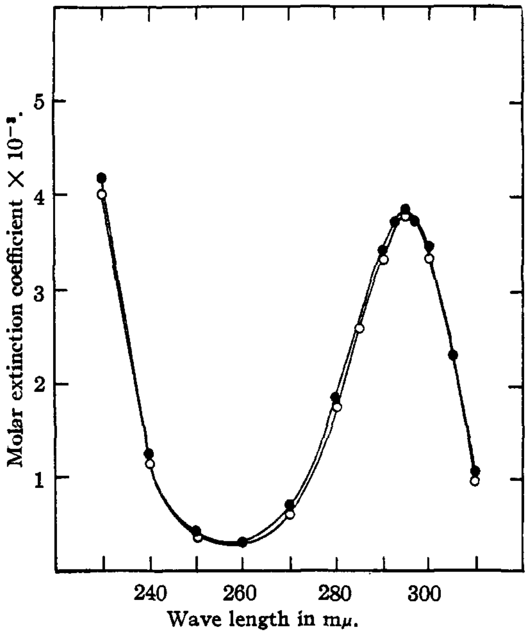

Fig. 3.—Absorption spectra: ○, 2-(2'-heptyl)-4,6,7-trimethyl-5-hydroxycoumaran; ●, 2-isopropyl-4,6,7-trimethyl-5-hydroxycoumaran[3]; solvent, 95% ethanol.

in warm water, and then the suspension was cooled and the solid (m. p. 129–131°) was removed and crystallized from benzene, when it melted at 130° and weighed 75 g. The alcoholic mother liquors were refluxed for ten hours, alcohol was removed by distillation, and water was added. The cooled solution was extracted with ether (extract discarded) and acidified with hydrochloric acid. The solid was removed and crystallized from benzene, when it melted at 127° and weighed 9.3 g. The total yield, 84.3 g., represents 86%.

4,6,7-Trimethylcoumaran-3-one, III.—The above phenoxyacetic acid (20 g.) was added, with shaking, to sulfuric acid at 90°. The cherry-red solution was heated for ten minutes at 90° and then poured into water (7000 cc.). The solid was removed, washed well with water, and the moist material was recrystallized from methanol, when it weighed 13.4 g. (76%) and melted at 89–91°. This procedure is superior to that previously reported,[3] although it must be followed exactly, otherwise the results are erratic and frequently the sole product will be an impure material of unknown structure, melting at 155–175°.

2-(2'-Heptylidene)-4,6,7-trimethylcoumaran-3-one, IVb.—A mixture of methyl *n*-amyl ketone[6] (44.1 g.) and zinc chloride (100 g., powdered, freshly fused) was stirred and heated on a steam-bath while a solution of III (13.6 g.) in methyl *n*-amyl ketone (44.1 g.) was slowly added (five hours), after which the mixture was heated and stirred for twenty-four hours. The mixture was poured into ice and water (500 g.) and the emulsion was filtered. The layers were separated and the aqueous

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(6) Marvel and Johnson, "Org. Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 351.

layer was extracted with ether. The combined organic solutions were washed with water and dried over sodium sulfate, and the solvent was removed. Excess ketone was removed by heating the residue at 100° under 25 mm. pressure, and the residual material was distilled molecularly from a pot-still under 0.0001 mm. With the bath temperature at 130–160°, a yellow oil (14.8 g., n^{25}D 1.5576) distilled. Redistilled twice under the same conditions, the oil weighed 9.65 g. (46%), had n^{25}D 1.5614, and gave the U. V. spectrum shown in Fig. 1.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.36; H, 8.88. Found: C, 79.61; H, 8.62.

2-Isobutylidene-4,6,7-trimethylcoumaran-3-one, melting at 81.5–82.5° after crystallization three times from petroleum ether (b. p. 40–70°), was prepared in the same way, substituting butanone-2 for methyl *n*-amyl ketone.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88. Found: C, 78.43; H, 7.79.

2-(2′-Heptyl)-4,6,7-trimethylcoumaran Vb.—A solution of the coumarone IVb (3.6 g.) in dry ethanol (4 cc.) was subjected to the action of hydrogen in the presence of Raney nickel catalyst at 225° for four hours, under an initial hydrogen pressure of 3500 lb. The catalyst and the solvent were removed, and the residue was distilled molecularly from a pot-still under 0.001 mm. at a bath temperature of 75–80°. The pale yellow oil weighed 2.78 g. and had n^{25}D 1.5045. It was still quite impure, but was nevertheless used for the next step.

