Polyterpenes. II[1]. *Oxidation of Thujopsene with Lead Tetra-acetate**

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It has been reported by Kawamura[2] and recently by Nozoe et al.[3], that thujopsene, the main constituent of Hiba (*Thujopsis dolabrata Sieb. et Zucc.*) wood oil, affords a glycol, m. p. 91°, by the oxidation with permanganate in acetone containing water. On the other hand, the authors obtained a ketonic acid, m. p. 165° as a main product and no glycol was found when the oxidation was carried out in acetone solution without addition of water[1].

To obtain the glycol by an alternate route, oxidation of this sesquiterpene with lead tetra-acetate was attempted. However, contrary to the expectation, a ketone and its enol acetate were found to be the main products.

It is well known that the olefines, when oxidized with lead tetra-acetate, usually give a mixture of acetates produced partly by the addition of acetoxyl group to the double bond and partly by the substitution to the alpha position of the double bond or simultaneous occurrence of these cases[4]. As a single example of ketone formation, there are some reports concerning the formation of R-homocamphenylone from camphene[5,6], which accompanied by ring-enlargement**. In the present case, however, the oxidation was considered to be accompanied by ring-contraction, a novel reaction which seems not to have appeared in literature. The reaction was carried out in two ways. (1) To the benzene solution of the terpene was added solid lead tetra-acetate in portions. (2) The minium was added to the mixture of the terpene and acetic acid. The reaction product was fractionated by distillation under reduced pressure, and the main fraction was found to be the same in both cases. As an example, one of the results obtained by method 1 is shown in Table I.

TABLE I

Frn.	b. p.	mm.	Yield g.	n_D^{25}	d_4^{25}	E. V.*
1	92~102°	8	3.25	1.4984	0.9296	—
2	~105°	7.5	2.90	1.5025	0.9232	—
3	~106°	7.5	3.31	1.5045	0.9355	—
4	~119°	7	1.15	1.5050	0.9517	16.5
5	~127°	7	13.25	1.4870	0.9802	68.5
6	~137°	6	2.97	1.4909	0.9897	97.7
7	~144°	6	3.81	1.4934	1.0026	174
8	~155°	6	2.45	1.4970	1.023	204

* Ester value. Calcd. for $C_{17}H_{26}O_2$: 214

The infrared spectra were examined concerning all fractions, and no appreciable band was found in 3400 cm^{-1} region. Fraction 5 had an infrared band at 1708 cm^{-1} (cf. Fig. 1) and its greater part proved to be a ketone I which gave a semicarbazone m. p. 214° (decomp.) and a 2, 4-dinitrophenylhydrazone m. p. 170°. The highest boiling fraction showed a band at 1745 cm^{-1} suggesting that it was probably a mixture of normal ester (1735~1740 cm^{-1}) and enol ester (1755 cm^{-1}). This was confirmed by the fact that the saponification product of this fraction showed bands at 3450 and 1708 cm^{-1} and gave a 2, 4-dinitrophenylhydrazone, m. p. 168°, which was identified with that of ketone I by mixed melting-point test and infrared spectrum. In the spectra of fractions 6 and 7, rather weak bands were observed at 1825 and 1666 cm^{-1}.

Since ketone I, $C_{15}H_{24}O$ gave an acid $C_{11}H_{22}O_2$, m. p. 102° (II) by hypohalite oxidation, it was presumed to be a methyl ketone. Alkaline permanganate oxidation

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1) Part I, This Bulletin, **30**, 886 (1957).

2) J. Kawamura, *Bull. Govt. Forest Expt. Station*, **30**, 59 (1930).

3) T. Ozeki, S. Seto and T. Nozoe, 10th Annual Meeting of the Chemical Society of Japan, April, 1957.

4) R. Criegee, *Ann.*, **481**, 263 (1930).

5) M. Ishidate, N. Inoue, and H. Fukushima, This Bulletin, **17**, 491 (1942): *J. Pharm. Japan* (*Yakugaku Zasshi*), **63**, 104 (1943).

6) Y. Matubara, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **76**, 1088, 1092 (1955), ibid., **78**, 726, 730 (1957).

** Added in proof: Another example of this type of reaction had been reported by P. Naffa and G. Ourisson (*Bull. soc. chim. France* **1954**, 1115., *C. A.*, **49**, 12386h (1955)), where longihomocamphenylone was obtained from longifolene by this reagent.

