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The Absolute Configuration of the Thujane Group

TORBJÖRN NORIN

Organisk-kemiska Institutionen, Kungl. Tekniska Högskolan, Stockholm, Sweden

Dedicated to Professor *Holger Erdtman* on his 60th birthday

A conjugated addition of hydrogen takes place when (+)-sabinene (3a), (+)-sabinol (3b) and (+)-sabinyl acetate (3c) are hydrogenated catalytically. The structures of the dihydro compounds thus formed are shown to be (7a), (7b), and (7c), respectively.

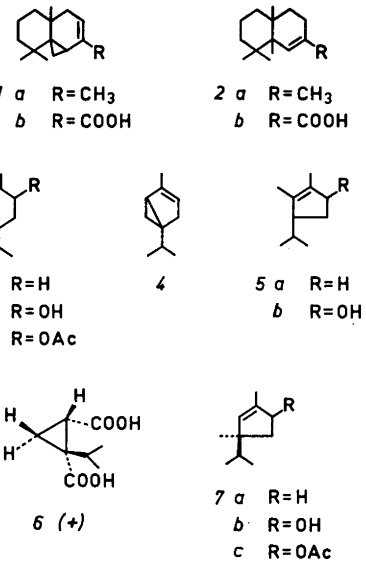
The main 1,2-addition product from the catalytic hydrogenation of (+)-sabinyl acetate (3c) is shown to be (+)-neoisothujyl alcohol, which now has been characterised for the first time. The stereochemistry of the various thujyl alcohols and thujones are briefly discussed.

The absolute configuration of the dihydro compounds (7b) and (7c) is established by their degradation to the known (+)-α-methyl-α-isopropylsuccinic acid (13). This in turn settles the absolute configuration of (+)-sabinol and (+)-sabinyl acetate, shown in stereoformulae (16b) and (16c). The absolute configuration of all the other monoterpenes of the thujane group follows from known interrelationships.

On catalytic hydrogenation of the alkenylcyclopropane system in thujopsene (1a) and hinokiic acid(1b) a conjugate addition of hydrogen takes place. The structures of the dihydro compounds were proved to be (2a) and (2b), respectively [1,2]. The formation of a new methyl group due to fission of the cyclopropane ring was studied in detail as it conclusively proved the presence and position of this ring. The same type of conjugate addition of hydrogen has been observed in vinylcyclopropane systems [3,4].

However, it has been reported by several authors that the cleavage of the cyclopropane ring occurred in another way during the catalytic hydrogenation of (+)-sabinene (3a), (−)-α-thujene (4) and (+)-sabinol (3b) [5]. The structure of the dihydro compound derived from (+)-sabinene (3a) and (−)-α-thujene (4) was said to be (5a) and that derived from (+)-sabinol (3b) to be (5b). In this paper, evidence is presented showing that the catalytic hydrogenations of (+)-sabinene (3a), (+)-sabinol (3b), and (+)-sabinyl acetate (3c) takes place in the same way as those of thujopsene (1a) and hinokiic acid (1b).

The thujane group is the only important class of monoterpenes in which the absolute configuration has remained unsettled [6]. The absolute configuration of (+)-*cis*umbellularic acid (6) has recently been proposed on the basis of a partial asymmetric synthesis [7]. This acid (6) is related to the monoterpenes of