Anal. Calcd. for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 79.32; H, 10.19.

No better results were obtained when the reduction was carried out (a) as above, but at 250° for four and one-half hours; (b) as above, but at 200° for four hours and an initial hydrogen pressure of 3000 lb.; (c) as above, at 225° for five hours and an initial pressure of 3600 lb.; (d) as above, but in the presence of a small amount of sodium hydroxide; (e) using copper chromium oxide catalyst; (f) by the Clemmensen method. Neither fractional distillation nor chromatography was effective in producing pure Vb from any of these products.

2-(2′-Heptyl)-4,6,7-trimethyl-5-bromocoumaran VIb.—The above impure Vb (2.8 g.) was dissolved in chloroform (5 cc.) and brominated by slow addition of a solution of bromine (1.9 g.) in chloroform (5 cc.). The solution remained colorless until nearly all of the bromine had been added; there was a copious evolution of hydrogen bromide. The solvent was removed and the residue was distilled in a pot-still at 120–135° bath temperature and under 0.001 mm. The distillate (2.73 g., active Br, 4.0%) was dissolved in benzene (10 cc., thiophene-free) and shaken with hydrogen under 35 lb. in the presence of a palladium–barium carbonate catalyst for three and one-half hours. After removal of the catalyst and solvent, the residue was dissolved in petroleum ether (20 cc.) and the solution was passed through a 5 × 0.5-cm. column of alumina (Brockman). Additional petroleum ether (20 cc.) was passed through the column, the solvent was removed from the combined solutions and the residue was distilled as before. The yellow oil distilled at a bath temperature of 100–110°, weighed 1.7 g., had n^{25}D 1.5334, and contained 2.3% of active bromine. It was not analyzed, but was used directly in the next step.

2-(2′-Heptyl)-4,6,7-trimethyl-5-hydroxycoumaran, Ib.—The above impure bromo compound (1.68 g.) and cyclohexyl bromide (1.61 g.) were dissolved in ether (10 cc.). A portion (2.5 cc.) of a solution of ethyl bromide (1.62 g.) in dry ether (10 cc.) was added to magnesium (1.08 g.) covered with boiling ether, and as the magnesium dissolved, the solution containing VIb, together with more (5 cc.) of the solution of ethyl bromide, were added over a period of two and one-half hours, with stirring. The remainder of the solution of ethyl bromide was then slowly added, and the whole was refluxed for two hours. The mixture was then cooled to −15° and dry oxygen was bubbled through it for two hours. The green solid was decomposed by addition of hydrochloric acid, the ether layer was removed, washed with water and dried. The solvent was removed and the residue was molecularly distilled from a pot-still under 0.001 mm. At 120° (bath) a yellow oil (0.43 g.) distilled; at 150° a waxy solid (0.40 g.) sublimed. The solid was dissolved in petroleum ether and the solution was cooled to −70°. The solid was removed by centrifugation and crystallized twice from petroleum ether. It was then dissolved in methanol and water was added slowly; the dark oil was removed by centrifugation and then addition of more water brought about deposition of a solid. This was removed and crystallized from petroleum ether, when it melted at 72–75°. The Folin–Denis test was strongly positive. The U. V. spectrum is shown in Fig. 3.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.39; H, 10.51.

6,10,14-Trimethylpentadecanone-2.—Phytol (24 g.) in purified ethyl acetate[7] (200 cc.) was ozonized (4% O_3 in O_2) at −5° and the ozonide was reductively decomposed. The ketone (14.4 g., 67%) boiled at 120–122° (1 mm.) and had n^{25}D 1.4441.[8]

2-(6′,10′,14′-Trimethyl-2′-pentadecylidene)-4,6,7-trimethylcoumaran-3-one IVc.—The coumaranone III (1.81 g.), the above ketone (27.6 g.) and zinc chloride (10 g. freshly fused and powdered) were heated on the steam-bath for twenty-four hours, with stirring during the first hour. The mixture was dissolved in chloroform, the solution was washed with water, dried over sodium sulfate, and the solvent was removed. Excess ketone was removed by distillation from a pot-still at 150° (bath temperature) under a pressure of 0.1 mm. The recovered ketone (19.6 g.) was heated with more III (1.29 g.) and zinc chloride (10 g.) and the mixture was processed as before. Again the recovered ketone (16.1 g.) was heated with III (1.06 g.) and zinc chloride and the mixture was similarly processed. The dark oils remaining after removal of excess ketone were combined and distilled and redistilled from a pot-still under 0.001 mm. The yellow oil distilling at 175–185° (bath temperature) weighed 3.5 g. (40%) and had n^{25}D 1.5140. The U. V. spectrum is shown in Fig. 1.

