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Synthetic Studies of α-Tocopherol. I. Synthesis of α-Tocopheryl Acetate

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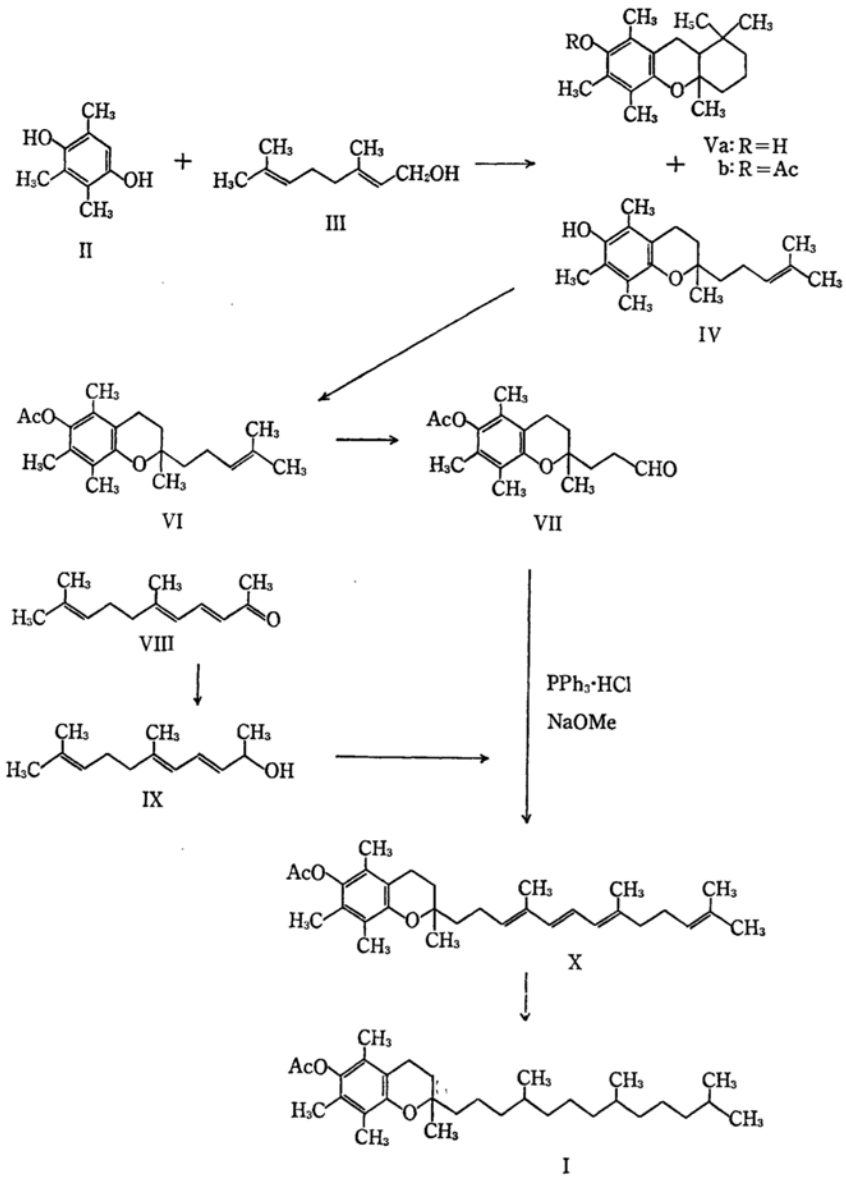
Geraniol (III) was reacted with trimethylhydroquinone (II) in the presence of boron trifluoride in benzene. The product was then acetylated to give a mixture of 2,5,7,8-tetramethyl-2-(4-methyl-3-penten-1-yl)-6-acetyloxychromane (VI) and 2,5,7,8-tetramethyl-2,3-(4,4-dimethylbutano)-6-acetyloxychromane (Vb). The VI was ozonized and decomposed with zinc and acetic acid to give 2,5,7,8-tetramethyl-2-(2-formylethyl)-6-acetyloxychromane (VII). Pseudoionone (VIII) was reduced with sodium borohydride to give pseudoionol (IX), but in certain cases the dehydration of IX occurred during the distillation. VII was condensed with IX by a Wittig reaction to give 2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-3,5,7,11-tridecatetraen-1-yl)-6-acetyloxychromane (X), which was then hydrogenated to give α-tocopheryl acetate (I).