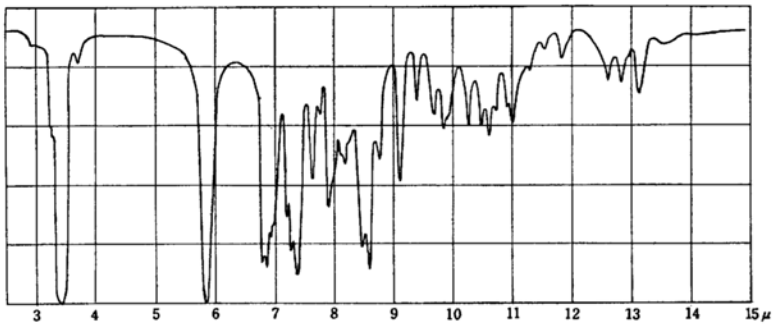


Fig. 1. Ketone I (regenerated from semicarbazone. Spectrum of Fraction 5 was essentially identical with this.)

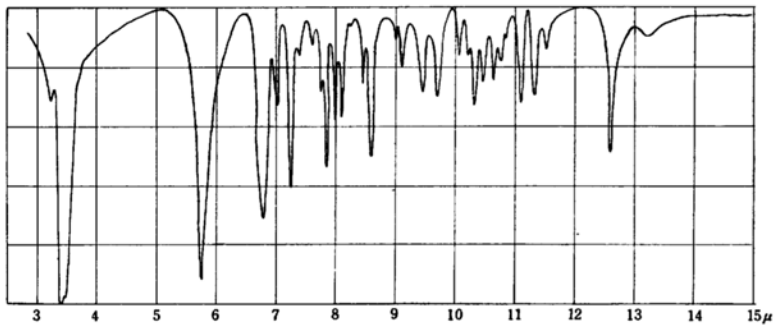


Fig. 2. Ketone VII (Nujol).

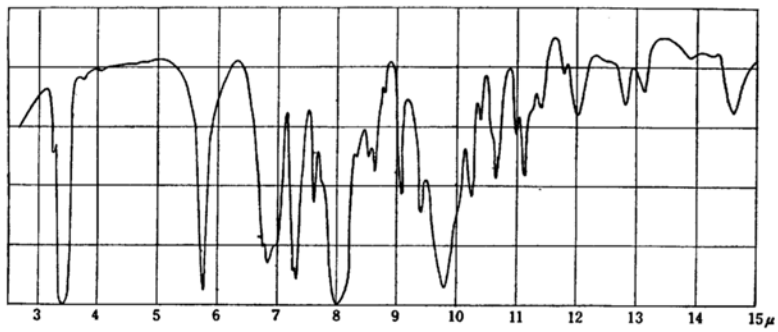


Fig. 3. Ester V.

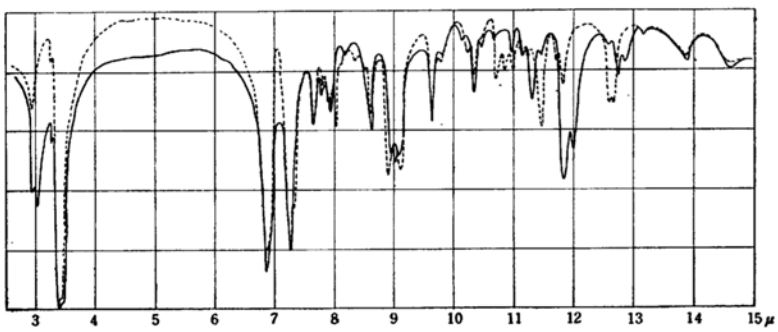
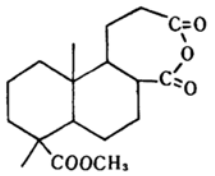


Fig. 4. —— Peroxide X, ------ Peroxide XI (Nujol).

of I gave mainly a dicarboxylic acid $C_{13}H_{20}O_4$ (III) accompanied by a small amount of acid II. Acid III was readily converted into an anhydride, m. p. 211~212° (IV) by heating or treating with acetic anhydride. Since this anhydride shows infrared absorption at 1799 and 1754 cm^{-1} (in carbon tetrachloride) and is stable toward heating, it may be considered to be of glutaric anhydride type.