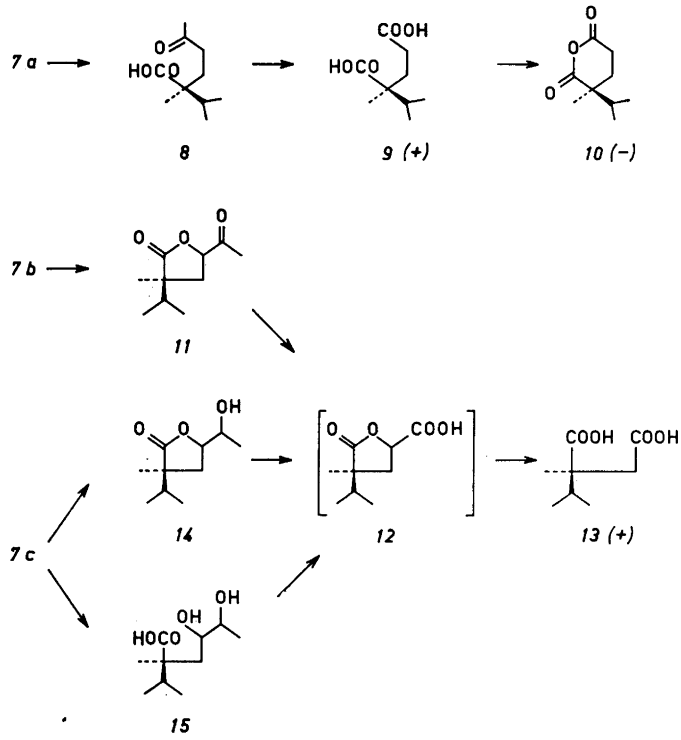
the thujane group and the absolute configuration of the group follows from this assignment. However, an independent solution of this problem was desirable.

The stereospecific opening of the cyclopropane ring during the catalytic hydrogenation of (+)-sabinene (3a), (+)-sabinol (3b) and (+)-sabinyl acetate (3c) and the degradation of the dihydro compounds to compounds of established absolute configuration would completely settle the absolute configuration of the monoterpenes of the thujane group.

The pure (+)-sabinene (3a) and (+)-sabinyl acetate (3c) used for this investigation were obtained from a careful distillation of oil of savin (from *Juniperus sabina* L.). The pure (+)-sabinol (3b) was obtained on hydrolysis of (+)-sabinyl acetate (3c).

(+)-Sabinene (3a) was hydrogenated in methanol using a palladium on charcoal catalyst. A gas liquid chromatogram of the dihydro-product showed only one main peak. Infra red and nuclear magnetic resonance spectra of this crude dihydro compound clearly indicate the presence of a trisubstituted double bond. On ozonisation, the dihydro compound (7a) gave the keto-acid (8). This keto-acid was found to be identical with the (+)-2-methyl-2-isopropyl-5-oxocaproic acid, recently obtained from a degradation of (−)-methylisopulegone [8] (see Table 1). As in the (−)-methylisopulegone work the keto-acid (8) was further degraded to the (+)-α-methyl-α-isopropylglutaric acid (9) and this dicarboxylic acid transformed to the (−)-α-methyl-α-isopropylglutaric anhydride (10).

(+)-Sabinol (3b) was hydrogenated under the same conditions as described for (+)-sabinene (3a). The yield of 1,4-addition product was 30 %, as shown by gas liquid chromatography. The crude dihydro-product was ozonised and the ozonisation product separated into a neutral fraction, containing the 1,2-



addition products (see below), and an acidic fraction. The acidic fraction was chromatographed on silica gel and the main product isolated was the oily ketolactone (11), further characterized as its crystalline 2,4-dinitrophenylhydrazone. Hypobromite oxidation of this ketolactone (11) gave a product consisting mainly of the lactone-acid (12), as shown by its infra red spectrum. Without further purification this crude product (12) was oxidised with permanganate to a dicarboxylic acid, which after purification by preparative paper chromatography, yielded crystalline (+)-α-methyl-α-isopropylsuccinic acid (13), identified by a direct comparison with an authentic sample [9].

(+)-Sabinyl acetate (3c) was hydrogenated under the same conditions as described for (+)-sabinene (3a) and the yield of 1,4-addition product was 20 % as shown by gas liquid chromatography. The crude dihydro-product was ozonised and the ozonisation product was separated into a neutral fraction, containing the 1,2-addition products, (see below) and an acidic fraction.

