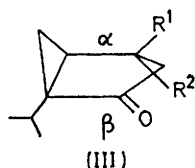
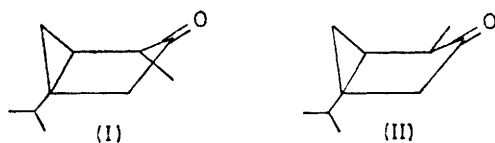


Stereochemistry of Reduction of Umbellulone (Thuj-3-en-2-one) and Isodihydrumbellulone (4 β H-Thujan-2-one)

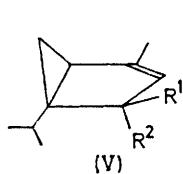
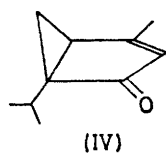
By Collette M. Holden, John C. Rees, Stephen P. Scott, and David Whittaker,* The Robert Robinson Laboratories, University of Liverpool, P.O. Box 147, Liverpool L69 3BX

The configurations of 4 β H-thujan-2-one (isodihydrumbellulone) and the two 4 β H-thujan-2-ols (neoiso- and iso-dihydrumbellulols) have been determined by ^1H and ^{13}C n.m.r. spectroscopy. Based on these data, the reduction of the title compounds by metal hydrides and alkoxides has been shown to be consistent with control of stereoselectivity by the reactant conformation.

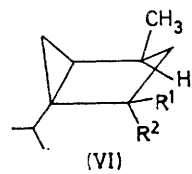
REDUCTION of thujone (4 α H-thujan-3-one) (I) and isothujone (4 β H-thujan-3-one) (II) with metal hydrides



a; $\text{R}^1 = \text{H}, \text{R}^2 = \text{CH}_3$
b; $\text{R}^1 = \text{CH}_3, \text{R}^2 = \text{H}$



a; $\text{R}^1 = \text{H}, \text{R}^2 = \text{OH}$
b; $\text{R}^1 = \text{OH}, \text{R}^2 = \text{H}$



a; $\text{R}^1 = \text{OH}, \text{R}^2 = \text{H}$
b; $\text{R}^1 = \text{H}, \text{R}^2 = \text{OH}$

gave mixtures of the isomeric thujols which were rationalised by postulating that 4 α H-thujan-3-one adopts a flattened chair conformation in the transition

state and 4 β H-thujan-3-one a flattened boat conformation.¹

Reaction of 4 α H-thujan-3-one (I) *via* a chair conformation must result from extra steric effects of the complexed reagent,¹ since all thujanes which have been studied have boat conformations.²

Reduction of the dihydrumbellulones (4H-thujan-2-ones) (III) to the dihydrumbellulols (4H-thujan-2-ols) (VI) should show similar stereoselectivity, but in this case, comparison with reduction of the conformationally rigid unsaturated ketone, umbellulone (thuj-3-en-2-one) (IV) should throw further light on the conformation of the transition state.

Reduction of thuj-3-en-2-one has been carried out by Wheeler³ who found that reduction with lithium aluminium hydride gives the unsaturated alcohols while reduction with sodium borohydride gives the saturated alcohols.³ This unexpected observation probably results from steric hindrance to the approach of the bulky reducing agent leading to 1,4-addition to form the enol of (III).⁴

EXPERIMENTAL

Thuj-3-en-2-one was distilled from Oil of California Mountain Bay Laurel at 138–139° and 70 mmHg. We are grateful to Fritzsche Bros. for a gift of the natural oil.

4 β H-Thujan-2-one.—Hydrogenation of thuj-3-en-2-one over a 10% palladium-charcoal catalyst in ethyl acetate solution gave 4 β H-thujan-2-one, >99% pure by g.l.c., semicarbazone, m.p. 157–158° (lit.,⁵ 158–159°).

Thuj-3-en-2-ols.—These were prepared and purified by the method of Wheeler and Chung.³

¹ D. V. Banthorpe and H. ff. S. Davies, *J. Chem. Soc. (B)*, 1968, 1356.

