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Synthetic Studies of α-Tocopherol. III.*1 Synthesis of Phytone

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Phytone (XI), an important intermediate in the preparation of α-tocopherol, was synthesized by a selective Wittig reaction between geranyltriphenylphosphonium halide (VII) and the aldehyde group of 2-methyl-6-oxoheptanal (VIII), followed by the hydrogenation of the product. VIII was prepared from 1,3-dimethyl-1-cyclohexene (V) by ozonolysis and reductive decomposition. V could not be obtained in a pure state by the dehydration of 2,6-dimethylcyclohexan-1-ol (II), presumably because of the isomerization of the intermediate carbonium ion. The pyrolysis of the acetate of II (III) was found to give pure V. That the hardly-pyrolizable stereoisomer of III was *cis,cis*-2,6-dimethylcyclohexyl-1-acetate (VI) is consistent with the *cis*-elimination mechanism.

Recent advances in biological study have revealed numerous biological activities of tocopherols, and their physiological significance has come to be increasingly recognized.[1] Phytone (XI), namely, 6,10,14-trimethyl-2-pentadecanone, serves as an important intermediate for the synthesis of α-tocopherol, and a large number of methods of synthesizing it have been described.[2] However, we have now attempted to develop the new, simple method of synthesis as indicated in Scheme 1.

2,6-Xylenol (I) was hydrogenated in the presence of Raney Nickel and sodium salt of 2,6-xylenol[3] to yield 2,6-dimethyl-1-cyclohexanol (II) in a nearly quantitative yield. The description of how Ruzicka *et al.*[4] obtained 1,3-dimethylcyclohexene (V) by the dehydration of II with potassium hydrogen sulfate has been found to be erroneous, for the NMR spectrum of the dehydrated product showed two olefinic protons of about the same intensities (δ 5.2 and 5.3), while that of the ketoaldehyde obtained by its ozonolysis and reductive decomposition showed two pairs of doublets of methyl groups of about equal intensities (δ 0.88 and 1.07, $C\underline{H}_3CH$–, doublets, $J=7$ cps) and two kinds of aldehyde groups (δ 9.55, –CH–C$\underline{H}$O, doublet, $J=2$ cps; 9.70, $-CH_2C\underline{H}O$, triplet, $J=2$ cps) (Fig. 1a). These results show that the dehydrated product is a 1 : 1 mixture of V and 2,4-dimethylcyclohexene (IV), and that the ketoaldehyde is a mixture of 2-methyl-6-oxoheptanal (VIII) and 4-methyl-6-ketoheptanal. Neither the 85% phosphoric acid[5] nor the aluminum oxide[6] employed in the dehydration has been found to be effective in obtaining V in a pure state, as can be seen from Figs. 1b and 1c, the isomerization of the carbon skelton has apparently occurred in the latter case. The bromination and dehydrobromination of II gave a very pure 1 : 1 mixture of V and IV (see Fig.

*1 Part II: T. Ichikawa, H. Owatari and T. Kato, This Bulletin, **41**, 1228 (1968).

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.

3) H. E. Ungnade and A. D. McLaren, *J. Am. Chem. Soc.*, **66**, 118 (1944); H. E. Ungnade and D. V. Nightingale, *ibid.*, **66**, 1218 (1944); R. B. Carlin, *J. Am. Chem. Soc.*, **67**, 931 (1945).

4) L. Ruzicka, D. R. Koolhaas and A. H. Wind, *Helv. Chim. Acta*, **14**, 1155, 1166 (1931).

5) B. B. Corson and V. N. Ipatieff, "Organic Syntheses," Coll. Vo. II, p. 152 (1950).

6) H. Pines, *J. Am. Chem. Soc.*, **55**, 3892 (1933).