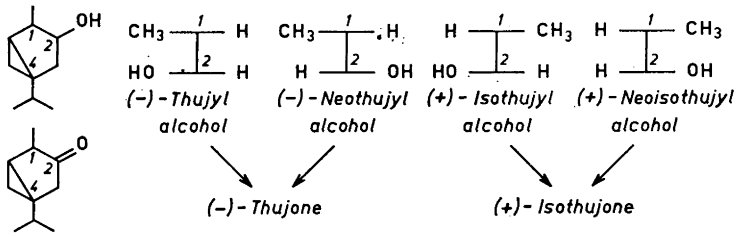
Alkaline hydrolysis of the acidic fraction to give the ketolactone (11) afforded a complex mixture as shown by paper chromatography. Treatment of the crude acidic fraction with alkaline potassium borohydride afforded two products, the oily hydroxylactone (14) and the crystalline diol-acid (15), which were isolated by chromatography on silica gel.

The hydroxylactone (14) and the diol-acid (15) were oxidised with hypobromite to give a crude product, the infra red spectrum of which showed that

it consisted mainly of the lactone-acid (12). This product, without further purification, was oxidised with permanganate to a crude dicarboxylic acid from which crystalline (+)-α-methyl-α-isopropylsuccinic acid (13) was isolated after purification by means of preparative paper chromatography.

There were no indications of the presence of a dihydro compound with the structure (5) in any of the hydrogenations discussed above. On the other hand, these hydrogenations are clearly shown to proceed partly by 1,4-addition with formation of the dihydro compounds (7a), (7b), and (7c).

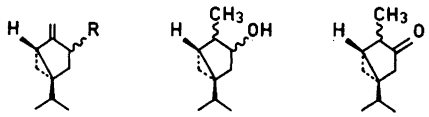
The catalytic hydrogenation of (+)-sabinol (3b) gave 70 % of a 1,2-addition product, the main constituent of which was identified as (−)-neothujyl alcohol in agreement with previous findings [14]. Gas liquid chromatography also indicates the presence of small amounts of (+)-neoisothujylalcohol (see below). (+)-Sabinyl acetate (3c) gave about 80 % of a 1,2-addition product which, after hydrolysis, was shown to be a mixture of about 30 % (−)-neothujyl alcohol and 70 % (+)-neoisothujyl alcohol. These alcohols were separated by fractional crystallisation of the *p*-nitrobenzoates. (+)-Neoisothujyl alcohol has not been characterised previously.* This alcohol gave (+)-isothujone on oxidation with chromic acid. Since (+)-neoisothujyl alcohol and (−)-neothujylalcohol both are formed on catalytic hydrogenation of (+)-sabinyl acetate (3c), these two alcohols must have the same stereochemistry at carbon atom C_2 (for nomenclature and numbering see Refs.[11,12]). The steric relationships previously proposed for the various thujyl alcohols and thujones [11,12] must therefore be changed and may now be expressed as follows:



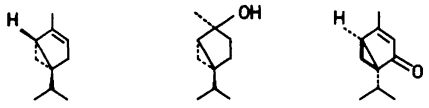
The *cis*- or *trans*-configuration of the C_1-methyl group and the C_4-isopropyl group each of these compounds is still unsettled [7,11,12]. Work on this problem is now in progress.

The absolute configuration of the dihydro compounds (7b) and (7c) is settled by the formation of the known [9] (+)-α-methyl-α-isopropylsuccinic acid (13). This in turn settles the absolute configuration of (+)-sabinol and (+)-sabinyl acetate, which must be represented by the stereoformulae (16b) and (16c), respectively. (+)-Sabinene and (+)-sabinol are both degraded to the same (+)-α-thujadicarboxylic acid [13] and thus (+)-sabinene possesses the absolute configuration shown in the formula (16a). The (+)-α-methyl-α-isopropylglutaric acid obtained from the degradation of the dihydrosabinene

* (+)-Neoisothujyl alcohol may possibly be identical with "δ-thujyl alcohol" isolated from the oil of wormwood, *Artemisia absinthum*, L, (Paolini, V. and Divizza, B. *Atti Accad. Lincei, Roma* **21** (1911) Vol. 1, 570 and Paolini, V. and Lomonaco, R. *ibid.* **23** (1914) Vol. 2, 123; Ref. *Chem. Abstracts* **6** (1912) 2233 and *ibid.* **9** (1915) 1323).



