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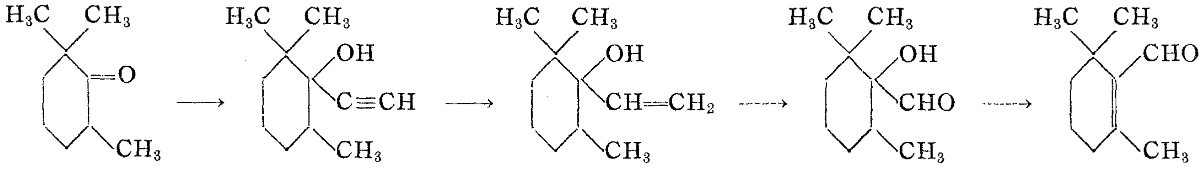
17. **Takuichi Miki and Yujiro Hara** : Studies on Ethylenic Compounds. I.* Synthesis of a New Isomer of Dihydroionone.

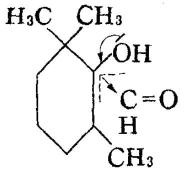
(*Research Laboratory, Takeda Pharmaceutical Industries, Ltd.***)

Although several reports on the synthesis of β-ionone have been published, the route starting from 2,6,6-trimethylcyclohexanone (I) is unknown yet, and this was investigated by the present authors.

First, the synthesis of cyclocitral (V), which is considered as an intermediate for the synthesis of ionone, was attempted. 1-Ethynyl-2,6,6-trimethylcyclohexanone(II)[1] prepared from (I) was partially reduced in hydrogen atmosphere using palladium catalyst deactivated with quinoline. The formation of 2,6,6-trimethyl-1-vinylcyclohexanone (III)[2] was ascertained by its infrared spectrum which indicates the presence of a vinyl group. With the intention of changing the vinyl group into formyl group, (III) was subjected to the hydroxylation reaction with peracid, but it remained intact even on heating. Moreover, the velocities of the decolorization of potassium permanganate and bromine solution are very slow. These facts show that the vinyl group of (III) is fairly hindered. Treatment of (III) with chromium trioxide in acetic acid, which is generally used to oxidize a hindered ethylenic bond,[3] gave 2,6,6-trimethylcyclohexanone (I) unexpectedly. The application[4] of the cleavage reaction of ethylenic bond by ozonization to (II) in carbon tetrachloride-acetic acid also afforded (I) in a good yield. The mechanism of the reaction is shown by the formula (IV).



(I) (II) (III) (IV) (V)



(IV)

Next, attempt was made to synthesize β-ionone (X) by the following route: (I)→(II)→(VI)→(VII) or (VIII)→(IX)→(X). By the condensation of (I) with the Grignard compound of but-1-yn-3-ol, 1-(1′-hydroxy-2′,6′,6′-trimethylcyclohexyl)but-1-yn-3-ol (VI)[1,5] was prepared. Being a mixture of isomers due to the three asymmetric carbons, the product (VI) was a viscous oil, but, after standing for a week, an isomer could be separated in a crystalline form. Since it took a long time to collect the crystals, the mixture of the isomers was used for the next reaction. When one mole of hydrogen was absorbed by (VI) under the catalysis of palladium-carbon deactivated with quinoline, 1-(1′-hydroxy-2′,6′,6′-trimethylcyclohexyl)but-1-en-3-ol (VII) was produced, which naturally has a *cis*-ethylenic bond. The oxidation of (VII) with manganese

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** Juso-Nishinocho, Higashiyodogawa-ku, Osaka (三木卓一, 原雄次郎).

[1] H. Sobotka, J. D. Chanley : J. Am. Chem. Soc., **71**, 4136(1949).

[2] E. B. Bates, E. R. H. Jones, M. C. Whiting : J. Chem. Soc., **1954**, 1854.