Peracetic acid oxidation of ketone I followed by saponification and alumina chromatography gave an alcohol $C_{13}H_{22}O$, m.p. 78° (VI), and a ketone $C_{13}H_{20}O$, m.p. 118.5~121° (VII) (Fig. 2). When chromatographic separation was performed prior to the saponification, an ester V (Fig. 3) was obtained. Saponification of ester V gave alcohol VI, which in turn gave ketone VII by the chromic acid oxidation***. It is noticeable that ketone VII shows infrared absorption at 1727 cm^{-1} (in carbon tetrachloride) which is intermediate value of cyclopentanone (1745 cm^{-1}) and cyclohexanone (1715 cm^{-1}). Alcohol VI was oxidized with permanganate under a condition similar to the oxidation of ketone I, giving the same dicarboxylic acid III.

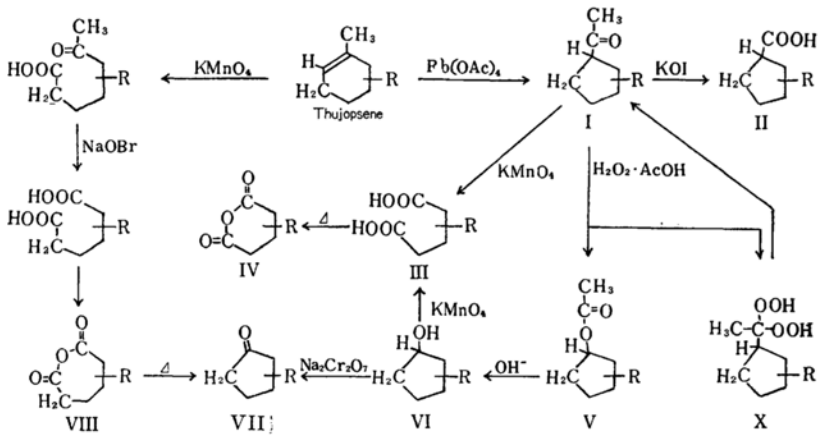
It has been reported[1] that the dicarboxylic acid obtained from thujopsene by permanganate oxidation followed by hypobromite treatment, gave an anhydride VIII, m. p. 110°, to which a glutaric anhydride was suggested from the infrared spectrum. However, an adipic anhydride IX from methyl vouacapenate showed anhydride bands at 1808 and 1764 cm^{-1} (in chloroform)[7]. Furthermore, Ozeki, Seto and Nozoe[3] obtained the "pyroketone" m. p. 121° by treating the dicarboxylic acid with acetic anhydride, followed by heating to 310°. On reexamining the experiment, it was confirmed that the pyroketone was identical with the above-mentioned ketone VII. Therefore, it must be considered that the anhydride VIII is of an adipic anhydride type, and the ring containing double bond in thujopsene is of a six-member type.



IX

The result mentioned above is formulated as Scheme I, assuming the cyclopentyl methyl ketone structure I for ketone I. Infrared absorption at 1708 cm^{-1} supports the validity of this inference.

In the case of the peracetic acid oxidation of ketone I, two kinds of crystalline ketone peroxide were separated. One of them $C_{15}H_{26}O_4$ (X) was obtained in 47% yield when the reaction was carried out below 20°. By means of iodometric titration, it was proved that two -OOH groups are present in X. When the acetic acid solution of X was warmed, the peroxide was decomposed and the original ketone I was regenerated. When the oxidation



Scheme I. R=C_9H_{18}

*** The same ketone VII was separated from the neutral parts of permanganate oxidation products of thujopsene.

7) M. Arakawa, Private communication.

was conducted at about 25°, another peroxide XI was obtained in a poor yield. It decomposed at 135~138°, but it was not studied further owing to lack of material. The infrared spectra of X and XI are shown in Fig. 4.

Further investigations on the structure of thujopsene are being carried on.

Experimental

Thujopsene was obtained by the fractionation of Hiba wood oil as previously described[1].