16 a R=H 17 18
b R=OH
c R=OAc



19 20 21

(7a) must accordingly possess the absolute configuration shown in formula (9). The recent degradation of (−)-methylisopulegone [8] led to the identical acid (see Table 1); however, the opposite absolute configuration was assigned to this acid. This discrepancy will be discussed in a separate paper.

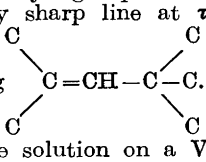
The absolute configurations of the various thujyl alcohols (17), thujones (18), of (−)-α-thujene (19), sabinene hydrate (20) [14] and umbellulone (21) follow from known interrelationships [15].

EXPERIMENTAL

Melting points are uncorrected and were taken on a Kofler micro hot stage. The infra red spectra were recorded on a Perkin-Elmer No. 21 instrument (NaCl-prisms; liquids and pure oils in 0.025 mm NaCl-cell; solids, in KBr-discs, unless otherwise stated). Rotations were measured in chloroform (unless otherwise stated). The gas liquid chromatographic (GLC) examinations were made on a Pye Argon Chromatograph; Cat. No 12 000; column length 1.2 m; internal column diameter 5 mm; stationary phase, 100−115 mesh Silocel C 22 brick powder impregnated with 2,4-dinitrophenyl-2-naphthyl ether (15 %) and dibenzyl pyridine (a mixture of 2,4- and 2,6-isomers, 0.75 %) [16]; charge 0.025 μl; temperature 150° (unless otherwise stated).

(+)-Sabinene (3a), (+)-sabinol (3b) and (+)-sabinyl acetate (3c). Oil of savin (40 g) from a steam distillation of the needles and the tops of the branches of *Juniperus sabina* L. (3.9 kg) grown in Stockholm, Sweden, was distilled under reduced pressure (20 mm) in a spinning band column (effective column length about 1.0 m and internal diameter 7 mm). This distillation gave pure (+)-*sabinyl acetate* (*3c*, 3.6 g) which was homogeneous according to GLC, $[\alpha]_D$ + 82° (*c* 1.8), n_D^{25} 1.4678. The first fractions obtained from the distillation were shown to be complex mixtures of hydrocarbons by GLC analysis (stationary phase 100−115 mesh Silocel C 22 brick powder impregnated with 10 % "polyethylene alkatene", a polyester supplied by Perkin-Elmer Co; temperature 60°). These hydrocarbon fractions were combined and redistilled in the same spinning band equipment under atmospheric pressure to give (+)-*sabinene* (*3a*, 1.2 g), $[\alpha]_D$ + 102° (*c* 1.0), n_D^{25} 1.4662 (infra red spectrum identical with that of authentic material [17]). (+)-*Sabinol* (*3b*), $[\alpha]_D$ + 8.3° (*c* 2.0), n_D^{25} 1.4850, was obtained on alkaline hydrolysis of pure (+)-sabinyl acetate (3c) as previously described [10].

