[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, FACULTY OF ENGINEERING, KYÔTO UNIVERSITY]

Structure of Thujopsene and Hinokiic Acid

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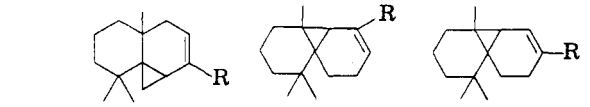
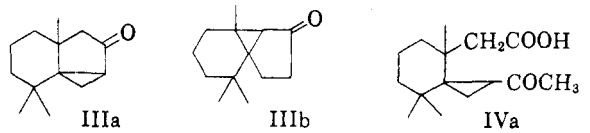
Ozonolysis of thujopsene afforded a new C_{15}-keto aldehyde (Va), which was cyclized to an α,β-unsaturated aldehyde (VIa'). Reactions and NMR spectra of these compounds supported the thujopsene structure Ia of Erdtman and others. Suggestions have been made that the plausible configuration of the angular methyl group in thujopsene should be *trans* with respect to the cyclopropane methylene group.

The structures of thujopsene[1] and hinokiic acid[2] have recently been re-investigated by several groups. Akiyoshi, Kobayashi, and Nagahama[3,4] studied the reactions of a C_{13}-ketone[5] (III) derived



R = CH_3 Ia Ib Ic
R = COOH IIa IIb IIc



IIIa IIIb IVa

from thujopsene to assign the formulas IIIa and IIIb with preference of IIIb and gave thujopsene the structure Ib, though the possibility of Ia had not been rigorously excluded. Erdtman and Norin[6] furnished spectrographic evidence for the presence of a bicyclo[3.1.0]hexane system in III with the keto group in conjugation with a cyclopropane ring. They preferred structure Ib, after considering possible formulas Ib and Ic for thujopsene. As hinokiic acid can be derived from thujopsene by the oxidation of the methyl group, attached to the double bond, into a carboxyl group,[6,7] it is represented by formula IIa, for example, if the formula Ia for thujopsene is valid.

In the light of Ruzicka's biogenetic isoprene rule,[8] an attempt was made to derive the ring systems characteristic to formulas Ib and Ic from farnesol, leading to the tentative structure Id for thujopsene.[9] Another possible structure Ie has been considered,[10] which might be formed as a result of prob-

Id, Ie:R = CH_3
IId, IIe:R = COOH

able double bond migration. Though formulas Id and Ie can be deduced by a seemingly reasonable cyclization mechanism from *cis*-farnesol *via* the same intermediate stages leading to humulene, zerumbone and caryophyllene,[11] they have remained to be confirmed by positive experimental supports. Very recently Erdtman and Norin[12] published a short communication presenting certain evidence in favor of formulas Ia for thujopsene and IIa for hinokiic acid. The present paper describes our experimental results, which have, however, incidentally furnished further grounds for formulating these compounds in accord with the Swedish investigators.[12]

Ozonolysis of thujopsene was carried out in glacial acetic acid and the resulting ozonide was decomposed by treating with zinc powder. Though

(1) S. Nagahama, H. Kobayashi, and S. Akiyoshi, *Bull. Chem. Soc. Japan*, **30**, 886 (1957), and earlier papers cited there.

(2) O. Okuda, *J. Pharm. Soc. Japan*, **73**, 9 (1953) and previous literature cited there.

(3) Presented by S. Akiyoshi, H. Kobayashi, and S. Nagahama at the 2nd Symposium on Perfumery, Terpene and Essential Oil Chemistry, Hiroshima, Japan, October 10–11, 1958. See also Abstracts of Papers presented at the 12th Annual Meeting of the Chemical Society of Japan, Kyôto, April 4, 1959, p. 281.

(4) H. Kobayashi, S. Nagahama, and S. Akiyoshi, *Bull. Chem. Soc. Japan*, **32**, 202 (1959). In this paper the authors did not discuss the possibility of the formula Ia for thujopsene, but only the formula Ib was given.

(5) S. Nagahama, H. Kobayashi, and S. Akiyoshi, *Bull. Chem. Soc. Japan*, **32**, 366 (1959). See also T. Ozeki, S. Seto, and T. Nozoe, Abstracts of Papers presented at the 10th Annual Meeting of the Chemical Society of Japan, Tôkyô, April 7, 1957, p. 211.

(6) H. Erdtman and T. Norin, *Acta Chem. Scand.*, **13**, 1124 (1959). These authors recorded the m.p. of III as 49.5–50.5°, while Nagahama, Kobayashi and Akiyoshi (Ref. 5) gave the m.p. 118.5–121° and Ozeki, Seto, and Nozoe (Ref. 5) mentioned the m.p. as 121°. In a recent communication (Ref. 12) the Swedish authors reported the m.p. as 114°.