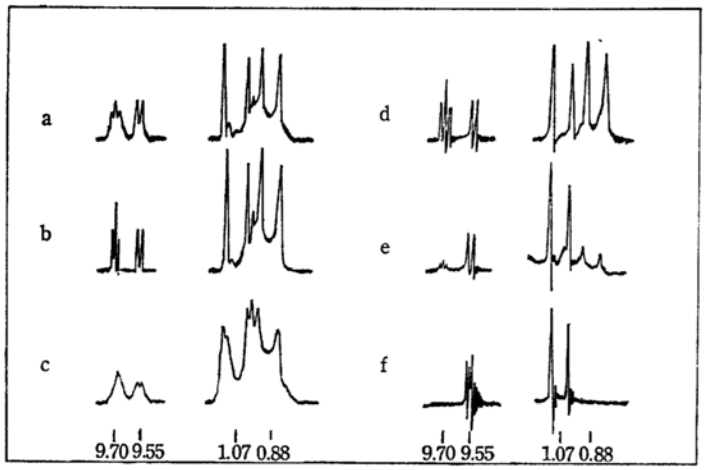
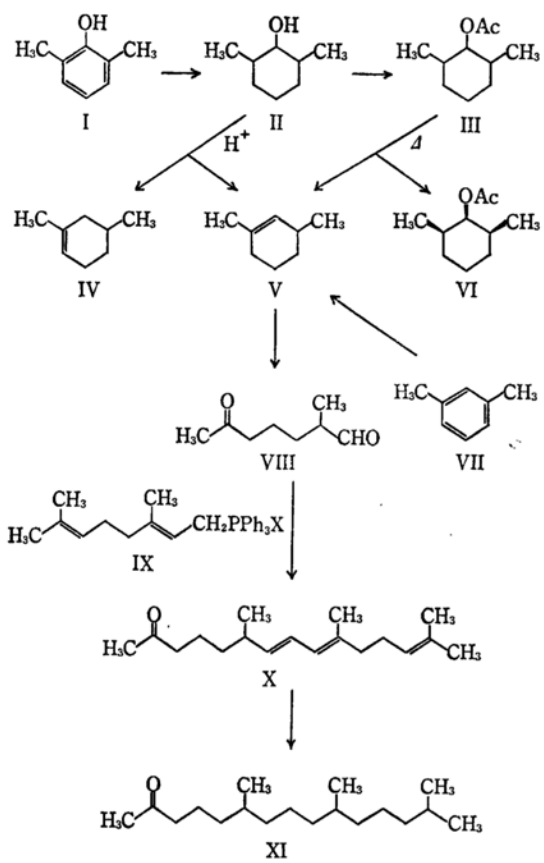
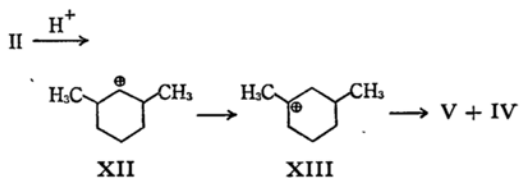


Fig. 1. NMR spectra of aldehyde and methyl groups of ketoaldehydes obtained from dehydrated products of 2,6-dimethylcyclohexan-1-ol (II) with potassium bisulfate (a), phosphoric acid (b), alumina (c), bromination and dehydrobromination (d), boric acid (e) and acetylation followed by pyrolysis (f), (in CCl_4).

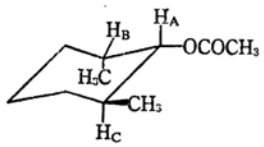


Scheme 1

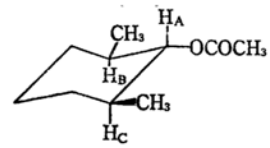
1d). These results seem to suggest that the secondary cation (XII) formed by the protonation of II rapidly isomerizes to the more stable tertiary cation (XIII), and that the subsequent abstraction of the proton from XIII gives rise to a 1 : 1 mixture of V and IV.