Catalytic hydrogenation of (+)-sabinene (3a). (+)-Sabinene (3a, 0.80 g) in methanol (4 ml) was hydrogenated over a 10 % palladium on charcoal catalyst (0.045 g). When the theoretical amount of hydrogen (1 mol. equiv.) had been consumed, the mixture was filtered, diluted with water and extracted with ether. The ether extract was dried (Na_2SO_4) and the solvent evaporated to give the crude *dihydro compound* (*7a*), $[\alpha]_D$ + 34° (*c* 1.7),

n_D^{25} 1.4420. On GLC under the same conditions as described for (+)-sabinene (3a), this crude dihydro compound showed one main peak with an area of about 95 % of the total peak areas and with the retention time 0.63 relative (+)-sabinene (3a). One minor peak was also present in the chromatogram, which had the retention time 0.69 relative (+)-sabinene (3a). The infra red spectrum of this crude dihydro compound (7a) showed characteristic bands at 1 660 and 840 cm^{-1} indicating the presence of a trisubstituted double bond. The nuclear magnetic resonance spectrum showed two signals, at τ 9.22 and 9.03, with areas corresponding to three methyl groups. A signal at τ 8.33 can be assigned to a methyl group on a double bond. The olefinic proton gave rise to a comparatively sharp line at τ 4.86 and the absence of spin-spin splitting suggests the grouping  C. The spectrum was obtained with a *ca.* 10 % carbon tetrachloride solution on a Varian V-4300 Spectrometer operating at 40 Mc/s and equipped with a Varian V-K 3506 Stabilizer. Tetramethylsilane was used as internal standard.

(+)-2-Methyl-2-isopropyl-5-oxocaproic acid (8). The crude dihydro compound (7a, 0.7 g) in ethyl acetate/methanol (6:1, 5 ml) was treated with ozone at −70° until a blue colour persisted. Excess ozone was removed by bubbling nitrogen through the solution until the colour disappeared. When the reaction mixture had reached room temperature, zinc dust (1.5 g), previously activated with acetic acid, was added in portions. The decomposition of the ozonides was completed by heating the mixture under gentle reflux for 15 min. Ether (50 ml) was added to the cooled mixture followed by dilute sulphuric acid (1 %, 50 ml). The mixture was filtered and the zinc residue washed with ether and dilute sulphuric acid (1 %). The organic phase was extracted with aqueous sodium hydroxide and separated into acidic (0.40 g) and neutral (0.28 g) fractions.

The acidic fraction was distilled under reduced pressure (p = 0.3 mm) to afford *(+)-2-methyl-2-isopropyl-5-oxocaproic aicd* (*8*, 0.37 g), $[\alpha]_D$ + 15° (*c* 1.0), whose infra red spectrum was identical with that of authentic sample obtained from a degradation of (−)-methylisopulegone [8] (see Table 1).

The neutral fraction contained mainly a keto-aldehyde according to its infra red spectrum, $\nu_{max}^{CCl_4}$ 2 700, 1 735, and 1 715 cm^{-1}. This crude neutral fraction (0.25 g) in dioxane (5 ml) was added to a stirred mixture of silver oxide in water [prepared from a saturated solution of silver nitrate (0.35 g) in water and aqueous sodium hydroxide (4 %, 2 ml)] and heated under reflux for 5 h. A silver mirror was formed. The acidic product (0.11 g), which was obtained from this reaction, was chromatographed on silica gel (4 g). Methanol/chloroform (2 %) eluted the keto-acid (8, 0.08 g) which was purified by distillation.

The *2,4-dinitrophenylhydrazone* of the keto-acid (8) was shown to be identical with an authentic sample, m.p. and mixed m.p. 122°. The infra red spectrum of this derivative was superimposable with that of the authentic sample (see Table 1).

The *methyl ester* of the keto-acid (8) and its *2,4-dinitrophenylhydrazone*, the *(+)-α-methyl-α-isopropylglutaric acid (9)* and the *(−)-α-methyl-α-isopropylglutaric anhydride (10)* were all prepared as described in the (−)-methylisopulegone work [8]. The melting points and rotations of these compounds are given in Table 1 and compared with those of the compounds obtained from (−)-methylisopulegone.