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.33; H, 11.14.

2-(6′,10′,14′-Trimethyl-2′-pentadecyl)-4,6,7-trimethylcoumaran Vc.—The above coumaranone IVc (1 g.) in ethanol was subjected to the action of hydrogen for four hours in the presence of Raney nickel catalyst at 250° under an initial hydrogen pressure of 3600 lb. The catalyst was removed by centrifugation, the solvent was removed by distillation, and the residue was distilled from a pot-still under 0.001 mm. at a bath temperature of 160–190°. The pale yellow oil weighed 0.85 g. and had n^{25}D 1.5036; analysis showed that it was not pure Vc, though it was sufficiently pure for use in the next step.

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 81.66; H, 12.41.

The hydrogenation did not always proceed uniformly; in an experiment duplicating the one described above, the product had n^{25}D 1.4886 and also was not pure Vc.

2-(6′,10′,14′-Trimethyl-2′-pentadecyl)-4,6,7-trimethyl-5-bromocoumaran VIc.—The above impure coumaran (0.72 g.) in carbon tetrachloride (10 cc.) was brominated by dropwise addition of a solution of bromine (0.312 g.) in carbon tetrachloride (2 cc.). The solution remained colorless until about two-thirds of the bromine was added, after which it became orange. The solution was washed successively with aqueous sodium bicarbonate and aqueous sodium bisulfite, dried, and the solvent was removed. The residue was distilled from a pot-still under 0.001 mm. The yellow oil distilling at 165–210° (bath temperature) weighed 0.72 g. It was dissolved in petroleum ether (30 cc., b. p. 40–70°) and passed through a 20 × 0.5-cm. column filled with alumina (Brockmann). Additional petroleum ether (30 cc.) was passed through

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[7] Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 364.

[8] Smith and Sprung, THIS JOURNAL, 65, 1271 (1943).

the column. The solvent was removed from the combined solutions and the residue was distilled under 0.001 mm. as before. It weighed 0.42 g., had n^{25}D 1,5059, and gave the U. V, spectrum shown in Fig. 2.

Anal. Calcd. for $C_{29}H_{49}OBr$: C, 70.56; H, 10.00. Found: C, 70.54; H, 9.83.

The bromocoumaran VIc (0.33 g.) and cyclohexyl bromide (0.22 g.) in ether (10 cc.) was stirred with magnesium (0.163 g.) while the magnesium was reacting with ethyl bromide (0.21 g.) in ether (10 cc.). The procedure and processing of the reaction mixture were carried out as described above in the preparation of Ib. The crude product was distilled from a pot-still at 170-200° (bath temperature) under 0.001 mm.; the orange distillate weighed 0.25 g. It gave a positive Folin-Denis test, and contained a trace of halogen. A solution of the oil in petroleum ether (30 cc.) was passed through a column of alumina (Brockmann); the column was washed with additional petroleum ether and the combined organic solutions were evaporated. The residue was distilled as before. The distillate (about 0.1 g.) gave an absorption spectrum in the U. V. which in no way resembled those of Ia and Ib. The column of alumina was eluted with ethanol, but very little material was present in the eluate and this material, likewise, was not a hydroxycoumaran.

Summary

1. Three ketones—methyl ethyl ketone, methyl *n*-amyl ketone, and "phytol" ketone—have been condensed with 4,6,7-trimethylcoumaran-3-one (III) to give the 2-alkylidene coumarones.
2. The alkylidene coumarones from the last two ketones were reduced to the coumarans, and the latter were brominated in the 5-position.
3. The 5-bromocoumaran thus obtained from methyl *n*-amyl ketone was converted to a Grignard reagent, and the latter was oxidized, producing the 5-hydroxycoumaran. Conversion of the 5-bromocoumaran derived from phytol ketone into the analogous 5-hydroxycoumaran was not achieved.
4. Curves are given showing the absorption spectra in the ultraviolet of several of the intermediates and final products.