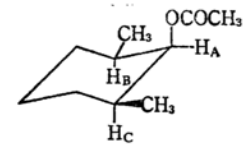
As no dehydrating process seems to serve in the present purpose, the pyrolysis of borate and acetate of II has been attempted. Boric acid and II were first reacted under mild conditions to give the borate of II; its following pyrolysis gave V as the major product (see Fig. 1e), but it was not free of IV. The dehydration of II seems to have taken place in part. The acetylation of II with acetic anhydride gave 2,6-dimethyl-1-cyclohexylacetate (III) in a quantitative yield. The pyrolysis of III was found to give pure V (δ 0.90, 3H, $C\underline{H}_3$–CH–, doublet, $J=7$ cps; 1.60, 3H, $C\underline{H}_3$–C=C, broad singlet, line width = 4 cps; 5.21, 1H, $\underline{H}$–C=C, broad singlet, line width = 6 cps), and the ketoaldehyde obtained from it was naturally pure VIII (see Fig. 1f). The pyrolysis of the acetate (III) was achieved by passing vaporized III through a heated quartz column at 500—550°C, along with a flow of nitrogen. Considerable amounts of side products were formed at temperatures above 550°C, whereas the yields of V were low below 500°C. The yield was only slightly influenced by the flow rate of III at 500°C, but it decreased considerably when the velocity was decreased to below 0.4 g/min at 580°C. The highest yield (71%) was obtained at



XIV



XV



VI

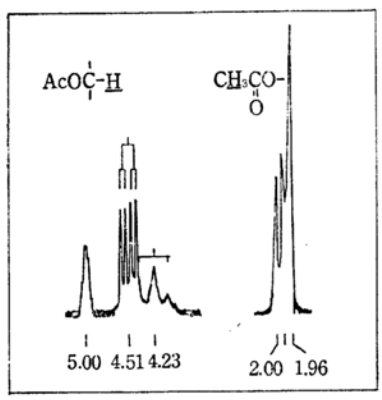
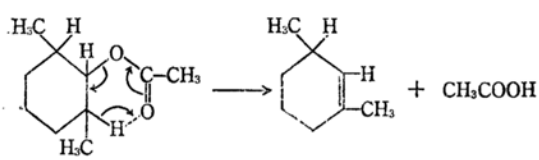


Fig. 2. NMR spectrum of 2,6-dimethylcyclohexyl-1-acetate (in CCl_4).

550°C with the flow rate of 1.5 g per minute. Although the recovered unreacted acetate was pyrolyzed under the same conditions, the yield of V amounted to only a few percent. A gas liquid chromatogram of III showed the presence of three stereoisomers (R_t: 11.6 (minor), 12.7 (minor), 13.8 (major) min); their ratio was slightly influenced by unknown factors during the hydrogenation of I. The recovered acetate was found to correspond to a minor component (R_t: 11.6 min). The NMR spectrum of III showed the presence of three kinds of –CH–OAc groups (δ 5.00, broad singlet, line width = 5 cps, 4.51, quartet, and 4.23, triplet) and three kinds of acetyloxy groups (δ 1.96, 1.97 and 2.00) (see Fig. 2), whereas the spectrum of the recovered acetate showed one –CH–OAc group, at δ 5.00, and one acetyloxy group, at δ 2.00. The possible conformations of V are XIV, XV, and VI. As J_{AB} ($\phi = 60°$) and J_{AC} ($\phi = 180°$) of XIV are expected to be about 2 cps and 9 cps respectively from the Karplus equation, the spectra of XIV, XV, and VI correspond to the signals at δ 4.51 and 1.96, at 4.23 and 1.97, and at 5.00 and 2.00 respectively. The pyrolysis of acetate is believed to feature intramolecular cis-elimination,[7] as is shown in XVI.



XVI

That VI is hard to pyrolyze is comprehensible from the fact that a conformation of sterically-hindered 1,3-diaxial methyl groups is inevitable when a cyclic transition state XVI is formed.

A recent method patented by Amagasa *et al.*[8] claims to be able to obtain V from *m*-xylene (VII) by reduction with sodium-water in liquid ammonia; this may offer a simpler way of obtaining V.