² R. J. Abraham, C. M. Holden, P. Loftus, and D. Whittaker, *Org. Magnetic Resonance*, 1974, **6**, 184.

³ J. W. Wheeler and R. H. Chung, *J. Org. Chem.*, 1969, **34**, 1149.

⁴ D. Whittaker and D. V. Banthorpe, *Chem. Rev.*, 1972, **4**, 305.

⁵ K. Todenhofer, *Jubiläumsbericht der Schimmel and Co.* 1929, 285, quoted by J. L. Simonsen and L. N. Owen, 'The Terpenes,' vol. 2, 2nd edn., Cambridge University Press, Cambridge, 1949, p. 58.

4 β H-*Thujan-2 α -ol*.—Reduction of compound (IIIb) with lithium aluminium hydride in ether followed by chromatography on a Florisil column with pentane-ether gave a product, m.p. 55–56°, 98% pure by g.l.c.

4 β H-*Thujan-2 β -ol*.—Reduction of compound (IIIb) with aluminium isopropoxide in propan-2-ol, followed by a similar purification to that for the α -ol gave a product, m.p. 66–67°, 99% pure by g.l.c.

Other reduction reactions were carried out following published procedures.¹

G.l.c. analyses were carried out on a Perkin-Elmer F.11 chromatograph, using a 14 ft packed glass capillary column, 15% Carbowax 20M on Chromosorb W at 170°.

¹H N.m.r. spectra were obtained on a Varian HA 100 spectrometer using a substrate concentration of ca. 150 mg ml⁻¹ in deuteriochloroform; Eu(fod)₃ was used as shift reagent where needed.

¹³C N.m.r. spectra were obtained on a Varian XL-100-15 spectrometer, using a substrate concentration of ca. 150 mg ml⁻¹ in deuteriochloroform.

RESULTS AND DISCUSSION

Previous ¹H n.m.r. work⁶ on the thuj-3-en-2-ols has established the configurations of the alcohols at C-2.

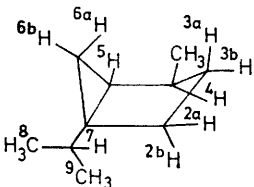
which 3b- and 4-H were replaced by deuterium, which confirmed their assignment, and permitted the assignment of the 6- and 7-H.

Assuming that hydrogenation of the double bond in thuj-3-en-2-one occurs from the least hindered (*i.e.* β) side of the molecule,⁸ then 4-H must be *trans* to the cyclopropyl ring. The observed values of 8.9 for $J_{3a,4}$ and 9.8 Hz for $J_{3b,4}$ require 4-H to be in a quasi-axial position, which is possible only if the molecule has a partial boat conformation. This is consistent with all other known thujanes.²

Application of the $\cos^2 \theta$ relationship⁹ to the $J_{3a,4}$ and $J_{3b,4}$ values of 8.9 and 9.8 Hz leads to dihedral angle values of ca. 160° for the 3a-H-4-H angle and ca. 8° for the 3b-H-4-H angle. These values will be satisfied if 4 β H-thujan-2-one exists as a flattened boat, with the planes C-1, -2, -4, and -5 and C-2—4 having a dihedral angle of ca. 5°.

The 100 MHz spectrum of 4 β H-thujan-2 β -ol was very sharp, and the signals are easily assigned except that for 3a-H, the position of which was found by irradiating the spectrum at 1.0 Hz, and noting the collapse of the

