Polyterpenes. III[1]. *The Structure of Thujopsene**

By Hiroshi KOBAYASHI, Shizuo NAGAHAMA and Saburo AKIYOSHI

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Thujopsene, the main component of Hiba wood oil, has attracted much attention in the last few years[2]. Hirose and Nakatsuka[3] pointed out that widdrene[4], which was later shown to be widely distributed in *Cupressaceae*[5], was identical with thujopsene. Erdtman and Norin[6] confirmed this identity and proposed structure Ia for this compound. Independently we also arrived at the same conclusion and proposed structure Ia and Ib[7], of which the former is preferred[8]. Subsequently Erdtman and Norin[9] presented further evidence and revised their structure to Ib. Sisido and Nozaki[10] proposed structure Ic for thujopsene, but later withdrew their suggestion[11] in favor of Erdtman and Norin's proposal. In view of the evidence presented[12] we also consider that the properties of thujopsene are best explained by the formula Ib.

We now wish to present our findings which have already been outlined in our short communication[8].

Thujopsene (I) possesses the molecular formula $C_{15}H_{24}$ and is a tricyclic hydrocarbon compound having an unsaturated bond. On the permanganate oxidation in acetone, it gives ketocarboxylic acid, $C_{15}H_{24}O_3$ (II), as a main product in addition to other by-products. Ozonolysis of thujopsene gives the same acid II. This acid II is therefore considered as the primary product to which thujopsene cleaves at the unsaturated bond without any other change. Thus, the purpose of the studies comes to determine the structure of acid II.

Hypobromite oxidation of II affords a dicarboxylic acid, $C_{14}H_{22}O_4$ (III), which shows the presence of the CH_3-CO- group in the keto acid II, and these results, when considered together with the preceding data, seem

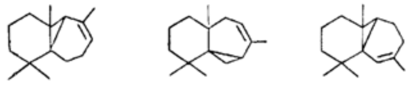
Ia Ib Ic

Fig. 1

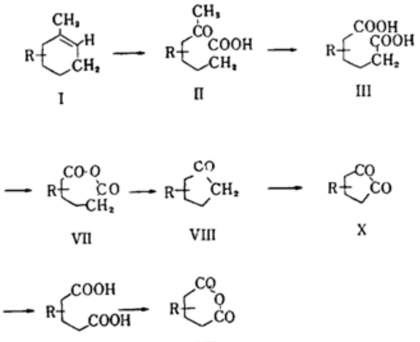

Fig. 2

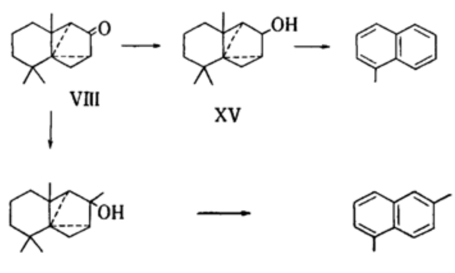

Fig. 3. In VIII, a cyclopropane ring is fused to a cyclopropanone ring in either of the ways which are showed above by the two broken lines.

The broken lines in XV and XVI present the same meaning as in VIII.

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[1] Previous paper: S. Nagahama, H. Kobayashi and S. Akiyoshi, This Bulletin, **32**, 366 (1959).

[2] For references to previous studies, see S. Akiyoshi and S. Nagahama, This Bulletin, **30**, 886 (1957).

[3] Y. Hirose and T. Nakatsuka, *J. Jap. Wood Res. Soc.*, **4**, 26 (1958).

[4] H. Erdtman and B. R. Thomas, *Acta Chem. Scand.*, **12**, 267 (1958).

[5] H. Erdtman and Z. Pelchowicz, *Chem. Ber.*, **89**, 341 (1956); C. Enzell, *Acta Chem. Scand.*, **14**, 81 (1960); C. Pilo and J. Runeberg, ibid., **14**, 353 (1960); J. Runeberg, ibid., **14**, 797 (1960).

[6] H. Erdtman and T. Norin, ibid., **13**, 1124 (1959).

[7] S. Akiyoshi, H. Kobayashi and S. Nagahama, presented at the 2nd Symposium on Perfumary of Terpene and Essential Oil Chemistry, Hiroshima, October, 1958.

[8] H. Kobayashi, S. Nagahama and S. Akiyoshi, This Bulletin, **32**, 203 (1959).

[9] H. Erdtman and T. Norin, *Chem. & Ind.*, **1960**, 622.

