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Synthetic Studies of α-Tocopherol. II.[*1] Synthesis of Trimethylbenzoquinone

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Trimethylbenzoquinone (XII), a raw material for the synthesis of trimethylhydroquinone (XIII), was synthesized from trimethylcyclohexenones and trimethylcyclohexene by oxidation. Ethyl α-propionylpropionate (II) prepared from ethyl propionate was condensed with methyl vinyl ketone to yield 4-methyl-4-ethoxycarbonylocta-3,7-dione (IV), which was then dehydrated with beryllium chloride to give 2,3,6-trimethyl-6-ethoxycarbonyl-2-cyclohexen-1-one (V). The product (V) was heated with alkali to give 2,3,6-trimethyl-2-cyclohexen-1-one (VI). The refluxing of a solution of IV in a mixture of acetic acid and hydrochloric acid also gave rise to VI. When II was condensed with crotonaldehyde, 2,5,6-trimethyl-2-cyclohexen-1-one (VIII) was obtained in a single step. 1,4(or 1,5)-Dimethyl-5-(or 4)-formyl-1-cyclohexene (IX), obtained by the Diels-Alder reaction of crotonaldehyde with isoprene, was reduced by hydrazine hydrate to give 1,4,5-trimethyl-1-cyclohexene (X). X was oxidized with *t*-butyl chromate and acetic anhydride to give 3,5,6-trimethyl-2-cyclohexen-1-one (XI). VI, VIII, XI, and X were oxidized with *t*-butyl chromate and acetic anhydride to give XII in 53, 52, 22, and 12% yields respectively. The oxidation of VIII by selenium dioxide gave XII in a 23% yield, but only a trace of XII was formed by the similar oxidation of X.

Numerous syntheses of trimethylhydroquinone (XIII), an indispensable raw material for the synthesis of α-tocopherol, have hitherto been reported, but the starting materials have been restricted to such aromatic compounds as pseudocumene, hydroquinone, *m*-xylenol[1]; no report of synthesis from trimethylcyclohexene nor trimethylcyclohexenones is known.

Oppenauer *et al.* have found that *t*-butyl chromate has oxidizing ability enough to convert 2-cyclohexen-1-one into benzoquinone.[2] This oxidation has now been applied to trimethylcyclohexene and

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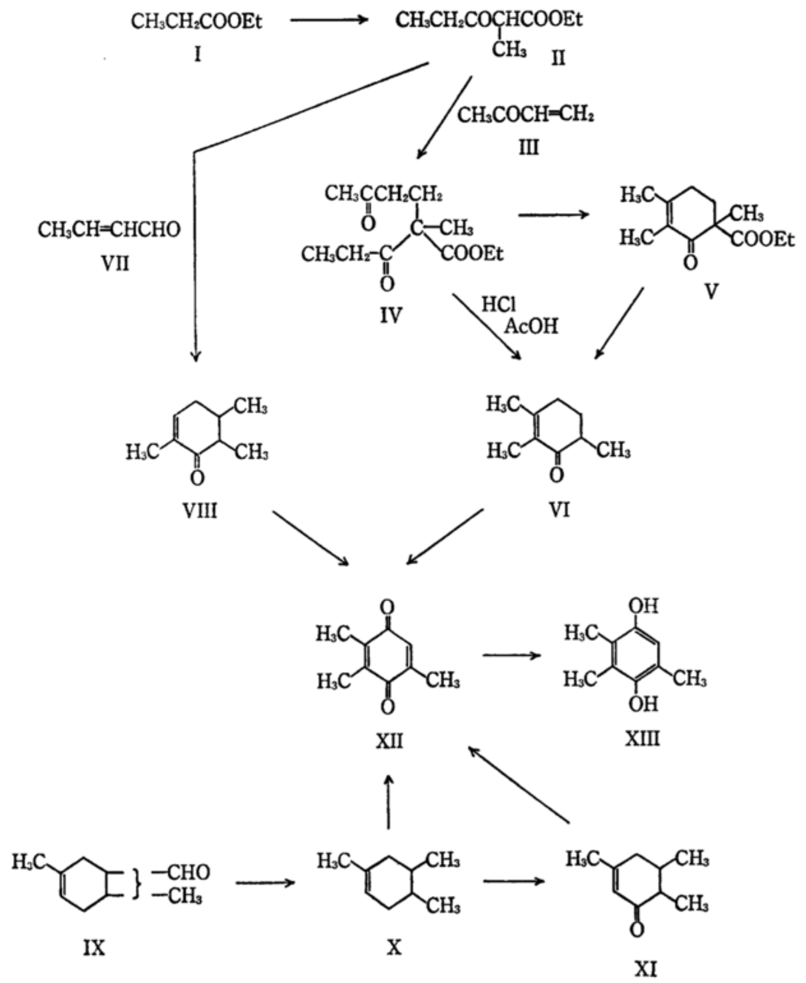
[*1] Part I: T. Ichikawa and T. Kato, This Bulletin, **41**, 1224 (1968).