Geranyl triphenylphosphonium bromide (IX, X = Br) was prepared by the method of Isler *et al.*[9] from linalool or geraniol. The corresponding phosphonium chloride (IX, X = Cl) was prepared in a similar manner, but the yield was not satisfactory. The ylid from geranyl triphenylphosphonium halide has been prepared at first with phenyl lithium in ether, and the ketoaldehyde was added to the solutions of the ylid. The infrared spectra of the product showed an absorption band at 1715 cm^{-1}, while no absorption band of the unsaturated carbonyl group was found to be present, so the aldol condensation

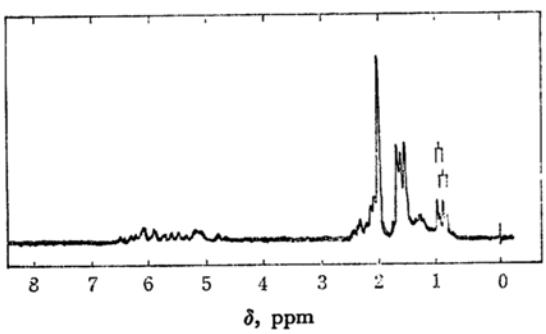


Fig. 3. NMR spectrum of 6,10,14-trimethylpentadeca-7,9,13-trien-2-one (X), (in CCl_4).

of aldehyde group seems not to have taken place. The Wittig reaction has been simplified in order to make it proceed in a better yield by adding sodium methoxide to a mixture of VIII and IX in an oxygen-containing solvent, such as ether, dioxane, tetrahydrofuran, dimethylformamide, or ethyl acetate. The yield was poor in a non-oxygen-containing solvent, such as chloroform or liquid ammonia. The NMR spectrum of the product shows an acetyl group (δ 2.00, 3H), three olefinic methyl groups (δ 1.58,

7) D. Y. Curtin and D. B. Kellom, *J. Am. Chem. Soc.*, **75**, 6011 (1953).
8) M. Amagasa and T. Yamaguchi, Japanese Pat. 40-11378 (1965).
9) O. Isler, H. Gutman, H. Lindler, M. Montavon, R. Ruegg, G. Ryser and P. Zeller, *Helv. Chim. Acta*, **39**, 463 (1956).

1.66, 1.70, 9H), and two kinds of methyl groups (δ 0.92, doublet, 3H, $J=7$ cps; 0.96, doublet, 3H, $J=7$ cps) and supports the expected structure, 6,10,14-trimethyl-7,9,13-pentadecatrien-2-one (X) (see Fig. 3). That the two kinds of secondary methyl group are present shows that the product is a mixture of 7-*cis*- and 7-*trans*-isomers, one of which, presumably *trans*-, predominates. For the hydrogenation of X, it was necessary to treat X with Raney Nickel or with cationic exchange resin, for example, Amberlist 15 (H^+), to remove the catalyst poison, which is presumably a trace of triphenylphosphine. Palladium (5%) on active carbon was satisfactory for hydrogenating the double bonds of X selectively, yielding phytone (XI) in a nearly quantitative yield. Its IR spectrum ($\nu_{C=O}$, 1720 cm^{-1}) showed the presence of ketone and no hydroxyl group; its NMR spectrum (δ 2.01, singlet, $C\underline{H}_3CO-$; 1.23, $-C\underline{H}_2-$; 0.88, doublet, $C\underline{H}_3-CH-$, $J=6$ cps; 2.32, triplet, $-CH_2-C\underline{H}_2-CO-$) is consistent with XI, and the shapes of the signals of methyl and methylene groups resemble those of authentic phytol.

Experimental

2,6-Dimethylcyclohexan-1-ol (II). To 2.5 g of xylenol (I), 0.5 g of sodium metal was added, after which the mixture was heated at 100°C for 30 min. After cooling, absolute benzene was added and the reddish white mass was crushed and filtered to afford a green precipitate of phenolate of I.

The hydrogenation of I (52 g) with Raney Nickel in the presence of 0.2 g of the phenolate[3] gave 50.4 g (93%) of II; bp 77—82°C/21 mmHg. For analysis a part of it was refractionated; bp 66.5°C/5 mmHg. $n_D^{16.8}$ 1.4660.