Catalytic hydrogenation of (+)-sabinol (3b). (+)-Sabinol (3b, 1.22 g) in methanol (5 ml) was hydrogenated over a 10 % palladium on charcoal catalyst as described for (+)-sabinene (3a). The dihydro-product showed, on GLC, two peaks with the retention times 0.91 and 0.76 relative (+)-sabinol (3b) and small shoulder with relative retention time 0.77. The areas of the peaks were about 70 % and 30 % of the total peak area, respectively.

The *ozonisation of the dihydro-product obtained from (+)-sabinol (3b)* was carried out as described for the ozonisation of the dihydro compound (7a) and gave similarly an acidic (0.37 g) and a neutral (0.80 g) fraction.

The acidic fraction was chromatographed on silica gel (30 g). Chloroform eluted the *ketolactone* (*11*, 0.15 g), $[\alpha]_D$ −5° (*c* 1.0), $\nu_{max}^{CCl_4}$ 1 775 and 1 720 cm^{-1}. The analytical

Table 1. Compounds obtained from the degradation of dihydrosabinene (7a) compared with those obtained from (−)-methylisopulegone.

Compounds obtained from (−)-methylisopulegone A / Compounds obtained from dihydrosabinene (7a) B		M.p. °C	$[\alpha]_D$ °	*c* in chloroform	Comments
(+)-2-Methyl-2-isopropyl-5-oxocaproic acid (8)	A	oil	+ 3.3	1.52	Identical infra red
	B	oil	+ 16.0	1.0	
2,4-Dinitrophenylhydrazone of this keto-acid (8)	A	122	—	—	Mixed m.p. 122° and identical infra red
	B	122			
Methyl ester of the keto-acid (8)	A	oil	+ 14.1	1.07	
	B	oil	+ 29.0	2.8	
2,4-Dinitrophenylhydrazone of the methyl ester of the keto-acid (8)	A	66−67	+ 32	0.93	
	B	66−67 and 77−78*	+ 34	0.94	
(+)-α-Methyl-α-isopropyl-glutaric acid (9)	A	60−62	+ 8.7	0.8	
	B	60−62 (68−70) **	+ 9.5	0.65	
(−)-α-Methyl-α-isopropyl-glutaric anhydride (10)	A	55−56	− 6.1	0.99	
	B	56−57	− 55	0.94	

* Dimorphous, needles which melt at 77−78° and leaflets with m.p. 66−67°.
** Recrystallised from water. The dried product showed the m.p. 60−62°.

sample was distilled at a pressure of 0.5 mm. (Found: C 65.6; H 8.9. $C_{10}H_{16}O_3$ requires C 65.2; H 8.8). *2,4-Dinitrophenylhydrazone*, m.p. 116−118°. (Found: N 15.2. $C_{16}H_{20}O_6N_4$ requires N 15.4). Methanol/chloroform (4 %) eluted a compound (0.11 g) which was a crude hydroxyketo-acid according to its infra red spectrum, $\nu_{max}^{CCl_4}$ 3 380, 1720 and 1 700 cm^{-1}.

The neutral fraction was distilled at water pump pressure. On GLC, the distilled product showed two peaks with retention times 0.91 and 0.77 relative (+)-sabinol (3b). The areas of the peaks were 98 % and 2 % of the total peak area, respectively. The *p*-nitrobenzoate of this product was recrystallised from methanol to give pure (−)-neothujyl *p*-nitrobenzoate as needles, m.p. 91−92°, $[\alpha]_D$ −12° (*c* 1.6)[10]. Hydrolysis with boiling methanolic potassium hydroxide, followed by steam distillation and distillation under reduced pressure as previously described [10], yielded pure (−)-*neothujyl alcohol*, m.p. 20−22°, $[\alpha]_D$ −9° (*c* 1.1 in ethanol). On GLC, this alcohol showed a peak with the same retention time, 0.91 relative (+)-sabinol (3b), as the "98 %-peak" of the crude neutral fraction. The "2 %-peak" of this neutral fraction had the same retention time as (+)-neoisothujyl alcohol, 0.77 relative (+)-sabinol (3b) (see below).