Reaction of Thujopsene with Lead Tetra-acetate.—(a) Thujopsene (35 g.) was dissolved in 165 cc. of dry benzene, and lead tetra-acetate (prepared from 305 g. of acetic acid, 105 g. of minium, and recrystallized from acetic acid) was added portionwise with stirring for half an hour. The flask was immersed now and then in the water bath to keep the temperature below 40°. Stirring was continued for an additional one and a half hours. The reaction mixture was filtered, sodium bicarbonate solution was added to the filtrate and the organic layer was separated. This was washed twice with water, again with diluted sodium bicarbonate solution and finally with water and dried over sodium sulfate. Solvent was removed and the residue was fractionated. The result of a typical run is shown in Table I. Fraction 5 which boiled mainly at 125~127°/7 mm., gave a yellow 2, 4-dinitrophenylhydrazone m. p. 170~170.5°, and a semicarbazone, m. p. 213~214°C (decomp.).

Anal. Found: C, 69.53; H, 9.83; N, 15.41. Calcd. for $C_{16}H_{27}ON_3$: C, 69.27; H, 9.81; N, 15.15%.

Regenerated ketone from the semicarbazone showed the following constants. B. p. 132~133°/9 mm. n_D^{20} 1.4920, d_4^{20} 0.979, M. R. 65.1. Calcd. for $C_{15}H_{24}O$, 64.91. Infrared spectrum, Fig. 1. The ketone separated in another run on the second distillations gave the following constants. B. p. 125°/5 mm. n_D^{26} 1.4897, d_4^{26} 0.9762, $[\alpha]_D^{30}$ +1.23°.

(b) To a mixture of 35 g. of thujopsene, 305 g. of acetic acid and 105 g. of acetic anhydride, was added 160 g. of minium in portions for 1.5 hours, the temperature being kept below 60°. Stirring was continued for one additional hour. Water was added, and the solution was neutralized with sodium carbonate, filtered and extracted with benzene. Fractionation gave 13.3 g. of ketone I, b. p. 125~127°/7 mm.

Hypohalite Oxidation of Ketone I.—The ketone (1 g.) was dissolved in 10 cc. of dioxane and oxidized with the hypobromite solution prepared from 4.8 g. of sodium hydroxide, 75 cc. of water and 2.1 cc. of bromine. When the mixture was warmed gradually, the reaction set in at about 80°. The crude acid II was precipitated by acidification of the alkaline solution, yield 850 mg. Repeated crystallization from methanol-water and final sublimation under reduced pressure gave a sample of m. p. 101~102°. The same acid was obtained by potassium hypoiodite oxidation according to the procedure of Heer and Miescher[8].

Anal. Found: C, 75.72; H, 10.10. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%.

Permanganate Oxidation of I.—The ketone (1 g.) was suspended in 40 cc. of 5% sodium hydroxide solution and 100 cc. of 4% potassium permanganate solution was added portionwise with stirring at 50~60°. Permanganate was consumed in 7 hours. On dissolving manganese dioxide with sodium bisulfite and hydrochloric acid, an acid mixture was precipitated, which was collected and dissolved in benzene. The benzene solution was extracted with sodium bicarbonate and sodium hydroxide solution successively. Acid III (122 mg.) was obtained from the former extract and recrystallized from methanol-water.

Anal. Found: C, 65.37; H, 8.05. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39%.

The sodium hydroxide extract gave 4 mg. of crude acid II m. p. 98~99°.

Anhydride IV.—Acid III (192 mg.) was heated with 5 cc. of acetic anhydride for 3 hours and acetic anhydride was removed under reduced pressure. The residue was crystallized by rubbing and recrystallized from acetic anhydride, m. p. 211~212°, yield 80 mg. When acid III was heated in a small tube, dehydration occurred at about 190° and melted at 211°. After being cooled, the contents solidified, and this solid also melted at 211°. The infrared spectrum coincided with that of the anhydride obtained by acetic anhydride treatment. Mixed melting point of III and IV showed no appreciable depression. Though the anhydride was heated to 450°, evolution of carbon dioxide was not observed practically and the anhydride could be recovered.