(7) Y. Hirose and T. Nakatsuka, *J. Japanese Wood Res. Soc.*, **4**, 26 (1958); *Chem. Abstr.*, **52**, 11362 (1958).

(8) (a) L. Ruzicka, A. Eschenmoser, and H. Heusser, *Experientia*, **9**, 357 (1953). (b) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955). (c) P. A. Stadler, A. Mechvatal, A. J. Frey, and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1373 (1957). (d) L. Ruzicka in A. Todd, *Perspectives in Organic Chemistry*, Interscience, New York, 1956, p. 265. (e) L. Ruzicka, *Proc. Chem. Soc.*, 341 (1959).

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

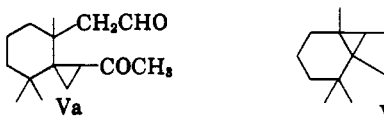
(10) Presented by K. Sisido, H. Nozaki, and T. Imagawa at the 4th Symposium on Perfumery, Terpene and Essential Oil Chemistry, Sapporo, Japan, July 16, 1960.

(11) J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).

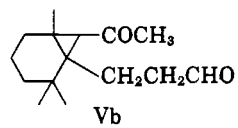
(12) H. Erdtman and T. Norin, *Chem. & Ind.*, 622 (1960).

Erdtman and co-workers[6,13] previously mentioned the formation of a C_{15}-keto acid (IV, correctly represented by IVa) in the same reaction, a new crystalline keto aldehyde $C_{15}H_{24}O_2$ (V) was isolated by purifying the product *via* sodium bisulfite addition compound. The qualitative aldehyde tests were positive and autoxidation afforded IV in good yields. The NMR spectrum[14] of V showed four methyl singlets at +98 (methyl ketone), 139, 146, and 162 c.p.s., respectively, besides a quartet centering at −194 c.p.s. and having an integrated intensity of one proton. The quartet is ascribed to an aldehydic proton coupled with an adjacent methylene group, whose free rotation appears to be restricted to a definite degree.

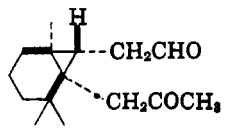
As no methylene group adjacent to an aldehyde group can arise from formulas Ic and Id upon ozonolysis of thujopsene, they have to be abandoned. Formulas Ia, Ib, and Ie would afford the keto aldehyde (V) of structures Va, Vb, and Ve which are compatible with respect to these findings.



Va



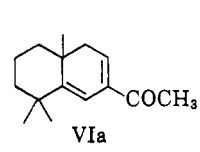
Vb



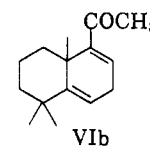
Ve

Treatment of V with ethanolic potassium hydroxide solution afforded a crystalline product (VI) of the formula $C_{15}H_{22}O$. This was confirmed further by analyses of its 2,4-dinitrophenylhydrazone. The infrared spectrum potassium bromide of VI showed absorptions at 1661 and 1613 cm.$^{-1}$, besides a very weak absorption at 2720 cm.$^{-1}$ In the NMR spectrum[14] of VI the presence of four methyl groups was shown by very sharp singlets at +106, 137, 148, and 168 c.p.s., respectively. In addition, a quartet centering at +188 c.p.s. was observed along with a sharp singlet at −200 c.p.s., each absorption having an integrated intensity of approximately one proton. No other definite absorption peak could be identified.

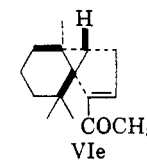
The change in molecular formulas shows that elimination of water has occurred by the action of caustic alkali on V with formation of α,β-unsaturated carbonyl compound *via* an aldol-type addition, as indicated by the infrared spectrum. The methyl signal at +106 c.p.s. of VI denotes that the methyl group originally attached to the keto group in V has been kept intact in VI. As VI did not show any qualitative aldehyde tests, VI appeared to be an α,β-unsaturated methyl ketone of probable formula VIe, though the iodoform test gave an inconclusive result. The methyl ketone formulas VIa and VIb derived from thujopsene formulas Ia and Ib, respectively, are rejected in the light of the NMR spectrum (not more than one olefinic proton) as well as of the facts that VI does not consume bromine in carbon tetrachloride solution below 0° and no Diels-Alder adduct is obtained by treatment of VI with maleic anhydride. Accordingly formula VIe is the only one which is able to explain all these observations, provided that VI is an α,β-unsaturated methyl ketone. The quartet centering at +188 c.p.s. would then be ascribed to the cyclopropane hydrogen adjacent to a methylene group.