Found: C, 74.80; H, 12.44%. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58%.

2,6-Dimethylcyclohexyl-1-acetate (III). To a mixture of 106 g of cyclohexanol (II) and 101 m*l* of acetic anhydride, three drops of concentrated sulfuric acid were added, and the mixture was shaken in a flask equipped with a calcium chloride tube. The temperature of the mixture was maintained below 100°C by cooling it with running water. After the vigorous reaction had subsided, the mixture was further heated at 100°C for 2 hr. The mixture was then poured into 300 m*l* of water, salt was added, and the mixture was shaken thoroughly. The aqueous layer was extracted with ether, and the extract was combined with an organic layer, washed with water, saturated sodium bicarbonate, and water, dried with anhydrous magnesium sulfate, and distilled; bp 87—92°C/24 mmHg, 130.6 g (93%). For analysis, a part of it was refractionated; n_D^{18} 1.4422, bp 72°C/4 mmHg.

Found: C, 70.62; H, 10.51%. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66%.

Dehydration of 2,6-Dimethyl-1-cyclohexanol (II).

a) Dehydration by Potassium Bisulfate.[2] A mixture of 12.8 g of II and 25.6 g of potassium bisulfate was heated in an oil bath kept at 180—190°C. The distillate was then freed from water and distilled; bp 115—130°C, 4.8 g (44%). Ozonolysis and reductive decomposition gave a mixture of ketoaldehydes (see Fig. 2a).

b) Dehydration with 85% *Phosphoric Acid.*[3] To 2 g of 85% phosphoric acid heated at 165—170°C in an oil bath, 12.8 g of II were added, drop by drop, and the distillate was dried, redistilled, and converted into a mixture of ketoaldehydes (see Fig. 2b).

c) Dehydration by Alumina. Through a 2 cm×25 cm column packed with 10-mesh active alumina and heated at 360—380°C, there were passed 10 g of II in 20 min. The pyrolysate was dried, redistilled, and converted into a mixture of ketoaldehydes by ozonolysis (see Fig. 2c).

d) Bromination and Dehydrobromination. To a solution of 19 g of II in 20 m*l* of tetrachloromethane, there was added, drop by drop, 17.6 g of phosphorous tribromide in 17 m*l* of tetrachloromethane. The mixture was then stirred for 1 hr at room temperature, poured into water, and extracted with ether; the ether extract was washed, dried, and distilled; bp 82—83°C/25 mmHg, 20.5 g. Five grams of the oil thus obtained were added, drop by drop, to a solution of 4.5 g of potassium hydroxide in 9 m*l* of methanol at 100—105°C. The mixture was then heated further 30 min, poured into water, and extracted with ether; the ether extract was washed, dried, distilled, and converted into ketoaldehydes (see Fig. 2d).

e) Dehydration by Boric Acid. To a solution of 6 g of II in 20 m*l* of 1,2-dichloroethane, 2.9 g of boric acid were added; the mixture was then distilled slowly through 1 cm×20 cm Vigreux column. Distillation was continued, with dichloroethane supplied occasionally, until water no longer distilled out and a clean solution was finally obtained. The supply of dichloroethane was then stopped, and distillation was continued further. When the temperature of the solution reached 240°C, decomposition began and the distillate was dried with magnesium sulfate and fractionated. Yield; 3.8 g (73%). The product was ozonolysed to give mainly 2-methyl-6-ketoheptanal (see Fig. 1e).

f) Pyrolysis of III, 1,3-Dimethyl-1-cyclohexene (V). 370 grams of acetate (III) were evaporated in a preheater (1 g/min) and passed through a quartz column (30 mm ×300 mm) heated at 550°C under a nitrogen stream of 60 m*l*/min. When the pyrolysate was then condensed with an efficient cooler, 306 g of the pyrolysate were recovered (97%). Water (800 m*l*) was added, and the mixture was neutralized carefully with 320 m*l* of 5 N sodium hydroxide (74% of acetic acid was assumed to be formed). The oily layer was separated and fractionated through a Widmer column; bp 119—125°C, 170 g (71%). n_D^{17} 1.4520.