[1] K. Sato and Y. Kurihara, *Yuki Gosei Kagaku Kyokaishi* (*J. Soc. Org. Synth. Chem. Japan*), **20**, 824 (1962), review.

[2] R. V. Oppenauer and H. Oberrauch, *Anales. asoc. quim. argentina*, **37**, 246 (1949); *Chem. Abstr.*, **44**, 3871 (1950).



Scheme 1

trimethylcyclohexenones to obtain trimethylbenzoquinone (XII), which can then be easily reduced to give XIII. Three kinds of cyclohexenones and a cyclohexene were prepared, as shown in Scheme 1. Ethyl α-propionylpropionate (II)[3] prepared from ethyl propionate (I) was subjected to Michael condensation with methyl vinyl ketone (III) to yield 4-methyl-4-ethoxycarbonyloctane-3,7-dione (IV) (IR: $\nu_{C=O}$; 1715, 1725 (shoulder), and 1740 cm^{-1} (shoulder); NMR: δ 2.06, singlet, 3H, $\underline{CH_3}CO$; 1.25, singlet, 3H, $\underline{CH_3}$–C–; 4.15, quartet, $J=7$ cps, 2H, $CH_3\underline{CH_2}O$–). The dehydration of IV with beryllium chloride gave 2,3,6-trimethyl-6-ethoxycarbonyl-2-cyclohexen-1-one (V) (IR: $\nu_{C=O}$; 1733, 1665 and 1640 cm^{-1}; NMR: δ 1.25, singlet, 3H, $\underline{CH_3}$–C–COO–; 1.20, triplet, $J=7$ cps, 3H, $\underline{CH_3}$–CH_2O–; 1.71, 3H, $\underline{CH_3}C=C$–; 1.89, 3H, $\underline{CH_3}C=C$; 4.08, 2H, quartet, $CH_3\underline{CH_2}O$–), which was then converted to 2,3,6-trimethyl-2-cyclohexen-1-one(VI) by aqueous alkali. The refluxing of IV with hydrochloric acid and acetic acid gave VI directly. The absorption maximum of VI (244 mμ, ε 12400; 305 mμ, ε 90) is in good agreement with the expected value (242±5 mμ); the IR spectrum showed the presence of α,β-unsaturated ketone ($\nu_{C=O}$; 1670 cm^{-1}), while the NMR spectrum exhibited peaks at δ 1.68, 1.88 (singlets, 6H, $\underline{CH_3}$–C=C) and 1.05 (doublet, $\underline{CH_3}$–CH–, $J=7$ cps). All these facts sustain the VI structure.

When ethyl α-propionylpropionate (II) was condensed with crotonaldehyde (VII) in aqueous alkali, Michael addition, dehydration, saponification, and decarboxylation took place in succession to give directly 2,5,6-trimethyl-2-cyclohexen-1-one (VIII) (IR: $\nu_{C=O}$; 1680 cm^{-1}). The UV absorption maximum of VIII at 235 mμ ($\pi\rightarrow\pi^*$, ε 8900) was shorter than that of VI by 9 mμ, and the absorption

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[3] S. M. McElvain, *J. Am. Chem. Soc.*, **51**, 3124 (1929).

maximum at 318 mμ ($n\rightarrow\pi^*$, ε 80) was longer by 13 mμ (305 mμ); these facts are consistent with the idea of VIII being short of one olefin methyl group compared with VI.