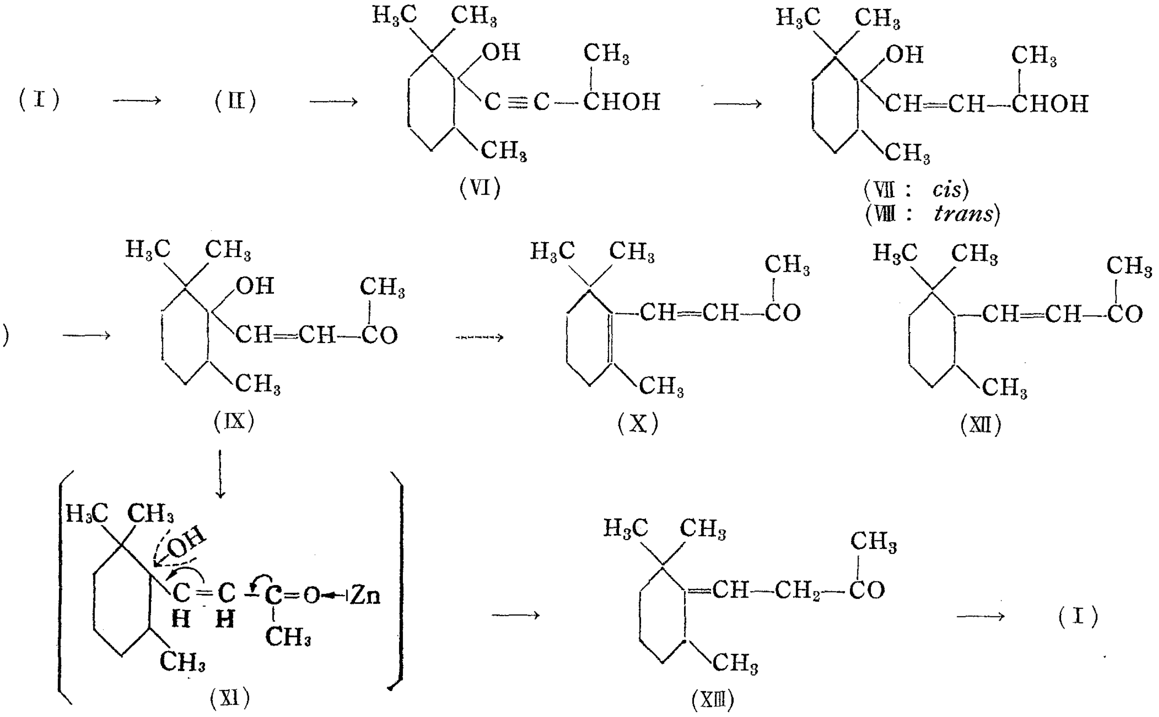
[3] H. Gilman; "Organic Chemistry," **1**, 636(1948).

[4] A similar reaction was performed in the synthesis of phellandral by D. T. C. Gillespie, P. R. Jefferies, A. K. Macbeth, M. J. Tompson : J. Chem. Soc., **1955**, 665.

[5] L. Weisler, J. M. Dieterle : U. S. Pat. 2,672,481(1954); C. A. **49**, 3260(1955).

dioxide[6] afforded a crystalline product, the structure of which remained undecided because it did not react with ketonic reagents.

On the other hand, when (VI) was treated with sodium in liquid ammonia–methanol–ether, a reduction product was obtained easily in a crystalline form. The infrared spectrum and the elementary analysis showed that it is *trans*-1-(1′-hydroxy-2′,6′,6′-trimethylcyclohexyl)but-1-en-3-ol(VIII). Treatment of (VIII) with manganese dioxide in petroleum ether gave a crystalline product.



Its infrared and ultraviolet spectra and 2,4-dinitrophenylhydrazone showed that it is the normal oxidation product, *trans*-1-(1′-hydroxy-2′,6′,6′-trimethylcyclohexyl)but-1-en-3-one (IX). The reason why there is such a difference between the attitudes of the *cis* and the *trans* compounds (VII and VIII) to manganese dioxide oxidation could not be clarified, but the fact is very interesting.

If one mole of water can be eliminated from the $C_{1'}$ and $C_{2'}$ in (IX) and the double bond is formed there, β-ionone (X) should be formed. All the attempts, however, with varieties of dehydrating agents were of no avail, giving always a non-lactonic and low-boiling product of unknown structure.