VIa

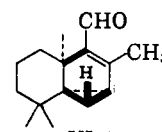


VIb

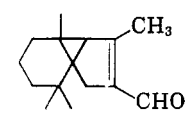


VIe

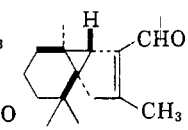
The assumption that the singlet at −200 c.p.s. originates from the olefinic proton in VIe is not fully justified, however. As examples are known[15] in which a cyclo-olefinic proton shows abnormally low coupling constants with adjacent methylene group, the apparent singlet structure of the signal can not necessarily be a token for excluding the presence of the methylene group adjacent to olefinic double bond. The chemical shift value should indicate that this signal better be ascribed to an aldehydic proton. The weak infrared absorption at 2720 cm.$^{-1}$ as mentioned above may also be indicative of the aldehyde group surviving in VI. Provided that VI is an α,β-unsaturated aldehyde, formulas VIa′, VIb′ and VIe′ are derived from Va, Vb and Ve, respectively. While formula VIa′



VIa′



VIb′



VIe′

explains completely the NMR spectrum of VI, the latter two can not be warranted because of the difficulty in explaining the quartet at +188 c.p.s. Inspection of the molecular model of VIa′ shows that one of the methylene protons of the cyclopropane ring is situated just above the plane of the olefinic double bond as indicated in the formula and therefore must be abnormally shielded.[16] The quartet centering at +188 c.p.s. is ascribed to this proton, which forms an ABX system with two other cyclopropane hydrogens. The absorption

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

(14) The NMR spectra herein recorded were taken in carbon tetrachloride solution with water capillary at 40 Mc. The authors are indebted to Professor Y. Yukawa and Mr. S. Satoh of Osaka University for the courtesy of obtaining the spectra and for helpful suggestions.

(15) L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, London, 1959, p. 87.

(16) Ref. 15, p. 129.

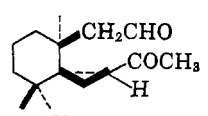
at +106 c.p.s. would then be attributed to a methyl group attached to the olefinic double bond instead of the one of a methyl ketone.

The diamagnetic shielding of the cyclopropane proton by the olefinic double bond will work most effectively, if the angular methyl group is in the *trans*-configuration with respect to the cyclopropane methylene group as shown in formula VIa'. The alternative possibility—*i.e.*, *cis*-orientation of the angular methyl group—is less favorable for the cyclopropane proton to be situated above the plane of the olefinic double bond because of the van der Waals repulsion between the methyl group and the cyclopropane methylene group.

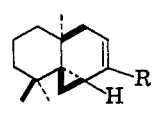
These arguments show that only two formulas VIe and VIa' are conceivable for VI and therefore formulas Ie and Ia for thujopsene. The final decision should be attained by determining rigorously whether VI is an α,β-unsaturated methyl ketone or an aldehyde. Following findings appear to have furnished evidences supporting that the latter is the case.

Though VI formed large plates when freshly recrystallized, the crystals were slowly transformed into a sirup upon standing in an open vessel and then the syrup resolidified. Recrystallization of this solid furnished another crystalline substance (VII) of the formula $C_{15}H_{22}O_2$. The NMR spectrum of VII consisted of four broad peaks and did not provide any useful structural evidences, while the infrared spectrum (potassium bromide) of VII showed a broad absorption at 3-4 μ region characteristic to a carboxylic acid, besides strong absorptions at 1668 and 1609 cm.$^{-1}$ VII was found to be soluble into aqueous sodium bicarbonate solution and stable in an excess of hot aqueous sodium hydroxide, as on acidification VII was recovered unchanged. These results indicate that VII is an α,β-unsaturated carboxylic acid formed by the autoxidation of VI.

Therefore, the aldol-type condensation of V should have occurred between the keto group and the methylene adjacent to the aldehyde group which has survived in the cyclization product VI, so that VI must be represented by the aldehyde formula VIa' instead of the ketone formula VIe. The rather unusual mode of this cyclization may be accounted for by restricted free rotation of the methylene group adjacent to the aldehyde group as stated above. Presumably dipole-dipole interaction of two carbonyl groups in V tends to stabilize a conformation, in which the keto carbonyl group is situated in close proximity to the methylene group adjacent to the aldehyde group.