Tocopherols have long been known as a fertile factor, but only recently have its widespread physiological activities been discovered; now the importance of α-tocopherol is increasingly being recognized.[1] Many methods of synthesizing α-tocopherol have already been established,[2] but an attempt has now been undertaken to synthesize α-tocopheryl acetate (I) in short stages, as is illustrated in Scheme 1.

The condensation of geraniol (III) and trimethylhydroquinone (II) in the presence of zinc chloride

1) S. Kijima, *Yuki Gosei Kagaku Kyokaishi* (*J. Soc. Org. Synth. Chem. Japan*), **24**, 92, 200 (1966), review.

2) K. Sato and Y. Kurihara, *ibid.*, **20**, 824 (1962), review.



Scheme 1

was reported by Smith *et al.*,[3] but the structure of his product was ambiguous. Green *et al.* later obtained 2,5,7,8-tetramethyl-2-(4-methyl-3-penten-1-yl)-6-hydroxychromane (IV) by the condensation of II and III in dioxane with the aid of boron trifluoride.[4] In the present study, the condensation was achieved in benzene with boron trifluoride etherate. A fair yield of chromanol (λ_{max}^{EtOH} 294 mμ) was obtained; the results of the elementary analysis of this chromanol were consistent with the IV structure. Two moles of III to one mole of II were necessary; 0.1—0.2 mol of boron trifluoride to one mole of II were appropriate to obtain a good yield. The condensation did not proceed at all in dioxane in the presence of 0.1—0.2 mol of boron trifluoride. The acetylation of the product gave the corresponding acetate; a part of it crystallized to give white crystals melting at 137—138°C. A gas chromatogram*1 of the acetylated product showed a major peak (R_t 10.5 min) and two minor peaks (R_t 6.6 min and 12 min), and the crystalline compound corresponded to one of the

3) L. I. Smith, H. E. Ungnade, J. R. Stevens and C. C. Christman, *J. Am. Chem. Soc.*, **61**, 2615 (1939).
4) J. G. Green and D. McHale, British Pat. 949715 (1964); *Chem. Abstr.*, **60**, 13227d (1964).

*1 Column: SE-30 on Diasolid H, 4 mm×3 m; carrier gas: helium; flow rate: 46 ml/min; temp.: 205°C.

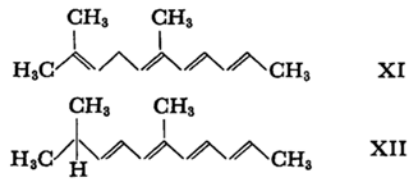
minor components (R_t 12 min). The results of the elementary analysis of the crystals were consistent with the experimental formula of $C_{21}H_{30}O_3$; hence, they may be considered to be isomers of 2,5,7,8-tetramethyl-2-(4-methyl-3-penten-1-yl)-6-acetyloxychromane (VI). The NMR spectrum in tetrachloromethane showed signals at δ 0.90 (singlet, 3H, $\underline{CH_3}C$–), 1.00 (singlet, 3H, $C\underline{H_3}$–C–), 1.16 (singlet, 3H, $\underline{CH_3}C$–O–), 2.35—2.6 (multiplet, 2H, Ar–$\underline{CH_2}$–); 1.3—1.8 (multiplet, 6H, –$\underline{CH_2}$–); 2.23 (singlet, 3H, $\underline{CH_3}COO$–), 2.05 (singlet, 3H, $\underline{CH_3}$–Ar), and 1.95 (6H, $\underline{CH_3}$–Ar), with no signal of the olefinic proton. The UV absorption was identical with that of α-tocopheryl acetate. These facts show the structure to be 2,5,7,8-tetramethyl-2,3-(4,4-dimethylbutano)-6-acetyloxychromane (Vb). The NMR spectrum of the original mixture of the acetate showed signals at δ 2.22 (singlet, 3H, $\underline{CH_3}COO$–); 2.06, 1.94, 1.90(singlets, 9H, $\underline{CH_3}$–Ar); 1.22 (singlet, 3H, $\underline{CH_3}C$–O–); 1.62, 1.56 (6H, $\underline{CH_3}$–$\underset{\underline{CH_3}}{\underline{CH}}$–CH–); 2.4—2.7 (multiplet, Ar–$\underline{CH_2}$–) and 5.10 (1H, –$\underline{CH}$=C–), along with the small peaks of Vb. The signals of the other methylene protons (δ 1.3—2.3) were covered by other signals. Its IR spectrum ($\nu_{C=C}$ 1780 cm^{-1}) and the UV spectrum were also consistent with the VI structure.