[10] K. Sisido and H. Nozaki, *J. Org. Chem.*, **25**, 875 (1960).

[11] K. Sisido, H. Nozaki and Y. Imagawa, presented at the 4th Symposium on Natural Organic Compounds, Kyoto, October, 1960.

[12] S. Forsén and T. Norin, *Acta Chem. Scand.*, in press. We thank Dr. Norin for the kind presentation of his manuscript of this paper.

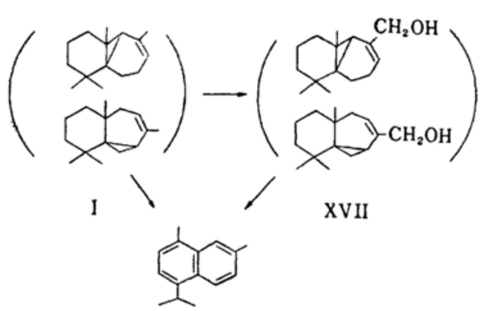


Fig. 4

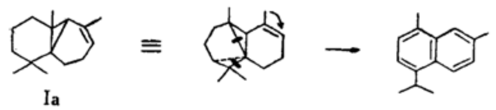
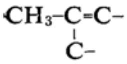


Fig. 5

to indicate the presence of the structure  $CH_3-\underset{\substack{|\\ C-}}{C}=C-$ in thujopsene.

The keto acid II is, when treated with mineral acid, easily isomerized to a ketolactone (carbonyl absorptions 1774 and 1724 cm^{-1}) accompanied with a cleavage of a ring in the keto acid II. It possibly indicates the presence of a small ring in the keto acid II.

The C_{14}-dicarboxylic acid (III) gives two different monomethyl esters, $C_{15}H_{24}O_4$, one (IV) of which is obtained by acid catalyzed esterification with methanol and the other (V) by hydrolysis of dimethyl ester (VI) with methanolic potassium hydroxide. The former (IV) is also obtained from the methyl ester of II, when treated with hypobromite in aqueous dioxane, and it seems therefore that one of the two carboxyl groups in III is much more hindered than the other and that the former results from CH_3-CO- group in II.

The C_{14}-dicarboxylic acid (III) is dehydrated to an anhydride, $C_{14}H_{20}O_3$ (VII) (carbonyl adsorptions 1799 and 1752 cm^{-1}), which is easily pyrolyzed at about 300°C to a cycloketone, $C_{13}H_{20}O$ (VIII), accompanying decarboxylation[13].

Calcium and barium salt of dicarboxylic acid III also give cycloketone VIII by pyrolysis but they do so in poor yield.

Cycloketone VIII is condensed with ethyl formate in the presence of sodium metal to an enol, $C_{14}H_{20}O_2$ (IX), and is oxidized to a yellow 1, 2-diketone, $C_{13}H_{18}O_2$ (X), with selenium dioxide in dioxane. Each of these two characteristic reactions results in the quantitative formation of the corresponding product and exclusively of only a single corresponding species. It seems therefore that the carbonyl group in VIII connects to a methylene group at one side and to a more substituted carbon atom at the other side. This presumption becomes more certain by the fact that 1, 2-diketone (X) is converted into a dicarboxylic acid, $C_{13}H_{20}O_4$ (XI), without loss of the carbon atom when treated with alkaline hydrogen peroxide.

The C_{13}-dicarboxylic acid (XI) gives the corresponding anhydride, $C_{13}H_{18}O_3$ (XII), by heating. All attempts to get C_{12}-cycloketone from XI have failed.

XII shows infrared absorptions of the carbonyl group at 1799 and 1754 cm^{-1}. Therefore XII is considered to be of glutaric anhydride type, and the cycloketone to be of structure VIII, and further the ring containing an unsaturated bond in thujopsene is six-membered.

C_{13}-dicarboxylic acid (X), like acid III, also easily gives two different monomethyl esters, $C_{14}H_{20}O_4$, one (XIII) by esterification and the other (XIV) through hydrolysis of dimethyl ester.

Cycloketone VIII gives an alcohol, $C_{13}H_{22}O$ (XV), when reduced with lithium aluminum hydride. It is of interest that the reduction with lithium aluminum hydride proceeds stereospecifically and the epimer of XV does not occur[14].