TABLE I
¹H N.m.r. data for 4 β H-thujan-2-one and -ols



	Chemical shift (δ)												
	2	3a	3b	4	5	6a	6b	7	8	9	10		
4 β H- <i>Thujan-2-one</i>		2.17	1.17	2.68	1.85	1.95 *	1.55 *	1.8	0.86	0.92	1.07		
4 β H- <i>Thujan-2α-ol</i>	4.13	~1.0	2.02	2.1	1.85	0.62	0.20	1.57	0.97	0.99	0.95		
4 β H- <i>Thujan-2β-ol</i>	4.17	~1.0	1.60	2.6	1.27	0.10	0.26	2.40	0.67	0.99	0.96		
	Coupling constant (J /Hz)												
	$J_{2,3a}$	$J_{2,3b}$	$J_{3a,3b}$	$J_{3a,4}$	$J_{3b,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	$J_{4,10Me}$	$J_{7,8Me}$	$J_{7,9Me}$	$J_{3b,5}$
4 β H- <i>Thujan-2-one</i>			17.5	8.9	9.8					6.5	2.25	2.25	1.20
4 β H- <i>Thujan-2α-ol</i>	14	2	12	6	6		8	8	9	6.5	7.0	7.0	
4 β H- <i>Thujan-2β-ol</i>	5.0		14.5	6	7.5	9	5	5	6	6.5	7.0	7.0	

* These assignments could be interchanged

The conformations of the alcohols are controlled by the effect of having a double bond in the cyclopentane ring which makes that ring flat. This has been confirmed by a ¹H n.m.r. study of α -thujene,⁷ so the ¹H spectra of the unsaturated ketone and alcohols were not studied.

The ¹H n.m.r. spectra of (IIIb) and the alcohols (VIa and b) were recorded and the results are given in Table I. Assignment of the 100 and 220 MHz spectra of 4 β H-thujan-2-one was reasonably straightforward; the addition of deuterium to (IV) gave a sample of (IIIb) in

2a-H doublet. Couplings of this peak were measured from a spectrum of the alcohol with Eu(fod)₃.

Assuming 4-H to be *trans* to the cyclopropyl ring, then since $J_{3a,4}$ and $J_{3b,4}$ are 6 and 7.5 Hz, while $J_{2a,3b}$ is ca. 0, it follows that, as in the ketone, the 4-methyl group is quasi-equatorial, and this molecule is also in a boat conformation with a quasi-axial hydroxy-group. In support of this, one of the 7-methyl groups is displaced upfield relative to that of the α -ol by the effect of the hydroxy-group; a similar phenomenon has been reported in the unsaturated alcohols.^{3,10}

Application of the $\cos^2 \theta$ relationship to the 3b-H-4-H

⁶ G. Cueille and R. Fraisse-Jullien, *Tetrahedron*, 1972, **28**, 1331.

⁷ M. A. Cooper, C. M. Holden, P. Loftus, and D. Whittaker, *J.C.S. Perkin II*, 1973, 665.

⁸ S. P. Acharya, H. C. Brown, A. Suzuki, S. Nozawa, and M. Itoh, *J. Org. Chem.*, 1969, **34**, 3015.

⁹ M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.

¹⁰ R. H. Chung, G. J. Lin, J. M. Nicholson, A. Tseng, O. Tucker, and J. W. Wheeler, *J. Amer. Chem. Soc.*, 1972, **94**, 2183.

coupling suggests a dihedral angle of 30° , corresponding to a C-1—5 to C-2—4 angle of *ca.* 18° .

In contrast, the 100 MHz spectrum of 4 β H-thujan-2 α -ol (VIa) was much less sharp, and was assigned only after decoupling experiments on the normal spectrum and on that with added Eu(fod)₃. In this case $J_{3a,4}$ and $J_{3b,4}$ are both *ca.* 6 Hz, while $J_{2,3a}$ is 14 and $J_{2,3b}$ *ca.* 2 Hz. Assuming the 4-methyl group to be quasi-equatorial, it follows that (VIa) must also exist as a boat conformation, with the hydroxy-group also in a quasi-equatorial position. The observed couplings, $J_{3a,4}$ and $J_{3b,4}$ are probably accurate only to ± 2 Hz, so the conformation cannot be accurately deduced, but is probably similar to that of the α -ol.

analysis since replacement of the sp^2 carbon of the ketone by an sp^3 carbon makes the molecule more flexible, so that bending the ring towards a classical boat pulls the methyl group into a more favoured quasi-equatorial position. Surprisingly, the position of the hydroxy-group has relatively little effect on the conformation, possibly because of the influence of the neighbouring isopropyl group.