Peracetic Acid Oxidation of Ketone I.—(a) Ketone I (3.0 g.) was dissolved in 30 cc. of acetic acid (treated with chromium trioxide) and 24 cc. of hydrogen peroxide (30%) was added with swirling. After being kept at room temperature (about 25°) for 38 hours, the mixture was diluted with water and extracted with ether, and the ether extract was washed three times with sodium bicarbonate solution and then twice with water. On evaporation of ether, 1.95 g. of reaction product was obtained. This was dissolved in 5 cc. of methanol, and sodium hydroxide solution (1 g. in 5 cc. of water) was added to it and the mixture was allowed to stand overnight; then it was poured into water, and extracted with ether. Ether was removed and the residue was dissolved in petroleum ether and chromatographed with alumina column of 1.8×10 cm. The petroleum ether eluate was an oil (0.5 g. n_D^{20} 1.4965) and the infrared spectrum suggested the presence of unchanged I. The benzene and ethyl acetate eluates gave a crystalline alcohol, 0.42 g., m. p. 74~76°. An analytical sample was prepared by purification with the aid of sublimation under reduced pressure, m. p. 78°.

8) J. Heer and K. Miescher, *Helv. Chim. Acta*, **28**, 156 (1945).

Anal. Found: C, 80.10; 11.64. Calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41%.

In another run where the reaction mixture was allowed to stand for 3 days, the product was distilled under reduced pressure, saponified and chromatographed; the petroleum ether eluate gave crystalline ketone, m. p. 113~114° (100 mg. from 2.9 g. of I) and its infrared spectrum was identical with that of ketone VII obtained by chromic acid oxidation of alcohol VI.

(b) The ketone (5.4 g.) was oxidized for 5 days as before and a solid substance XI (195 mg.) was separated from the reaction mixture. This was filtered and recrystallized from benzene-petroleum ether mixture, which decomposed at 135~138°. The infrared spectrum is shown in Fig. 4. The attempted elementary analysis failed because of an explosion. The filtrate was treated as before (without distillation and saponification) and the product was chromatographed. Petroleum ether eluate (0.4 g. n_D^{26} 1.4863, d_4^{22} 0.9957) and benzene eluate (1.3 g. n_D^{20} 1.4858, d_4^{22} 1.044, infrared spectrum Fig. 3) were combined and saponified with methanolic sodium hydroxide solution, and alcohol VI was obtained in quantitative yield. Although ethyl acetate eluate (0.5 g. n_D^{22} 1.5000) did not crystallize, its infrared spectrum was essentially identical with that of VI.

(c) The ketone (3.67 g.) was dissolved in 45 cc. of acetic acid, to which 30 cc. of hydrogen peroxide (30%) was added. When the reaction mixture being kept below 20° overnight, a large quantity of crystalline substance X separated out. This was collected on a glass filter, recrystallized from benzene, yield 2.11 g. (47%), decomposed at about 120°.

Anal. Found: C, 66.78; H, 9.69. Calcd. for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69%.

A 13.2 mg. and a 15.0 mg. portion of the sample required 1.98 cc. and 2.19 cc. of 0.1 N sodium thiosulfate solution (f=1.008). Calcd. for $C_{15}H_{24}\cdot 2OOH$: 1.93 and 2.19 cc.

Acetic acid solution of X was warmed and water was added. On cooling there separated out an oil, from which a semicarbazone of m. p. 214° (decomp.) was obtained. The infrared spectrum of this semicarbazone was identical with that of semicarbazone of I.

Chromic Acid Oxidation of VI.—Sodium dichromate (100 mg.) was dissolved in 0.5 cc. of acetic acid and alcohol VI (194 mg.) in 0.5 cc. of acetic acid was added. The mixture was warmed for a few minutes and allowed to stand for one day. Water was added and the oil which separated was extracted with ether. Ether was evaporated and residue was crystallized by rubbing. Yield 148 mg. Recrystallization from methanol-water and sublimation under reduced pressure gave a sample of m. p. 118.5~121°C.

Anal. Found: C, 81.46; H, 10.37. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48%.

2, 4-Dinitrophenylhydrazone orange m. p. 215~216°.

Permanganate Oxidation of VI. — Alcohol VI (1.0 g.) was suspended in 40 cc. of 5% sodium hydroxide solution and 50 cc. of 4% permanganate solution was added to it dropwise with vigorous stirring. The temperature was kept below 55° by cooling with a water bath. After being stirred for 4 hours, the reaction mixture was acidified with hydrochloric acid and sodium bisulfite was added to it. The precipitate which separated was dissolved in sodium bicarbonate solution, filtered and reprecipitated with hydrochloric acid; yield 647 mg. The infrared spectrum of it was identical with that of III obtained from ketone I. It gave the anhydride of m. p. 211~212°.

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