Alcohol XV is dehydrogenated by selenium to 1-methylnaphthalene with loss of two carbon atoms. If the two carbon atoms eliminated on dehydrogenation are regarded as that of one methyl of the geminal dimethyl group and that of the angular methyl group, the skeleton of alcohol XV is considered as formula XV. The position of the hydroxyl group is determined as follows. By means of methyl magnesium iodide, a methyl group is introduced on the carbon atom of the carbonyl group in VIII, which leads to a corresponding alcohol, $C_{14}H_{24}O$ (XVI). Selenium dehydrogenation of alcohol XVI gives 1, 6-dimethylnaphthalene. The methyl group introduced is on 6-position unless a migration of the methyl group occurs on dehydrogenation, and thus the groups in question are considered to be on the position indicated.

The enlarging of the five-membered ring in alcohol XV to the six-membered ring by aromatization, when considered together with the acid-catalyzed cleavage of a ring in the keto acid II, seems to indicate the presence of the

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[13] This ketone was first reported by T. Ozeki, S. Seto and T. Nozoe at the 10th Annual Meeting of the Chemical Society of Japan, Tokyo, 1957, and called "pyroketone" by them. On the preparation of this ketone by another route, see previous paper, Ref. 1.

[14] The epimer of alcohol XV was obtained from lead tetraacetate oxidation product of thujopsene, see Ref. 1.

cyclopropane ring fused to the five-membered ring in XV. In addition, the infrared and ultraviolet spectral data of keto acid II, its methyl ester and cycloketone VIII are corroborative of the conjugation of the ketonic group with the cyclopropane ring[15].

Thus Ia or Ib is proposed for the structure of thujopsence. The fact that the dehydrogenation of thujopsene and its alcoholic derivative, $C_{15}H_{24}O$ (XVII), afford 1, 7-dimethyl-4-isopropylnaphthalene is unfavorable for structure Ib which is less amenable to the rearrangement in regard to the naphthalene derivatives.

Experimental

Ester of Ketocarboxylic Acid II.—Methylation with diazomethane gave a methyl ester which was purified by distillation under reduced pressure, b. p. 151~158°C/7 mmHg, m. p. 42~43°C. Infrared max. (Nujol) 1700 and 1735 cm^{-1}; ultraviolet max. 222 mμ (ε 3160) and 284 mμ (ε 40). $[\alpha]^{26}_{D}-94.0°$ (*c* 1.54).

Found: C, 71.96; H, 9.84. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%.

Esters of Dicarboxylic Acid III.—Dimethyl ester VI was prepared through methylation with diazomethane in ether. The solution was evaporated to dryness, and the residue was purified by recrystallization from methanol, m. p. 72~73°C. Infrared max. (carbon tetrachloride) 1737 cm^{-1}.

Monomethyl ester IV was prepared from dicarboxylic acid III by esterification with methanol. The details were presented in the previous paper. Melting point 59~60°C. Infrared max. (Nujol) 1700 and 1736 cm^{-1}. This monomethyl ester was also obtained by treating the methyl ester of the ketocarboxylic acid II (2.50 g.) with excess of sodium hypobromite solution (aqueous dioxane 1 : 1) for 2.5 hr. at room temperature. The reaction mixture was diluted with water, acidified and extracted with ether. The ethereal extract was washed twice with water, extracted with aqueous sodium bicarbonate (7%) and then with aqueous sodium hydroxide (5%). When the sodium bicarbonate extract acidified, dicarboxylic acid III was mainly obtained, m. p. 209~210°C, mixed melting point with dicarboxylic acid III undepressed. From the sodium hydroxide extract the monomethyl ester (1.30 g.) was obtained, m. p. 58~59°C and mixed melting point with that obtained by esterification of III undepressed.

Monomethyl Ester V.—The dimethyl ester prepared by methylation with diazomethane was refluxed in methanolic potassium hydroxide (5%) for 6 hr. The reaction mixture was diluted with water, washed with ether, acidified, and extracted with ether. The last ethereal extract was washed with water, and extracted with aqueous sodium bicarbonate (7%) and then with aqueous sodium hydroxide (5%). The sodium bicarbonate extract was acidified and extracted with ether. The extract was washed with water, evaporated to dryness, the residue being recrystallized from aqueous methanol, m. p. 208~209°C. Mixed melting point with dicarboxylic acid III (m.p. 209~210°C) was undepressed. The sodium hydroxide extract was acidified and then treated as above. The product obtained was a monomethyl ester of m. p. 114.5~115.5°C. Infrared max. (chloroform) 1693 and 1720 cm^{-1}.

Found: C, 67.02; H, 9.02. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02%.