The hydroboration of VI for the purpose of obtaining a ω-hydroxychromane derivative gave only a hydroborated product in a poor yield. The yield could not be improved, presumably because of the steric hindrance of the double bond.

The ozonolysis of VI in methylene chloride, followed by reductive decomposition by zinc and acetic acid, gave 2,5,7,8-tetramethyl-2-(2-formylethyl)-6-acetyloxychromane (VII). Its IR spectrum (1755 cm^{-1}, CH_3COO–; 1720 cm^{-1}, –CHO), its NMR spectrum (δ 9.61, triplet, 1H, –$\underline{CHO}$; 2.21, singlet, 3H, $\underline{CH_3}COO$–; 2.03, 1.95 and 1.95, singlets, 9H, $\underline{CH_3}$–Ar; 1.14, singlet, $\underline{CH_3}$–C–O), and the results of elementary analysis were all consistent with the VII structure.

The oxidation of VII with potassium permanganate gave its corresponding carboxylic acid, 2,5,7,8-tetramethyl-2-(2-carboxyethyl)-6-acetyloxychromane.*2

Pseudoionone (VIII) was reduced with sodium borohydride in ethanol, treated with an aqueous solution of sodium hydroxide, and distilled. The oil thus obtained was consistent with pseudoionol (IX) (IR: ν_{OH} 3300 cm^{-1}, NMR in carbon tetrachloride: δ 1.19, doublet, J=6 cps, 3H, $\underline{CH_3}$–CH–OH; 1.72, 1.66 and 1.58, singlets, 9H, $\underline{CH_3}$–CH=C–; 2.12, 2.06 and 2.02, 4H, –$\underline{CH_2}$–CH=C; 3.26, 1H, singlet, –$\underline{OH}$; 4.30, 1H, multiplet, $CH_3C\underline{H}(OH)$–; 4.8—6.6, 4H, multiplet, –$\underline{CH}$=C–). When the reaction product was not treated with aqueous alkali, the product obtained by distillation occasionally had no hydroxyl group (judging from the IR spectrum), and its absorption maximum (λ_{max}^{EtOH} 270 mμ, ε 48000) was longer than that of VIII (λ_{max}^{EtOH} 241 mμ, ε 24000). Accordingly, the product may be deduced to be the dehydrated product of IX, namely, 2,6-dimethylundeca-2,5,7,9-tetraene XI. As its NMR spectrum is accompanied by a small signal at δ 0.88 (doublet, CH_3–C–H, J=6 cps), the isomerized conjugated tetraene (XII) might be present in the product.



As the product before distillation always exhibits an absorption maximum at 241 mμ, the dehydration apparently takes place during distillation by the boric acid produced from the borohydride. However, the similar reduction of mesityl oxide, as an example of α,β-unsaturated ketone, always gave 4-methylpent-3-en-2-ol as a normal product and dehydration never occurred.

A simplified method of Wittig reaction proposed by Pommer *et al.*[5] has been applied to the condensation of VII and IX. Triphenylphosphine hydrochloride was reacted with IX in acetonitrile to yield the corresponding phosphonium salt. After the solvent had been substituted by dimethylformamide, VII was added and ylid was formed by the gradual addition of sodium methoxide and reacted *in situ* with VII. The product had an absorption maximum at 280 mμ, which was close to the expected value (278 mμ) of all *trans*-2,5,7,8-tetramethyl-2-(4,-8,12-trimethyl-3,5,7,11-tridecatetraen-1-yl)-6-acetyloxychromane (X). It can not be purified by distillation because it is very unstable to heat. Its IR spectrum showed the presence of the ester group ($\nu_{C=O}$ 1760 cm^{-1}), but no aldehyde group around 1720 cm^{-1}. The NMR spectrum showed signals at δ 1.22 ($\underline{CH_3}$–C–O–); 2.22 ($\underline{CH_3}COO$–); 2.05, 1.94 and 1.90 ($\underline{CH_3}$–Ar); 1.5—1.58 (CH_3–C=C–); 4.5—6.5 (–$\underline{CH}$=C–), supporting the idea of the X structure.

The hydrogenation of crude X with Raney Nickel was not feasible, presumably due to the presence of triphenylphosphine remaining in the product, so repeated treatment with Raney Nickel was necessary

*2 Green *et al.*[4] reported a melting point of 154°C.