An attempt to obtain 1,4,5-trimethyl-1-cyclohexene (X) by the direct Diels-Alder reaction between isoprene and 2-butene was a failure; the main product was the isoprene dimer, for it was identical with the product from isoprene alone under the same conditions. Therefore, 1,4(or 1,5)-dimethyl-5(or 4)-formyl-1-cyclohexene (IX), obtained by the Diels-Alder reaction of crotonaldehyde with isoprene,[4] was subjected to a Huang-Minlon reduction to give X. The IR spectrum showed a weak band at 1670 cm^{-1} ($\nu_{C=C-}$). The structure was further confirmed by ozonolysis and by converting the keto-aldehyde obtained into its disemicarbazone. When X was oxidized with *t*-butylchromate, an unsaturated ketone ($\nu_{C=O}$; 1670 cm^{-1}) with a small amount of trimethylbenzoquinone was obtained. The elementary analysis of its 2,4-dinitrophenylhydrazone is consistent with its being a trimethylcyclohexenone. The IR spectrum was quite different from the spectra of either VI or VIII, and the absorption maxima at 234 mμ (ε 12900) and 322 mμ (ε 70) coincided well with the expected value of 3,5,6-trimethyl-2-cyclohexen-1-one (XI). Each cyclohexenone can be distinguished from the others by gas liquid chromatography[*2] and was gas chromatographically pure. It is reasonable that the less-hindered methylene group of X was selectively oxidized; the fact that the oxidation to XII can not proceed further easily is presumably due to the separation of the chromate complex during the reaction.

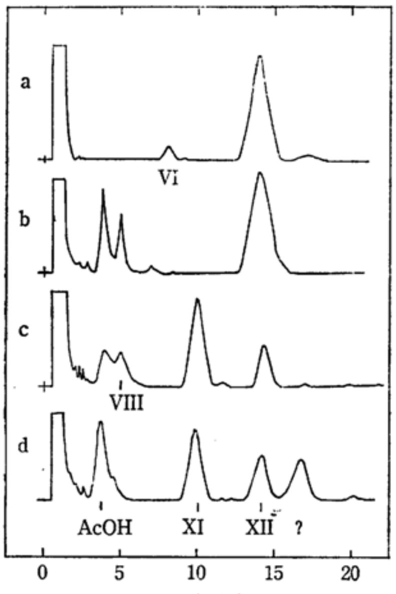

Fig. 1. Gas liquid chromatograms of oxidation products of VI(a), VIII(b), X(c) and XI(d) by *t*-butyl chromate.
Column: 5% PEG 6000 on Diasolid M, 4 mm $\times$3 m; carrier gas: helium; flow rate: 86 m*l*/min; temp: 205°C.

The three cyclohexenones (VI, VIII, XI) and one cyclohexene (X) thus obtained were then oxidized with *t*-butyl chromate in the presence of acetic anhydride. The chromatogram of the oxidation product of VI (Fig. 1a) showed the formation of benzoquinone (XII), accompanied by a small amount of the unreacted VI. Ten moles of the chromate to one mole of VI and refluxing for 12 hr in benzene were necessary to obtain the best yield of XII (53%). On long refluxing (24 hr), the yield of XII decreased to 38%. A similar oxidation of VIII gave 52% of XII (*t*-butyl chromate: 10 mol; refluxing time: 20 hr). The results (see Fig. 1b) were very similar to the case of VI, perhaps because of a similar steric hindrance at the C-4 positions. When XI was oxidized under similar conditions, an unknown side product (see Fig. 1d) was formed along with XII. The yield of XII was 22% (*t*-butyl chromate: 10 mol; refluxing time: 25 hr), which was rather low compared with those in the former cases. As the side product (R_t: 17 min, Fig. 1d) was not reduced by hydrosulfite, the olefinic methyl group might be oxidized in place of the sterically-hindered C-4 of XI.