This monomethyl ester was reconverted to dimethyl ester VI by methylation with diazomethane in ether.

Cycloketone VIII.—The acid anhydride VII (5.0 g.) was pyrolyzed at 280~320°C for 40 min. under air-cooling reflux; distillation of the product gave 3.4 g. of a distillate, which was refluxed in methanolic potassium hydroxide (5%) for an hour. The reaction mixture was diluted with water, extracted with ether, and the ethereal extract was washed with water and then the solvent was removed to dryness. The residue was steam-distilled and ketone VIII separated as crystalline precipitates was dissolved in ether and dried over sodium sulfate. After the solvent was removed to dryness, the residue was recrystallized from petroleum ether, m.p. 117~118°C, and was further purified by sublimation under reduced pressure, m.p. 118~119.5°C, yield 1.7 g.. Infrared max. (Nujol) 1727 cm^{-1}. Ultraviolet max. (ethanol) 278 mμ (ε 55.5). $[\alpha]^{26}_{D}+62.2°$ (*c* 0.602).

This ketone was also obtained by pyrolysis of calcium salt and of barium salt of III.

Hydroxymethylation of VIII, Enol IX.—The cycloketone VIII (600 mg.) and ethyl formate (700 mg.) were allowed to react in cold benzene solution (8 ml.) in the presence of sodium dust (200 mg.) for two days, when methanol was added to decompose the residual sodium metal. Water was added and the aqueous layer was acidified. The crude enol was collected (250 mg., m. p. 97~98°C) and decolorized with active charcoal. Recrystallization from aqueous ethanol gave white needles of m.p. 105~106°C, which gave purple color in the ferric chloride test. Infrared max. (chloroform) 1668 cm^{-1}, (Nujol) 1681 and 2680 cm^{-1}.

Found: C, 75.63; H, 9.22. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%.

From the benzene layer, the starting material (330 mg.) was recovered.

Diketone X.—Cycloketone VIII (130mg.), selenium dioxide (130 mg.) and dioxane (2.5 ml.) were heated in a sealed tube for 6 hr. at 200°C. Selenium was filtered off and washed with petroleum ether. The filtrate and washings were combined and water (30 ml.) was added to it; the yellow diketone was dissolved in ethereal layer. The aqueous layer was extracted with petroleum ether until the extract was no longer colored yellow. The combined extract was washed with water and dried over sodium sulfate. After the solvent was removed from the dried solution the residue solidified

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[15] E. N. Trachtenberg and G. Odian, *J. Am. Chem. Soc.*, **80**, 4018 (1958); R. J. Mohrbacher and N. H. Cromwell, ibid., **79**, 401 (1957).

immediately. Yield of crude product 130 mg., m.p. 170～171°C. Recrystallization from petroleum ether raised the melting point to 180～181°C. Infrared max. (Nujol) 1736 cm^{-1}.

Found : C, 75.78 ; H, 8.87. Calcd. for $C_{13}H_{18}O_2$: C, 75.69 ; H, 8.80%.

Dicarboxylic Acid XI[16].—To the mixture of diketone X (50 mg.), ethanol (6 ml.) and hydrogen peroxide (30%, 2 ml.) was dropwise added aqueous sodium hydroxide (10%, 2 ml.), and after being allowed to stand for half an hour, the reaction mixture was warmed at 80°C in a water bath for a few minutes and, after being cooled, was acidified and the crystalline precipitatates wese recrystallized from aqueous ethanol, m. p. 210～211°C. The dicarboxylic acid XI was dehydrated to the acid anhydride XII with acetic anhydride, and recrystallized from benzene-petroleum ether, m. p. 211～212°C.

No ketone formation was observed during the pyrolysis of the acid anhydride XII, which was also true in the cases of calcium- and barium dicarboxylate XI.

Alcohol XV.—An ethereal solution of lithium aluminum hydride (30 mg.) was added with swirling into an ethereal solution of cycloketone VIII (500 mg.). After being allowed to stand overnight, a small amount of water was added to decompose the residual lithium aluminum hydride. The resultant mixture was extracted with an additional amount of ether. The ethereal extract was washed with dilute sulfuric acid the then several times with saturated salt solution, and was dried over sodium sulfate. The solvent was evaporated to dryness and the residue was crystallized immediately, yield 450 mg., and recrystallized from petroleum ether, m.p. 132～133°C. Infrared max. (Nujol) 3280 cm^{-1}. $[\alpha]_D^{26}+19.2°$ (c 0.802).