5) H. Pommer, *Ang. Chem.*, **72**, 816 (1960).

to remove the catalyst poison in advance of the reduction. Heating during the reduction must be avoided since the isomerization of the side chain has been found to occur very easily. Reduction at room temperature with high-pressure hydrogen gave α-tocopheryl acetate (I), the structure of which was confirmed by a comparison of its IR, UV, and NMR spectra with those of an authentic sample.

Experimental

2,5,7,8-Tetramethyl-2-(4-methyl-3-penten-1-yl)-6-hydroxychromane (IV). To a solution of 50 g of trimethylhydroquinone (II) and 4.16 m*l* of boron trifluoride etherate in 1300 m*l* of anhydrous benzene, there were added, drop by drop, 101.2 g of geraniol (III) under stirring and refluxing. After it had then been heated to reflux for 3 hr, the benzene solution was washed with water, a sodium bicarbonate solution, and water, dried with anhydrous magnesium sulfate, and distilled; bp 130—156°C/0.01 mmHg, 81 g. A gas liquid chromatogram of the acetylated product showed the IV content to be 73%. Accordingly, the yield of IV from II was 62%. Rectification gave a pale yellow oil; bp 154—154.5°C/0.01 mmHg, λ_{max}^{EtOH} 294 mμ.

Found: C, 79.44; H, 9.92%. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79%.

2,5,7,8-Tetramethyl-2-(4-methyl-3-penten-1-yl)-6-acetyloxychromane (VI) and 2,5,7,8-Tetramethyl-2,3-(4,4-dimethylbutano)-6-acetyloxychromane (Vb). A mixture of 54 g of IV (73% pure) and 52 m*l* of acetic anhydride was refluxed for 3 hr. Fractional distillation then gave an oil; bp 143—158°C/0.02 mmHg, 54 g. For analysis, a part of it was redistilled; bp 133—134°C/0.04 mmHg, λ_{max}^{EtOH} 285 mμ (ε 1920).

Found: C, 76.58; H, 9.40%. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15%.

A part of the product crystallized to give white crystals, which were then triturated with methanol and filtered. Recrystallization from methanol gave white needles of Vb; mp 138—139°C, λ_{max}^{EtOH} 285 mμ (ε 1970).

Found: C, 76.53; H, 9.27%. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15%.

2,5,7,8-Tetramethyl-2-(2-formylethyl)-6-acetyloxychromane (VII). A solution of 16.5 g of VI (70% pure) was dissolved in 200 m*l* of methylne chloride and then cooled to −50°C. Oxygen containing 2.7% of ozone was introduced into the solution for 1 hr (the total amount thus corresponded to 1.2 g of ozone). The reaction mixture was immediately stirred, drop by drop, into a mixture of 4.3 g of zinc dust and 170 m*l* of 50% aqueous acetic acid. After the addition, the mixture was stirred for an hour; then the methylene chloride was distilled out, and the remaining mixture was heated at 100°C for 1 hr. After cooling, the mixture was extracted three times with 80 m*l* portions of ether, and the ether extract was washed with water, a sodium carbonate solution, and water to remove acetic acid. The ether layer was dried and concentrated. The residue was shaken vigorously with a solution of 10 g of sodium bisulfite in 15 m*l* of water, and the white precipitate was filtered and washed with petroleum ether. The precipitate was dissolved in 400 m*l* of water, an aqueous solution of 11 g of sodium carbonate was added, and the mixture was extracted with ether. The ether extract was washed with water, dried, and concentrated. The residue was almost pure VII (7.0 g, 66%). Distillation *in vacuo* gave an oil, bp 145—146°C/0.005 mmHg; which crystallized on standing; mp 48—49°C, λ_{max}^{EtOH} 285 mμ (ε 1880).

Found: C, 70.92; H, 8.02%. Calcd for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95%.

2,5,7,8-Tetramethyl-2-(2-carboxyethyl)-6-acetyloxychromane. To a solution of 3.04 g of VII in 30 m*l* of acetone, there was added, drop by drop, 0.53 g of potassium permanganate in 20 m*l* of acetone at 0—2°C. The mixture was then stirred at the same temperature for 1 hr and poured into 200 m*l* of water. The precipitate was filtered and washed with ether. The filtrate was acidified with hydrochloric acid and extracted with ether. The combined ether solution was washed with water, dried with magnesium sulfate, and concentrated. The residue was triturated with petroleum ether and filtered to give white crystals; 1.0 g, mp 159.5—160.5°C (recrystallized from ethyl acetate).