As has been stated before, the oxidation of X gave XI as a major product, but small amounts of VIII and XII were also formed (see Fig. 1c). The employment of a small excess of the oxidizing agent and a long refluxing time gave a fair yield of XI, but that of XII did not exceed 12% even when an oxidizing agent was employed in a large excess (40 mol), under

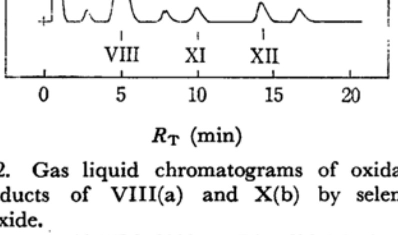

Fig. 2. Gas liquid chromatograms of oxidation products of VIII(a) and X(b) by selenium dioxide.
Column: 5% PEG 6000 on Diasolid M, 4 mm$\times$ 3 m; carrier gas: helium; flow rate: 86 m*l*/min; temp: 205°C.

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4) O. Diels and K. Alder, *Ann.*, **470**, 621(1929).

[*2] Column: PEG 6000, 5% on Diasolid M, 4 mm $\times$3 m; carrier gas: helium; flow rate: 86 m*l*/min; temp.: 134°C.

which conditions cyclohexenones completely vanished.

When VIII (1 mol) was oxidized with selenium dioxide (1.1 mol) in glacial acetic acid, XII was obtained in a 23% yield; this yield is considerably inferior to that obtained by the chromate oxidation. As can be seen from Fig. 2a, a side product was formed. This is probably an oxidized product of VIII at the olefinic methyl group. When one mole of X was oxidized with 1.5—2.0 mol of selenium dioxide, the major product was found to be VIII (5% from X), plus a trace of benzoquinone (see Fig. 2b). The yield of VIII was low, but it is interesting that this oxidation seems to have taken place at the more sterically-hindered methylene group.

When these oxidized products were reduced by sodium hydrosulfite, trimethylhydroquinone (XIII) was obtained in a quantitative yield.

Experimental

4-Methyl-4-ethoxycarbonyloctane-3,7-dione (IV). To 40 g of ethyl α-propionylpropionate (II) there was added a solution of sodium ethoxide prepared from 0.32 g of sodium and 20 m*l* of ethanol, with the temperature kept below 10°C. Freshly-distilled methyl vinyl ketone (19.6 g) was added, drop by drop, to the above solution under stirring at the same temperature. The reaction mixture was then stirred for 1 hr and left standing overnight at room temperature. The mixture was poured into 200 m*l* of water containing 1 m*l* of acetic acid, and then extracted with ether. The ether extract was washed with water, dried, and evaporated, and the residue was distilled under reduced pressure; bp 151—167°C/4 mmHg, 45 g (75%). Redistillation gave a colorless oil boiling at 123—124°C/3.5 mmHg.

Found: C, 63.32; H, 8.92%. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83%.

2,3,6-Trimethyl-6-ethoxycarbonyl-2-cyclohexen-1-one (V). A solution of IV (8.3 g) and beryllium chloride (2.9 g) in benzene (30 m*l*) was refluxed for 4 hr in a flask equipped with a calcium chloride tube. The reaction mixture was then poured into a mixture of 50 m*l* of 1 N hydrochloric acid and ice, extracted three times with benzene; the benzene extract was washed with a sodium bicarbonate solution and then with water, dried over calcium chloride, and distilled; bp 105—107°C/17 mmHg, 4.9 g (65%).

Found: C, 68.27; H, 8.41%. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63%.

2,3,6-Trimethyl-2-cyclohexen-1-one (VI). a) To a solution of potassium hydroxide (7 g) in 30 m*l* of water 3 g of V were added, and the mixture was refluxed for 2 hr. After cooling, the mixture was extracted with ether, and the ether extract was washed with water, dried, and distilled; bp 92—96°C/16 mmHg, 1.6 g (80%).

b) To 33.5 g of IV there were added 35 m*l* of concentrated hydrochloric acid and 70 m*l* of acetic acid, after which the mixture was refluxed for 6 hr. The mixture was concentrated under diminished pressure. The residue was added to water, neutralized with sodium bicarbonate, and extracted with ether. The ether extract was washed with water, dried, and distilled; bp 93—96°C/16 mmHg, 13.5 g (67%). The IR spectrum was identical with that of the product obtained by a).

Found: C, 78.48; H, 10.23%. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21%.