Found : C, 80.30 ; H, 11.68. Calcd. for $C_{13}H_{22}O$: C, 80.35 ; H, 11.41%.

Alcohol XV (2.0 g.) was oxidized to cycloketone VIII by treatment with sodium bichromate (1.5 g.), water (2 ml.) and acetic acid (16 ml.) for 30 hr. at room temperature. The reaction mixture was diluted with water and was extracted with ether. The ethereal extract was washed several times with aqueous sodium bicarbonate (7%), with water and dried over sodium sulfate. After the solvent was removed to dryness the residue was crystallized immediately. Repeated recrystallization from petroleum ether gave m.p. 117～118°C. This substance was identified as being the original cycloketone VIII by mixed melting point test and infrared spectrum comparison.

Dehydrogenation of Alcohol XV.—The alcohol XV (2.0 g.) and selenium (3.0 g.) were heated under reflux at 400°C for 165 hr. The oily product was distilled and the main fraction (b.p. 230～240°C) was eluted from alumina (50×70 mm. column) with petroleum ether, yield 0.30 g., n_D^{17} 1.5803. The picrate of the above hydrocarbon compound was orange needles and recrystallizations from ethanol afforded the material of m. p. 137～138°C. The pure hydrocarbon compound was regenerated from picrate by elution from alumina with petroleum ether. n_D^{17} 1.6125.

Found : C, 92.86 ; H, 7.33. Calcd. for $C_{11}H_{10}$: C, 92.91 ; H, 7.09%.

Picrate of the purified material showed m.p. 138～139°C, and mixed melting point with the picrate of 1-methylnaphthalene[17] (m.p. 139～140°C) was undepressed.

Found : C, 54.89 ; H, 3.63 ; N, 11.39. Calcd. for $C_{17}H_{13}O_7N_3$: C, 54.99 ; H. 3.53 ; N, 11.32%.

Methylcarbinol XVI.—The ethereal solution of cycloketone (4.3 g.) was dropwise added to ethereal methyl magnesium iodide (from methyl iodide (3.6 g.), magnesium (0.6 g.) and ethyl ether (13 ml.)). The Grignard complex was decomposed by treatment with aqueous ammonium chloride. The methylcarbinol was extracted with an additional ether from the above reaction mixture, yield 4.2 g., and was purified by recrystallization from petroleum ether and sublimation under reduced pressure, m.p. 62～63°C. $[\alpha]_D^{20}+14.3°$ (c 1.87). Infrared max. 3245 cm^{-1}.

Found : C, 80.92 ; H, 11.76. Calcd. for $C_{14}H_{24}O$: C, 80.71 ; H, 11.61%.

Dehydrogenation of Methyl Carbinol XVI.—Methyl carbinol XVI (2.0 g.) and selenium (3.0 g.) were heated at 400°C for 104 hr. The same treatment as that of alcohol XV yielded an oily product (0.3 g.), the main fraction distilling at 240～250°C. The infrared spectrum of the hydrocarbon compound coincided with that of 1,6-dimethylnaphthalene and its picrate recrystallized from ethanol was of m.p. 111～112°C. The pure hydrocarbon compound was regenerated from picrate by means of elution from alumina with petroleum ether. n_D^{12} 1.6047.

Found : C, 92.13 ; H, 8.02. Calcd. for $C_{12}H_{12}$: C, 92.26 ; H, 7.74%.

Esters of the Dicarboxylic Acid XI.—The dimethyl ester was prepared by methylation with diazomethane by a method similar to the case of the dicarboxylic acid III. M. p. 70～72°C.

Monomethyl Ester XIII.—Dicarboxylic acid anhydride XII (490 mg.) was refluxed in methanol (2 ml.) containing two drops of concentrated sulfuric acid for half an hour. The reaction mixture was diluted with water and extracted with ether. The ethereal extract was washed with water and extracted with aqueous sodium bicarbonate (7%). The aqueous extract was washed with ether, acidified and extracted again with ether. The last ethereal extract was evaporated to dryness and the solid residue was recrystallized from aqueous methanol to give a compound, m.p. 58～62°C, which decomposed at about 90°C and again solidified and melted at 208～209°C. The decomposed product was identical with the dicarboxylic acid anhydride XII (mixed melting point test and infrared spectrum comparison).

The monomethyl ester was converted to the dimethyl ester with diazomethane, and hydrolyzed

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[16] The same dicarboxylic acid had been obtained in the series of lead tetraacetate oxidation of thujopsene and the chemical data of acid XI and its anhydride XII had been presented in Ref. 1.