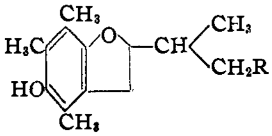
MINNEAPOLIS 14, MINNESOTA RECEIVED APRIL 2, 1948

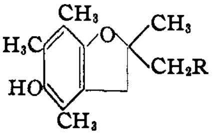
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Vitamin E. XLVII.[1] The Coumaran Isomer of α-Tocopherol

BY LEE IRVIN SMITH AND GERALD A. BOYACK[2]

Early in the history of the work upon the structure and synthesis of α-tocopherol, there was some discussion as to whether the vitamin was best represented as a coumaran, I, or as the isomeric chroman, II.[3]



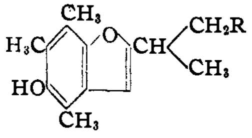


I, R = $C_{16}H_{31}$ = 3,7,11-trimethyldodecyl. II, R = $C_{16}H_{31}$

Although the structure was definitely settled in favor of II,[4] a synthesis of the isomeric coumaran I would be of some interest, in view of the vitamin E activity of many compounds related to II. This paper describes a successful synthesis of I and one of its homologs X (R = n-$C_{13}H_{27}$). The coumaran I was obtained as a yellow oil and, although it showed vitamin E activity, the activity was only about 5% of that of α-tocopherol.

The synthetic route to I involved the sequence of compounds III to VII (R as in formula I): the coumaron VII was then catalytically reduced to I.

III, $RCH_2C(CH_3)=CHCH_2OH$
IV, $RCH_2CH(CH_3)CH_2CH_2OH$
V, $RCH_2CH(CH_3)CH=CH_2$
VI, $RCH_2CH(CH_3)R'$
VIa, R' = COOH
VIb, R' = COCl
VIc, R' = $COCH_3$
VId, R' = $COCH_2COCH_3$



VII

Phytol (III) was catalytically reduced to dihydrophytol (IV) and the latter was converted to the stearate. When the crude stearate was pyrolyzed, phytene-1 (V) resulted. Although phytene-1 had been reported twice previously[5] no proof that the double bond is terminal has ever been given. The phytene-1 prepared in the present work had the proper iodine number and its reaction with perbenzoic acid was very slow—much slower than the rate with which oleic acid reacts, and slower even than the reaction of undecylene-1, indicating in this phytene the absence of a disubstituted double bond. Finally, ozonolysis of phytene-1 followed by oxidative decomposition of the ozonide, led to apophytoic acid VIa. The acid was converted into the acid chloride VIb and from this the methyl ketone VIc was prepared by action of dimethylcadmium.[6] A solid derivative of the methyl ketone VIc was not obtained; both the

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(1) Smith and Boyack, XLVI, THIS JOURNAL, **70**, 2687 (1948).

(2) Abstracted from a thesis by Gerald A. Boyack presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, September, 1947.

(3) (a) Bergel, Todd and Work, *J. Chem. Soc.*, 253 (1938); (b) Karrer, Salomon and Fritzsche, *Helv. Chim. Acta*, **21**, 309 (1938); (c) Karrer, Fritzsche, Ringier and Salomon, *ibid.*, **21**, 520 (1938); (d) Fernholz, THIS JOURNAL, **60**, 700 (1938); (e) John, *Z. physiol. Chem.*, **252**, 222 (1938).

(4) (a) John, Dietzel, Günther and Emte, *Naturwiss.*, **26**, 366 (1938); (b) Karrer, Escher, Fritsche, Keller, Ringier and Salomon, *Helv. Chim. Acta*, **21**, 939 (1938); (c) Smith, Ungnade and Prichard, *Science*, **88**, 37 (1938); (d) Tishler and Wendler, THIS JOURNAL, **63**, 1532 (1941); (e) Smith, Ruoff and Wawzonek, *J. Org. Chem.*, **6**, 236 (1941); (f) Smith and King, THIS JOURNAL, **65**, 441 (1943).

(5) (a) Willstätter and Hocheder, *Ann.*, **354**, 255 (1907); (b) Willstätter, Mayer and Huni, *ibid.*, **378**, 91 (1911); (c) Karrer, Helfenstein and Widmer, *Helv. Chim. Acta*, **11**, 1201 (1928).

(6) Cason and Prout. THIS JOURNAL, **66**, 46 (1944).