It is well known[7] that by the action of zinc and acetic acid, α-hydroxy ketone undergoes hydrogenolysis at C–OH bond. The application of this reaction to (IX) having the vinylog system of α-hydroxy ketone gave an unknown dihydroionone, splitting $C_{1'}$ hydroxyl group as expected. Two isomers of dihydroionone have already been described, the one[8] having a double bond at the α-positon to the ketone and the other[9] at *endo*-cyclic position, although the purity of the latter is doubtful. Since the ultraviolet spectrum of the present product shows no absorption specific to α,β-unsaturated ketones and the semicarbazone (m.p. 178°) is clearly different from that of (XII) (m.p. 172°), the double bond must be *exo*-cyclic to the cyclohexane

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[6] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jensen, T. Walker : J. Chem. Soc., **1952**, 1095.

[7] V. Prelog, K. Schenker, W. Küng : Helv. Chim. Acta, **36**, 471(1953).

[8] L. Colombi, A. Bosshard, H. Schiz, C. F. Seidel : *Ibid.*, **34**, 265(1951).

[9] A. Skita : Ber., **45**, 3312(1912); L. Ruzicka : Helv. Chim. Acta, **2**, 358(1919).

ring or situated inside the ring. In order to decide the position of the double bond it was subjected to oxidative cleavage with ozone in acetic acid to give 2,6,6-trimethylcyclohexanone (I) in agood yield. Thus 1-(2',6',6'-trimethylcyclohexylidene)butan-3-one (XIII) was assigned to the structure of the new isomeride of dihydroionone. The mechanism of the reaction can be formulated as (XI). This has an odor of camphor.

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Experimental

2,6,6-Trimethyl-1-vinylcyclohexanol (III)—66 g. of acetylenic alcohol (II) in 200 cc. of MeOH was shaken in H_2 atmosphere with 10 g. of 1% Pd-C poisoned by 0.3 cc. of quinoline as catalyst and 9.0 L. of H_2 was absorbed at 22° to convert the triple bond into a double bond. The resulting solution was filtered and, after the addition of ether, washed with dil. H_2SO_4 and water. The ethereal solution was dried over anhyd. Na_2SO_4. After evaporation of the solvent, the residual oil was distilled at atmospheric pressure to give 65 g. of a colorless liquid, b.p. 212~213°. ν_{max} 920, 1002, 1842 cm^{-1}(vinyl), 1648 cm^{-1}(double bond), 3530 cm^{-1}(hydroxyl). *Anal.* Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found : C, 77.52; H, 11.79.

Oxidation of the Vinyl Alcohol (III) with Chromium Trioxide—To a solution of 5 g. of the vinyl alcohol (III) in 70 cc. of AcOH was slowly added a mixture of 5 g. of CrO_3, 10 cc. of AcOH, and 5 cc. of water under vigorous stirring. The temperature of the reaction mixture was maintained at 10~20° during the procedure. After the addition, the mixture was stirred for 4 hrs. further, poured into $NaHSO_3$ solution, and thoroughly extracted with benzne. The benzene extract, after washing with Na_2CO_3 solution and water, and drying over anhyd. Na_2SO_4, was fractionated *in vacuo*. The main fraction (2.0 g.), b.p_{35} 120~125°, gave 2,4-dinitrophenylhydrazone, m.p. 124°, which showed no depression on admixture with the authentic sample prepared from 2,6,6-trimethylcyclohexanone (I).

Ozonization of the Vinyl Alcohol (III)—A solution of 3 g. of the vinyl alcohol (III) in 50 cc. of AcOH was ozonized in the usual manner over a period of 3 hrs. The resulting mixture was heated with Zn powder at 50° for 7 hrs. to decompose the ozonide, and upon cooling, benzene and water were added. The benzene layer was treated with $FeSO_4$ solution, Na_2CO_3 solution, and water, and the solvent evaporated. The residue was subjected to vacuum distillation to give 2 g. of a colorless liquid, b.p_{25} 90°. The 2,4-dinitrophenylhydrazone, m.p. 120°, showed no depression on admixture with that of 2,6,6-trimethylcyclohexanone (I).