[17] An authentic sample was synthesized according to the direction of O. Grummitt et al., *J. Am. Chem. Soc.*, 65, 295 (1943).

to the original dicarboxylic acid with aqueous potassium hydroxide.

Monomethyl Ester XIV.—Dimethyl ester (1.0 g.) prepared by methylation with diazomethane was refluxed in methanolic potassium hydroxide (10%, 25 ml.) for 5 hr. The reaction mixture was diluted with water, and the neutral oil which separated, on solidification, was filtered off. The aqueous portion was acidified and the crystalline precipitates collected, yield 300 mg., were recrystallized from petroleum ether, m.p. 145~145.5°C, which was reconverted to the starting material by the methylation.

Dehydrogenation of Thujopsene.—Thujopsene (5.0 g.) and selenium (10.0 g.) were heated at 330°C for 190 hr. The oily product obtained on distillation (b.p. above 120°/5 mmHg) was eluted from alumina (50×50 mm. column) by petroleum ether, yield 0.54 g., n_D^{18} 1.5702; the product when chilled on dry ice gradually solidified. Repeated recrystallizations from methanol afforded colorless plates of m.p. 60~61°C. The infrared spectrum of the hydrocarbon compound agreed with that of 1, 7-dimethyl-4-isopropylnaphthalene.

Found: C, 90.72; H, 9.41. Calcd. for $C_{15}H_{18}$: C, 90.85; H, 9.15%.

The picrate was recrystallized from ethanol and had m.p. 88~89°C.

Found: C, 58.96; H, 4.96; N, 9.85. Calcd. for $C_{21}H_{21}O_7N_3$: C, 59.01; H, 4.95; N, 9.83%.

Aldehyde[18].—Thujopsene (9.5 g.) was added to the ethanol solution of selenium dioxide (5.2 g. of selenium dioxide in 60 ml. of absolute ethanol). The mixture was gently refluxed for 20 hr. at boiling point. The reaction mixture, after the selenium (2.2 g.) was filtered off, was concentrated to about 20 ml. under reduced pressure and a large amount of water was added to the remainder, the organic portion of which was extracted by benzene. The benzene extract was washed twice with saturated salt solution, with saturated aqueous lead acetate and again with salt solution three times, and dried over sodium sulfate. After the solvent was removed the remainder was fractionated. The aldehyde was obtained from the fraction of b.p. 133~134.5°C/3.5 mmHg, yield of crude product 7.1 g.. Repetition of recrystsllization raised the melting point to 74~75°C. Infrared max. (Nujol) 1683 cm^{-1}.

Alcohol XVII.—The warm solution of aldehyde (5.54 g. of aldehyde in 26 ml. of methanol) was added to the solution of sodium borohydride (0.344 g. of the hydride in 3 ml. of methanol). After being heated for ten minutes, the mixture was left to cool at room temperature for two hours. Aqueous acetic acid was added to the reaction mixture to decompose the residual hydride. When the resulting mixture was diluted with water, the product was immediately solidified. The crystalline precipitates were collected and washed with water thoroughly. White needles of m. p. 102.5~103.5°C were obtained by recrystallization from petroleum ether. $[\alpha]_D^{20}-109°$ (*c* 0.90). Infrared max. (Nujol) 3320 cm^{-1}.

Found: C, 81.84; H, 11.01. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98%.

Dehydrogenation of Alcohol XVII.—Alcohol XVII (5.0 g.) and selenium (10.0 g.) were heated at 330°C for 30 hr. The oily product obtained (b.p. above 120°C/4.5 mmHg) was eluted from alumina (20×100 mm. column) with petroleum ether, yield 0.20 g., n_D^{18} 1.5642. Though the picrate was prepared, its melting point could not be raised to that reported by Sŏrm[19]. The infrared spectrum of the hydrocarbon compound which was regenerated from the crude picrate coincided to a fair extent with that of 1,7-dimethyl-4-isopropylnaphthalene. The regenerated hydrocarbon compound was semi-solid, and rigid determination of its melting point was not conducted owing to the lack of a sample.

Department of Organic Synthesis
Faculty of Engineering
Kyushu University
Hakozaki, Fukuoka

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[18] This aldehyde is that reported by Erdtman and Norin, Ref. 6.

[19] J. Príva, V. Herout, B. Schneider and F. Sŏrm, *Collection Czechoslov. Chem. Communs.*, **18**, 500 (1953).