Reduction of the Ketones.—The products of reduction of the unsaturated and saturated ketones are given in Table 3.

Reduction of thuj-3-en-2-one. Hydrogenation of thuj-3-en-2-one (IV) over a palladised charcoal catalyst at atmospheric pressure yielded only 4 β H-thujan-2-one

TABLE 2
¹³C Chemical shifts for thujane derivatives (δ values downfield from Me₄Si)

	1	2	3	4	5	6	7	8	9	10
Thuj-3-en-2-one (IV)	40.5	193.1	123.7	176.8	20.9	37.8	26.5	19.3	19.3	18.5
Thuj-3-en-2 β -ol (Va)	41.2	78.0	124.0	150.0	24.0 *	22.5	30.1 *	22.2 *	18.6 *	16.2
Thuj-3-en-2 α -ol (Vb)	35.3	78.5	133.3	147.4	31.6 *	21.4	31.0 *	20.0 *	19.6 *	16.2
4 β H-Thujan-2-one ² (IIIb)	43.5	186.1	40.8	25.9 *	31.7	13.4	28.4 *	19.7 *	19.5 *	18.1
4 β H-Thujan-2 β -ol (VIb)	38.7	75.8	39.7	24.3	27.1	5.0	31.6	20.9	20.9	17.7
4 β H-Thujan-2 α -ol (VIa)	38.0	74.6	39.0	20.4	28.4	6.2	31.0	19.9	19.9	17.7
Thuj-3-ene ²	34.1	36.7	121.0	141.5	31.5	21.5	33.0	20.0 *	20.1 *	16.3

* These assignments could be reversed.

TABLE 3
Reduction of thuj-3-en-2-one and 4 β H-thujan-2-one

Reagent	Ratio, ketone : reagent	Product (%)									
		Thuj-3-en-2-one					4 β H-Thujan-2-one				
		(Va)	(Vb)	(VIa)	(VIb)	(IV)	(IIIb)	(VIa)	(VIb)	(IIIb)	Other
LiAlH ₄ in ether	2 : 1	42	30			28		70	22	8	
	1 : 1	49	44			7		76	24		
NaBH ₄ in ether	4 : 1			5		83	12	26	10	64	
	2 : 1			40	10	34	40	66	19	15	
	1 : 3			75	20	4	1	73	21	6	
	1 : 7			77	23						
NaBH ₄ in propan-2-ol	1 : 1			77	18	5					
NaBH ₄ in propan-2-ol-water (5 : 2 molar ratio)	1 : 1			87	13	0					
NaBH ₄ in methanol-water (1 : 1 molar ratio)	1 : 1			80	20	0					
Al(OPr ⁱ) ₃ in propan-2-ol								35	63	2	
Li in NH ₃ -propan-2-ol								17	36		47
Catalytic hydrogenation							100				
Li in NH ₃							34	66			

Since application of the $\cos^2 \theta$ relationship to strained rings has been criticised,¹¹ though successfully applied to rigid thujenes,⁷ we used ¹³C n.m.r. spectra to confirm the assignments suggested above. Earlier work on the thujenes² has shown that the chemical shift of C-6 is diagnostic of the cyclopentane ring conformation.

The spectrum of thuj-3-en-2-one is atypical² but the C-6 shifts of the thuj-3-en-2-ols are similar to that of α -thujene, confirming the planar cyclopentene ring. That of the saturated ketone is shifted upfield, consistent with a bent ring, while the saturated alcohols are strongly shifted, consistent with greater bending. The ¹³C spectra are also consistent with the two 4 β H-thujanols having approximately similarly bent rings.