Found: C, 67.34; H, 7.68%. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55%.

Pseudoionol (IX). A solution of 9.6 g of pseudoionone (VIII) was dissolved in 100 m*l* of 95% ethanol; after 0.68 g of sodium borohydride in ethanol had been added at room temperature, the mixture was stirred for 2 hr and then left standing overnight. The mixture was added to a solution of 2 g of sodium hydroxide in 500 m*l* of water. The mixture was extracted with ether, and the ether extract was washed with water, dried, and concentrated. The distillation of the residual oil *in vacuo* gave a colorless oil; bp 112—120°C/5 mmHg, 7.7 g (80%).

Found: C, 80.03; H, 11.36%. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41%.

2,6-Dimethyl-2,5,7,9-undecatetraene (XI). A solution of 29 g of VIII was dissolved in 100 m*l* of 99.5% ethanol, 2.1 g of sodium borohydride in ethanol were added at room temperature, and the mixture was stirred for 2 hr and then left standing overnight. The mixture was added to 500 m*l* of water and extracted with ether. The ether layer was washed with water, dried, and concentrated. Distillation *in vacuo* gave an oil; bp 89—103°C/2.5 mmHg, 23.4 g. The IR spectrum showed that a small quantity of a hydroxyl group was present. A part of the distillate was treated overnight with *p*-nitrobenzoyl chloride in pyridine; the mixture was then poured into water and extracted with ether, and the ether extract was washed with water, dried, and concentrated. The residue was dissolved in petroleum ether and passed through an alumina column to remove *p*-nitrobenzoic acid and its ester. The concentration and distillation of the petroleum ether solution gave an oil, bp 93—94°C/4 mmHg, which showed no hydroxyl group upon IR analysis; n_D^{15} 1.5328, λ_{max}^{EtOH} 270 mμ (ε 48000).

Found: C, 88.25; H, 11.26%. Calcd for $C_{13}H_{20}$: C, 88.56; H, 11.44%.

2,5,7,8-Tetramethyl-2-(4,8,12-trimethyl-3,5,7,11-tridecatetraen-1-yl)-6-acetyloxychromane (X) and α-Tocopheryl Acetate (I). To a solution of 2.97 g of IX in 10 m*l* of acetonitrile, there were added, under stirring and while the temperature was kept below 30°C, 4.53 g of triphenylphosphine hydrochloride which had been obtained by passing dry hydrogen chloride into a solution of triphenylphosphine in dry ether. After the mixture had then been left standing overnight at room

temperature, the acetonitrile was removed under reduced pressure below 50°C. To the residue there were added 4.2 g of VII in 15 m*l* of dimethylformamide, and the mixture was stirred. When a clear solution was obtained, sodium methoxide prepared from 0.352 g of sodium and 7 m*l* of anhydrous methanol was stirred in, drop by drop, below 15°C. The reaction mixture was turned red by the ylid formed. After the addition was complete, stirring was continued for 30 min at 10°C; then the mixture was gradually heated to 80°C, when the red color disappeared. The product was poured into 200 m*l* of 50% aqueous methanol and extracted with petroleum ether. The petroleum ether extract was washed three times with 50% methanol, dried, and concentrated *in vacuo*. The residual oil was dissolved in 20 m*l* of ether, and an ethereal solution of mercuric chloride was added until no more precipitate formed. When the precipitate was filtered and the filtrate was washed with water, dried, and concentrated, 4.7 g of a yellow oil were obtained (λ_{max}^{EtOH} 280 mμ). The oil solidified at about 120°C *in vacuo*, which made distillation impossible. To a solution of 3.0 g of the above oil in 50 m*l* of ethanol, 2 g of Raney Nickel were added, and the mixture was shaken under 22 atm of hydrogen at room temperature. The catalyst was renewed 3 times, whereby the calculated amount of hydrogen had been absorbed. The catalyst was filtered, and the filtrate was concentrated and distilled *in vacuo* to give an oil; bp 180—185°C/0.05 mmHg, 2.0 g. Its IR and UV spectra were identical with those of an authentic sample of α-tocopheryl acetate. A part of it was hydrolyzed by methanolic potassium hydroxide and converted into allophanate; mp 165—166°C (recrystallized from methanol).

Found: C, 72.15; H, 10.01; N, 5.32%. Calcd for $C_{31}H_{52}N_2O_4$: C, 72.05; H, 10.14; N, 5.42%.

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