1-(1'-Hydroxy-2',6',6'-trimethylcyclohexyl)but-1-yn-3-ol (VI)—Procedure A : A Grignard reagent was prepared from 600 cc. of dry ether, 13.4 g. of Mg, and 66 g. of EtBr. The mixture was chilled to 0°, and 17.5 g. of but-1-yn-3-ol in 70 cc. of dry ether was added dropwise with rapid stirring in the course of 1 hr. and refluxed for 1.5 hrs. on a steam bath to complete the reaction. To the Grignard compound thus formed was added dropwise 40 g. of (I) in 100 cc. of dry ether under vigorous stirring and then allowed to stand overnight at room temperature. The mixture, after heating for 3 hrs., was decomposed with 1 L. of 20% NH_4Cl solution. The ethereal layer was then distilled *in vacuo*. The product (30.3 g.), b.p_{15} 161~162°, was collected as a viscous liquid which solidified after kept standing for several days at room temperature. The crude solid was recrystallized from petroleum ether (b.p. 60~80°) as colorless prisms, m.p. 100~106°. *Anal.* Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found : C, 74.44; H, 10.51.

Procedure B : To a Grignard reagent prepared from 600 cc. of dry ether, 66 g. of EtBr, and 13.4 g. of Mg was added dropwise 44 g. of the acetylenic alcohol (II) in 70 cc. of dry ether at room temperature over a period of 2 hrs. and then the mixture was heated for 2 hrs. To the Grignard compound was added dropwise 12 g. of acetaldehyde in 50 cc. of dry ether under stirring and ice-cooling, heated for an additional 2 hrs., and then the mixture was hydrolyzed with 1 L. of 20% NH_4Cl solution. The product (32.5 g.), b.p_{16} 164~165°, was obtained upon vacuum distillation. *Anal.* Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found : C, 73.80; H, 10.55, The liquid gave colorless prisms, m.p. 100~106°, by the same treatment as described in Procedure A.

***cis*- -(1'-Hydroxy-2',6',6'-trimethylcyclohexyl)but-1-en-3-ol (VII)**—The acetylenediol (VI)(4.5 g.) was partially hydrogenated in 50 cc. of AcOEt using 10 g. of 1% Pd-C deactivated with 0.3 cc. of quinoline as catalyst and 250 cc. of H_2 was absorbed. After treating the mixture in the usual manner, the residual oil gave 3.5 g. of a colorless liquid, b.p_{27} 169°. *Anal.* Calcd. for $C_{13}H_{24}O_2$: C, 73.53; H, 11.37. Found : C, 74.09; H, 11.71.

Oxidation of *cis*-Enediol (VII) with Manganese Dioxide—A solution of 3 g. of *cis*-enediol (VII) in 100 cc. of petr. ether (b.p. 30~60°) was shaken with 15 g. of precipitated $MnO_2$6) for 24 hrs. at room temperature. The solid was filtered and washed thoroughly with ether. The combined filtrate and washings was concentrated *in vacuo*. Distillation of the residue afforded 1.5 g. of a colorless liquid, b.p_{25} 162°. From the liquid a solid material separated on standing for several days at room temperature, and then recrystallized from MeOH as colorless prisms, m.p. 98°, which did not give the 2,4-dinitrophenylhydrazone. *Anal.* Calcd. for $C_{13}H_{20}O_2$: C, 74.96, H, 9.68. Found: C, 74.99; H, 9.48.

trans-**1-(1′-Hydroxy-2′,6′,6′-trimethylcyclohexyl)but-1-en-3-ol (VIII)**—In a 1-L. three-necked flask equipped with a sealed stirrer, an exit tube for escaping gas, and a dropping funnel, a solution of 15.7 g. of the acetylenediol (VI) in 45 cc. of MeOH and 50 cc. of ether was placed. The flask was chilled in a vessel filled with a mixture of dry ice and acetone to about −50°. Liq. NH_3(300 cc.) was then dropped into the chilled solution. The separating funnel was removed and 5.3 g. of Na was added in small portions under vigorous stirring over a period of 1 hr. The mixture was allowed to stand overnight at room temperature and NH_3 was evaporated at the same time. To the residual solid was added finely shaved ice and the solid material was dissolved. The solution was extracted with ether, the ethereal solution was washed successively with dil. H_2SO_4, Na_2CO_3 solution, and water, and dried over Na_2SO_4. The residue, obtained by the removal of the solvent, gave 14.0 g. of a viscous liquid, b.p_{17} 163°, which solidified after kept standing for several days at room temperature. The crude solid was recrystallized from petr. ether (b.p. 60~80°) to colorless prisms, m.p. 124°. ν_{max} 974 cm^{-1}(*trans* peak). *Anal.* Calcd. for $C_{13}H_{24}O_2$: C, 73.53; H, 11.37. Found : C, 73.36; H, 11.27.