(+)-α-Methyl-α-isopropylsuccinic acid (13) from the ketolactone (11). The ketolactone (0.11 g) in aqueous sodium hydroxide (10 %, 2 ml) was treated with an ice-cold freshly prepared sodium hypobromite solution [from aqueous sodium hydroxide (10 %, 10 ml) and bromine (0.75 ml)] and the mixture kept at room temperature for 3 h. The bromoform was removed by extraction with ether. The aqueous solution was decolourised with sodium bisulphite, acidified and extracted with ether. Drying (Na_2SO_4) and evaporation of the ether left a viscous liquid (0.093 g). The infra red spectrum showed that this product was the crude *lactone-acid (12)*, $\nu_{max}^{CCl_4}$ 1 773 and 1 702 cm^{-1}, which, without further purification, was oxidised with potassium permanganate (0.085 g) in aqueous sodium carbonate (10 %, 20 ml) at room temperature. After 12 h the mixture was treated with sodium bisulphite, acidified and extracted continously with ether. Drying (Na_2SO_4) and evaporation of the ether left a viscous liquid (0.053 g). This product showed only one main spot when chromatographed on dimethyl sulphoxide-impregnated paper [18] (ether as mobile phase, R_F 0.20). Preparative paper chromatography on dimethyl sulphoxide-impregnated paper (25 × 50 cm, Whatman 3 MM) according to the previous description [2] gave crystalline *(+)-α-methyl-α-isopropylsuccinic acid (13,* 0.032 g), m.p. 132—133°, $[\alpha]_D$ + 12.5 (*c* 1.87 in water). When mixed in the ratio 1:1 with an authentic sample of the (—)-acid [9], the m.p. was 152—153°. This mixture gave an undepressed m.p. when further mixed with the authentic racemic acid. The identity of the (+)-α-methyl-α-isopropylsuccinic acid (13) was also confirmed by comparing its infra red spectrum with that of the authentic (—)-acid.

The crude hydroxyketo-acid from the silica gel chromatography of the acidic ozonisation product (see above) gave a further amount of (+)-α-methyl-α-isopropylsuccinic acid (13), after a similar hypobromite oxidation followed by permanganate oxidation.

Catalytic hydrogenation of (+)-sabinyl acetate (3c). (+)-Sabinyl acetate (3c, 1.5 g) in methanol (5 ml) was hydrogenated over a 10 % palladium on charcoal catalyst as described for (+)-sabinene (3a). On GLC, the dihydro-product showed two peaks with areas corresponding to the relative amounts of about 80 % and 20 %. The retention times relative (+)-sabinol (3b) were 1.23 and 1.05, respectively. The "80 %-peak" was not symmetrical and seemed to consist of two overlapping peaks.

The *ozonisation of the dihydro-product obtained from (+)-sabinyl acetate (3c)* was carried out as described for the ozonisation of the dihydro compound (7a), and gave similarly, an acidic (0.325 g) and a neutral (0.850 g) fraction.

A preliminary experiment in which a small sample (0.020 g) of the acidic fraction was hydrolysed with boiling methanolic potassium hydroxide (5 %, 3 ml) gave an acidic product (0.013 g) which, according to paper chromatography (dimethyl sulphoxide-impregnated paper and ether as mobile phase [18]), was a complex mixture. No ketolactone (11) could be isolated from this product.