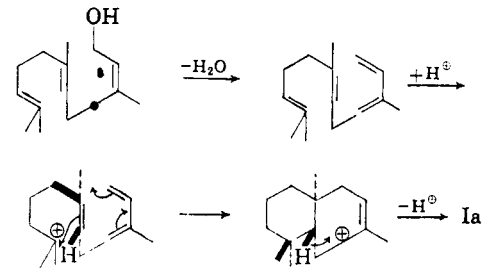


Va'



Ia': R = CH_3
IIa': R = COOH

As formula VIa' is valid, the keto aldehyde (V) must be indicated by formula Va' and consequently thujopsene and hinokiic acid should be Ia' and IIa', respectively, with the carbon skeleton of farnesol being retained. Though the cyclization mechanism is not so clear-cut, as this has been the case in the derivation of formulas Id and Ie,[9] it may be assumed tentatively as shown below.



EXPERIMENTAL[17]

Ozonolysis of thujopsene; preparation of the keto aldehyde (Va). Thujopsene was obtained by fractional distillation of *Hiba* tree oil[18] and a fraction boiling at 92–98° (6 mm.) was subjected to ozonolysis. The infrared spectrum of this fraction was found superimposable with the recorded one.[1]

A solution of 30 g. of thujopsene in 300 ml. of glacial acetic acid was saturated with ozonized oxygen at 10–15° during 4 hr. The solution was then diluted with 150 ml. of ether containing 1 ml. of water and treated with 30 g. of zinc powder added in small portions under stirring below 10°. The whole mixture was finally heated under reflux for an hour (negative potassium iodide-starch reaction) and filtered to remove excess zinc powder. The filtrate was treated with an equal amount of water and extracted several times with ether. After having been washed with water and then with saturated sodium bicarbonate solution, the combined ethereal extracts were treated with 104 g. of sodium bisulfite dissolved in 300 ml. of water and the precipitates collected by filtration. The sodium bisulfite addition product (about 15 g.) was suspended in a mixture of 60 ml. of water and 100 ml. of ether, treated with 40 ml. of 10% sodium carbonate solution, and the upper layer was washed with water, dried and concentrated. Recrystallizations of the residual solid from petroleum ether (b.p. 40–60°) afforded 3–4 g. of Va as colorless prisms, m.p. 69–70°, $[\alpha]_D^{26}$ −124° (*c* 1.72, ethanol). The NMR data were given in the discussion part. The infrared absorptions (potassium bromide): 2730, 1710 (—CHO), 1692, 1362 cm.$^{-1}$ (—$COCH_3$).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.20; H, 10.21.

Autoxidation of the keto aldehyde (Va). Keeping 0.1 g. of the crystalline Va in an open vessel at room temperature for several weeks, followed by recrystallizations from aqueous ethanol, afforded about 80 mg. of an acid melting at 164.5° which showed no depression upon mixed m.p. with an authentic sample (m.p. 164.5°) of the C_{15}-keto acid (IVa)[1] and gave correct analyses for carbon and hydrogen.

Cyclization of the keto aldehyde (Va); *preparation of the α,β-unsaturated aldehyde* (VIa'). A solution of 1.2 g. of potassium hydroxide in 2 ml. of water diluted with 20 ml. of ethanol was added dropwise to 2.3 g. of Va dissolved in 20 ml. of ethanol under stirring and cooling with an ice bath. The reaction mixture was allowed to stand at room temperature for 30 min., poured into 100 ml. of ice water containing

(17) All temperatures are uncorrected. Microanalyses by Miss Kenko Ogawa.

(18) Supplied by Dr. Y. Matubara, Saisei Syônô (Camphor Distillation) Co., Kôbe, Japan.

3 ml. of concd. hydrochloric acid and extracted several times with ether. The combined ethereal extracts were washed, dried and concentrated. Distillation of the residual oil gave a fraction, b.p. 135–140° (7 mm.), which was recrystallized from petroleum ether to afford 1.8 g. of VIa′ as colorless plates, m.p. 72.5–73.5°, $[\alpha]_D^{27}$ −14° (*c* 1.6, ethanol). For infrared and NMR properties see the discussion part. The 2,4-dinitrophenylhydrazone melted at 197° after recrystallizations from ethanol.

Anal. Calcd. for $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58. Found: C, 63.29; H, 6.78.

Autoxidation of the α,β-unsaturated aldehyde (VIa′); *preparation of the α,β-unsaturated acid* (VII). When 1.4 g. of the α,β-unsaturated aldehyde (VIa′) was kept in an open vessel at room temperature for 2 weeks, the crystals first liquefied and then resolidified. Recrystallizations from petroleum ether afforded 1.0 g. of colorless prisms melting at 150–150.5°. Infrared absorptions were given above.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.78; H, 9.59.