2,5,6-Trimethyl-2-cyclohexen-1-one (VIII). Into 21.3 g of ethyl α-propionylpropionate (II) there was stirred a solution of 0.3 g of sodium hydroxide in 50 m*l* of ethanol at 5—10°C. Crotonaldehyde (11.7 g) was stirred into the reaction mixture at the same temperature, and the solution was left standing overnight. It was then refluxed for 2 hr with a solution of 15 g of potassium hydroxide in 75 m*l* of water, poured into 300 m*l* of water, and neutralized with diluted hydrochloric acid. The mixture was extracted with ether, and the ether extract was washed with a 10% sodium bicarbonate solution and water, dried, and distilled; bp 92—100°C/24 mmHg, 8.9 g (48%). Semicarbazone; mp 230—231 °C.

Found: C, 61.01; H, 8.71; N, 22.00%. Calcd for $C_{10}H_{17}ON_3$: C, 61.51; H, 8.78; N, 21.52%.

1,4,5-Trimethyl-1-cyclohexene (X). A mixture of aldehydes prepared by the Diels-Alder reaction of isoprene and crotonaldehyde (IX, 40 g) and potassium hydroxide (50 g) was dissolved in 200 m*l* of diethylene glycol. Hydrazine hydrate (80%, 40.2 m*l*) was then added to the reaction mixture. On stirring, an exothermic reaction took place and the temperature of the reaction mixture rose to 80°C. The mixture was refluxed for 1 hr and then steam-distilled. The distillate was extracted with ether, and the ether extract was washed with water, dried, and distilled; bp 143—155°C, 22.5 g (63%). For analysis, a part was ozonized and reduced with zinc and acetic acid, and the product was precipitated as disemicarbazone, mp 176.5—178.5°C (decomp.).

Found: C, 49.34; H, 8.34; N, 30.83%. Calcd for $C_{11}H_{22}O_2N_6$: C, 48.87; H, 8.20; N, 31.09%.

3,5,6-Trimethyl-2-cyclohexen-1-one (XI). Fifteen grams of X were added to a mixture of 244 m*l* of the solution of *t*-butyl chromate (prepared from 185 g of chromic anhydride and 470 m*l* of *t*-butyl alcohol, diluted to 1.3 *l* with benzene, dried, and concentrated to 1 *l*) and 23 m*l* of acetic anhydride. The mixture was then refluxed for 22 hr under stirring and then steam-distilled. The distillate was extracted with ether, and the ether extract was washed with water, dried over magnesium sulfate, and distilled; bp 99—113°C/24 mmHg, 6.3 g (38%). Redistillation gave an oil; bp 104.5—106.5°C/21.5 mmHg. 2,4-Dinitrophenylhydrazone; mp 177—178°C (decomp.).

Found: C, 56.78; H, 5.93; N, 17.40%. Calcd for $C_{15}H_{18}O_4N_4$: C, 56.59; H, 5.70; N, 17.60%.

Oxidation by *t*-Butyl Chromate (General Procedure). To a trimethylcyclohexene or a cyclohexenone (1 g) dissolved in 10 m*l* of benzene, a solution of *t*-butyl chromate in benzene and acetic anhydride equimolar to the chromate were added and the mixture was heated to reflux under stirring. The reaction product was poured into water and steam-distilled until the distillate was no longer yellow. The distillate was then extracted with ether; the ether extract was washed with water, dried over sodium sulfate and concentrated to 10 m*l*, and the sample was submitted to gas chromatographic analysis.

Oxidation by Selenium Dioxide. To a trimethylcyclohexene or a cyclohexenone (2.8 g), 3 m*l* of glacial acetic acid were added. Selenium dioxide was then stirred in, portion by portion. After the addition was complete, the temperature of the reaction mixture was gradually elevated until the mixture was finally heated to reflux. The product was steam-distilled as long as the distillate was yellow. The distillate was then extracted with ether, and the ether extract was washed with water, dried over sodium sulfate, concentrated to 20 m*l*, and submitted to gas chromatography.

Trimethyl Hydroquinone. The ethereal solution of trimethylbenzoquinone (XII) obtained by the oxidation described above was treated with an aqueous solution of sodium hydrosulfite until the yellow color vanished. The ether layer was then washed with water, dried, and concentrated. The residue was triturated with petroleum ether, and white crystals of trimethylhydroquinone were obtained. When the substance was recrystallized from water, its mp was 169—170°C; this mp was not depressed when it was admixed with an authentic sample, and its IR spectrum was identical with that of the authentic sample.

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