trans-**1-(1′-Hydroxy-2′,6′,6′-trimethylcyclohexyl)but-1-en-3-one**(IX)—A solution of 14.0 g. of the *trans*-enediol (VIII) in 500 cc. of petr. ether (b.p. 30~60°) was shaken with 90 g. of precipitated MnO_2 at 27° for 24 hrs. The solid was filtered and washed thoroughly with ether, and then the combined filtrate and washings was worked up as previously described. A product (10.2 g.) was obtained as a viscous liquid, b.p_{17} 164~166°, which solidified on standing for several days at room temperature. The crude solid was recrystallized from petr. ether (b.p. 60~80°) to colorless needles, m.p. 92°. λ_{max}^{EtOH} 234 mμ(ε 11,800). *Anal.* Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.08; H, 10.34.

The 2,4-dinitrophenylhydrazone, m.p. 163°, was recrystallized to red plates from a mixture of petr. ether (b.p. 60~80°) and MeOH. *Anal.* Calcd. for $C_{19}H_{26}O_5N_4$: C, 58.45; H, 6.71. Found: C, 58.65; H, 6.51.

1-(2′,6′,6′-Trimethylcyclohexylidene)butan-3-one (XIII)—A mixture of 5 g. of (IX), 6 g. of zinc powder and 50 cc. of AcOH was heated at 100° for 2 hrs. under vigorous stirring. To the mixture was added ether and water, and the organic layer, after washing successively with Na_2CO_3 solution and water and then drying over anhyd. Na_2SO_4, was distilled *in vacuo* to give 2 g. of colorless liquid, b.p_{18} 136°, n_D^{19} 1.4959. 2,4-Dinitrophenylhydrazone : Orange needles (from MeOH containing a small amount of benzene), m.p. 102°. *Anal.* Calcd. for $C_{19}H_{26}O_4N_4$: C, 60.94; H, 7.00. Found: C, 61.13; H, 7.04. Semicarbazone : Colorless prisms (from MeOH), m.p. 178°. *Anal.* Calcd. for $C_{14}H_{25}ON_3$: C, 66.89; H, 10.03. Found : C, 66.78; H, 9.99.

Ozonization of Dihydroionone(XIII)—A mixture of 1.5 g. of (XIII) in 15 cc. of CCl_4 and 3 cc. of AcOH was ozonized in the usual manner over a period of 3 hrs. To the resulting mixture was added benzene and water, and the organic layer, after washing with Na_2CO_3 solution and water and then drying over Na_2SO_4, was distilled *in vacuo*. A product (0.9 g.), b.p_{20} 80°, was obtained. The 2,4-dinitophenylhydrazone, m.p. 120°, and the semicarbazone, m.p. 205°, showed no depression in m.p. on admixture with authentic samples derived from (I).

Summary

The synthesis of β-ionone starting from 2,6,6-trimethylcyclohexanone (I) was investigated. Oxidation of 2,6,6-trimethyl-1-vinylcyclohexanol (III) with chromium trioxide or ozone unexpectedly afforded(I). 1-(1′-Hydroxy-2′,6′,6′-trimethylcyclohexyl)-but-1-yn-3-ol (VI) was reduced with sodium in liquid ammonia and the product was oxidized with manganese dioxide to *trans*-1-(1′-hydroxy-2′,6′,6′-trimethylcyclohexyl)but-1-en-3-one (IX). An attempt to prepare β-ionone by the dehydration of (IX) was unsuccessful. Treatment of (IX) with zinc-acetic acid yielded a new isomer of dihydroionone, 1-(2′,6′,6′-trimethylcyclohexylidene)butan-3-one (XIII).

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