Found: C, 87.41; H, 12.80%. Calcd for C_8H_{14}: C, 87.19; H, 12.81%.

The residue (89 g, 24%) was fractionated under a vacuum; bp 73—79°C/13 mmHg, 8.4 g. It was found to be *cis,cis*-2,6-dimethylcyclohexyl-1-acetate (VI), which gave only 5% of the cyclohexene under the above pyrolytic conditions.

Found: C, 70.62; H, 10.49%. Calcd for $C_{10}H_{18}O$: C, 70.54; H, 10.66%.

2-Methyl-6-ketoheptanal (VIII). A solution of 22 g of V in 200 m*l* of dichloromethane was cooled to −50—−60°C, and then oxygen gas (350 m*l*/min) containing ozone was introduced for 7 hr (0.03 mol/hr). The solution was immediately added, drop by drop, to a mixture of 15 g of zinc dust and 140 m*l* of 70% acetic acid. After the addition was complete, the mixture was refluxed for 2 hr and neutralized to pH 6 with sodium hydroxide. Care was taken to keep the pH of the solution below 6 and the temperature below 20°C. The mixture

was extracted with ether, dried, and distilled; bp 49—57°C/0.3 mmHg, 20.3 g (71%). A part of it was fractionated with efficient column for analysis; bp 67°C/0.5 mmHg, n_D^{14} 1.4376.

Found: C, 67.51; 9.80%. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93%.

Geranyltriphenylphosphonium Bromide (IX, X=Br). Geraniol (10 g) purified through a calcium chloride complex was converted into the phosphonium bromide IX (X=Br; 23 g) in a 73% yield by Isler's method[9]; mp 178—183°C. The product was used in the subsequent reaction without further purification. Geraniol can be successfully replaced by linalool.

6,10,14-Trimethyl-7,9,13-pentadecatriene-2-one (X). To 60 m*l* of anhydrous dioxane there were added 2 g of ketoaldehyde (VIII) and 6.6 g of IX (X=Br), and the mixture was stirred under an atmosphere of dry nitrogen. A methanolic solution of 2 N sodium methoxide (7 m*l*) was added, drop by drop, to the above mixture at 25°C over a 30-min period. After the addition was over, the mixture was heated at 55°C for 30 min under stirring. Then the mixture was poured into 50% aqueous methanol and extracted with petroleum ether. The petroleum ether extract was washed twice with 50% methanol and water, dried with anhydrous magnesium sulfate, and distilled; bp 113—119°C/0.1 mmHg, 2.44 g (66%). Redistillation for analysis gave an oil; bp 121—123°C/0.17 mmHg, n_D^{21} 1.4960. λ_{max}^{EtOH} 242 mμ (ε 2.98 $\times 10^4$).

Found: C, 82.18: H, 11.42%. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52%.

When geranyltriphenylphosphonium chloride was used in place of the bromide, the yield was 64%. When the reactions were carried out in methanol, X was not obtained.

Phytone (XI). To 38 g of X 4 m*l* of methanol and 4 g of Raney Nickel were added and the mixture was heated to reflux for 1 hr. The treatment with Raney Nickel can successfully be replaced by a treatment with a cationic resin such as Amberlist 15 (H^+) at room temperature. The catalyst was filtered off, 2 g of palladium charcoal (5%) were added, and the mixture was shaken at room temperature in an autoclave under the initial hydrogen pressure of 125 kg/cm^2. After the calculated amount of hydrogen had been absorbed, the catalyst was filtered and the filtrate was fractionated; bp 114—117°C/0.2—03 mmHg, 35. 3 g (91%). For analysis, a part of it was refractionated; bp 115°C/0.2 mmHg.

Found; C, 80.57; H, 13.51%. Calcd for $C_{18}H_{36}O$: C, 80.52; H, 13.52%.

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