The acidic fraction (0.30 g) in methanol (5 ml) was treated with alkaline potassium borohydride [potassium borohydride (0.6 g), potassium hydroxide (0.2 g), water (5 ml) and methanol (5 ml)] for 24 h at room temperature. The alkaline solution was diluted with water, acidified and extracted with ether. Drying (Na_2SO_4) and evaporation of the ether left a viscous liquid which was chromatographed on silia gel (10 g). Chloroform eluted the oily *hydroxylactone (14,* 0.19 g) with characteristic infra red spectrum, $\nu_{max}^{CCl_4}$ 3 600, 3 460, and 1 775 cm^{-1}. The analytical sample was distilled at a pressure of 1.0 mm. (Found: C 65.1; H 9.9. $C_{10}H_{18}O_3$ requires C 64.5; H 9.7). Methanol/chloroform (3 %) eluted the crystalline *diol-acid (15,* 0.067 g) which after one crystallisation from chloroform had m.p. 110—113° (decomp.), $[\alpha]_D$ + 32° (*c* 0.5). (Found: C 59.0; H 9.6. $C_{10}H_{20}O_4$ requires C 58.8; H 9.9).

On GLC, the neutral ozonisation product showed only one peak with the same retention time as the "80 %-peak" of the crude dihydroproduct. This peak also seemed to be an unresolved doublet. The neutral product was hydrolysed with boiling methanolic potassium hydroxide and the hydrolysed product distilled at water pump pressure. GLC of the distilled product showed two peaks with the retention times 0.91 and 0.77 relative (+)-sabinol (3b) and with relative areas of 30 % and 70 %, respectively. This product (0.75 g) was treated with *p*-nitrobenzoyl chloride (1.0 g) in the usual manner to give the oily ester which crystallised on standing. Five crystallisations from methanol furnished pure *(+)-neoisothujyl p-nitrobenzoate* (0.190 g) as needles, m.p. 88—89°, $[\alpha]_D$ + 27° (*c* 1.7). (Found: C 67.1; H 6.9. $C_{17}H_{21}O_4N$ requires C 67.3; H 6.9). The mother liquors from the

first two crystallisations were concentrated and, on seeding with (−)-neothujyl *p*-nitrobenzoate, a crude product crystallised out. After five crystallisations from methanol pure *(−)-neothujyl p-nitrobenzoate* was obtained as needles, m.p. and mixed m.p. 91−92° and infra red spectrum identical with that of an authentic sample.

Hydrolysis of the (+)-neoisothujyl *p*-nitrobenzoate (0.150 g) with boiling methanolic potassium hydroxide (5 %, 5 ml) gave a neutral product (0.050 g) which was distilled under reduced pressure and pure *(+)-neoisothujyl alcohol* was obtained as a colourless oil, $[\alpha]_D$ + 42° (*c* 1.8), n_D^{25} 1.4647. On GLC, this alcohol showed a peak with the same retention time, 0.77 relative (+)-sabinol (3b), as the "70 %-peak" of the crude hydrolysed neutral fraction.

Oxidation of (+)-neoisothujyl alcohol with chromic acid as previously described[10] gave a crude ketone, $[\alpha]_D$ + 51 (*c* 0.63) which had an identical infra red spectrum as (+)-isothujone. The semicarbazone of this crude ketone was purified by crystallisation from methanol/water and gave small amounts of the pure *(+)-isothujone semicarbazone*, m.p. and mixed m.p. 170−172°, $[\alpha]_D$ + 220° (*c* 0.46 in methanol). The infra red spectrum was identical with that of an authentic sample.

(+)-α-Methyl-α-isopropylsuccinic acid (13) from the hydroxylactone (14) and the diol-acid (15). The hypobromite oxidation was carried out as described for the oxidation of the ketolactone (11), to afford a product which was identical with the lactone-acid (12) according to its infra red spectrum and its paper chromatographic behaviour (dimethyl sulphoxide-impregnated paper and ether as mobile phase[18]). This lactone-acid (12) was further oxidised with permanganate and yielded, after purification by means of preparative paper chromatography, as described above, the crystalline *(+)-α-methyl-α-isopropylsuccinic acid (13)*, m.p. and mixed m.p. 132−133°, $[\alpha]_D$ + 12.9 (*c* 1.42 in water).

Similarly the diol-acid (15) was oxidised in two steps, first with hypobromite and then with permanganate, to the (+)-α-methyl-α-isopropylsuccinic acid (13).

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