KYÔTO, JAPAN

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE A. E. STALEY MANUFACTURING CO.]

Reactions of Sugars in the Presence of Acids: a Paper Chromatographic Study

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Three percent solutions of D-glucose, D-mannose, D-galactose, D-fructose, L-sorbose, maltose and sucrose were heated in 0.05*N* to 4.0*N* hydrochloric acid at 98° for various lengths of time. The reactions (furan ring formation, condensation, hydrolysis) were followed by paper chromatography. D-Glucose showed the greatest tendency to form reversion products, followed in decreasing order by D-galactose and D-mannose. D-Fructose and L-sorbose showed no formation of reversion products. No monomolecular anhydro sugar formation was observed for any of the sugars. Sucrose hydrolyzed rapidly; the resulting mixture of D-glucose and D-fructose did not form condensation products of D-glucose with D-fructose. Maltose hydrolyzed slowly enough to co-exist with reversion products of D-glucose.

Many workers have reported the general finding that sugars in solution exposed to acidic environments form anhydro sugars, furan derivatives and condensation products.[1–3] D-Altrose forms an anhydro sugar in 57% yield[4]; D-glucose, treated in analogeous manner, produces 1,6-anhydro-β-D-glucopyranose in trace quantities only.[5] The chief factor deciding the stability of 1,6-anhydropyranoses is believed to be steric strain due to repulsion between substituents in the chair configuration.[6] Heating with oxalic acid under pressure converts 54% of D-fructose or of the D-fructose moiety of sucrose into 5-hydroxymethyl-2-furaldehyde.[7,8] The D-glucose moiety of the molecule can be isolated almost quantitatively from the reaction. 5-Hydroxymethyl-2-furaldehyde is formed in only small percentage yield from D-glucose.[9,10]

The condensation of sugars under conditions generally prevailing during the acid hydrolysis of carbohydrates is termed reversion. Reversion of D-glucose has been investigated mainly, but other sugars have also been considered. Reversion products from D-glucose have been isolated chromatographically and identified as their crystalline acetates.[5,11] The reversion products from D-glucose consist mainly of β-isomaltose and β-gentiobiose besides trace products including seven other disaccharides and 1,6-anhydro-β-D-glucopyranose. A mixture of oligosaccharides results from the interaction of D-galactose, D-mannose or L-arabinose and hydrochloric acid at room temperature.[12,13] Transglycosidation products have been obtained when solutions of various single disaccharides or mixtures of sugars are heated in a boiling water bath in the presence of acetic, hydrochloric, or sulfuric acid.[14] Concentration by rapid evaporation of solutions of D-glucose and other simple sugars in hydrochloric acid yielded condensation products.[3] Hexose condensation products were prepared by the action of gaseous hydrogen chloride on D-glucose, maltose, D-galactose and lactose.[14a,15]

(1) W. Pigman, ed., *The Carbohydrates*, Academic Press, New York, 1957, p. 57.
(2) F. Micheel, *Chemie der Zucker und Polysaccharide*, Akademische Verlagsgesellschaft, Leipzig, 1956, p. 50.
(3) E. Pacsu and P. T. Mora, *J. Am. Chem. Soc.*, **72**, 1045 (1950).
(4) N. K. Richtmyer and C. S. Hudson, *J. Am. Chem. Soc.*, 61, 214 (1939).
(5) A. Thompson, K. Anno, M. L. Wolfrom, and M. Inatome, *J. Am. Chem. Soc.*, **76**, 1309 (1954).
(6) J. A. Mills, *Advances in Carbohydrate Chem.*, **10**, 50 (1955).
(7) F. H. Newth, *Advances in Carbohydrate Chem.*, **6**, 83 (1951).
(8) W. N. Haworth and W. G. M. Jones, *J. Chem. Soc.*, 667 (1944).
(9) B. L. Scallet and J. H. Gardner, *J. Am. Chem. Soc.*, **67**, 1934 (1945).
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(11) A. Thompson, M. L. Wolfrom, and E. J. Quinn, *J. Am. Chem. Soc.*, **75**, 3003 (1953)
(12) C. N. Turton, A. Bebbington, S. Dixon, and E. Pacsu, *J. Am. Chem. Soc.*, **77**, 2565 (1955).
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(14) K. Täufel, H. Iwainsky, and H. Ruttloff, *Biochem. Z.*, **327**, 531 (1956); *J. Prakt. Chem.*, (4) **4**, 89 (1956).
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