These data are readily rationalised by conformational

¹¹ R. J. Abraham, K. Parry, and W. A. Thomas, *J. Chem. Soc. (B)*, 1971, 444.

(IIIb). Reduction of the double bond with lithium in ammonia gives a product showing a single peak by g.l.c. but whose ¹³C n.m.r. spectrum was consistent with impure (IIIb). The semicarbazone of this product had m.p. 157—158°, compared with 158—159° for the ketone from hydrogenation and was not depressed by admixture with the latter. Clearly (IIIb) is the main product of lithium in ammonia reduction of (IV). This is consistent with the early reports of Semmler¹² and Tutin,¹³ who reduced thuj-3-en-2-one with sodium in alcohol to give a ketone whose semicarbazone had m.p. 156° and which they called β -dihydroumbellulone, identical with Todenhofers' ketone,⁵ semicarbazone, m.p. 158—159°, obtained by hydrogenation of umbellulone.

The thermodynamic equilibrium between 4 β H- and

¹² F. W. Semmler, *Ber.*, 1907, **40**, 5019; 1908, **41**, 3988.

¹³ F. Tutin, *Ber.*, 1908, **41**, 1118.

4 α H-thujan-2-one clearly favours the former. This can be understood by considering the conformation of the 4 β H-ketone; the boat conformation places the methyl group on C-4 in a pseudo-equatorial position while placing the methyl group of the isomeric ketone in the less favoured pseudo-axial position. A similar situation between 4 α H- (I) and 4 β H-thujan-3-one (II) results in the latter, which has a pseudo-equatorial methyl group, forming 65% of the equilibrium mixture.

Reduction of thuj-3-en-2-one with lithium aluminium hydride in ether reduces only the carbonyl function, giving a mixture of *ca.* 55% *trans*- and 45% *cis*-thuj-3-en-2-ols (Va and b). Approach of the reagent to C-2 is hindered on the α -face by the cyclopropane ring, and on the β -face by the isopropyl group. These appear to exert a similar effect on the reagent, so that attack from the α -face to give (Va) is slightly favoured over attack from the β -face to give (Vb).

Reduction of 4 β H-thujan-2-one (IIIb). Reduction of (IIIb) with aluminium isopropoxide in propan-2-ol and with lithium in methanol-ammonia gave similar (36 : 64 and 32 : 68) mixtures of (VIa and b). Reduction of (IIIb) with lithium aluminium hydride or sodium borohydride in ether gave a *ca.* 76 : 24 mixture of (VIa and b). Since (IIIb) has a flattened boat conformation, access to the α -face of the molecule should be decreased, relative to the half-chair structure of (IV), so the reduction products

show the effect of a change in the conformation of the starting material on the reaction, even though it involves a transition state in which the bulky metal hydride group is close to the isopropyl group. The effect is increased by shifting to a solvent in which solvation of the reagent would be expected to increase its bulk.

These results contrast with those obtained for reduction of 4 β H-thujan-3-one. In our case, reaction occurs close to bulky groups, so approach of the reagent is important. Access to the carbonyl group of 4 β H-thujan-3-one is relatively easy on either side, so that the differences in the product stabilities have a more important influence on the transition state. Thus, in the case of 4 α H-thujan-3-one (I) the methyl group on C-4 is pseudo-axial in the boat form of the ketone, so strain is released as the cyclopentane ring approaches planarity. However, attack of a bulky reagent from the β -face would require the cyclopentane ring to bend away from planarity in order to put the metal hydride group equatorial. On the other hand, attack from the α -face, followed by bending of the ring into a chair form, would permit both methyl and metal hydride groups to be equatorial, and is consequently favoured. In 4 β H-thujan-3-one, the 4-methyl group is best stabilised in a flattened boat, favouring attack of reagent on the β -face to put the bulky metal group quasi-equatorial.

[5/1454 Received, 23rd July, 1975]