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The Chemistry of the Natural Order Cupressales

49 *. The Configuration of Thujopsene

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The relative configuration of thujopsene (1a) is established by chemical, infrared, optical rotatory dispersion, and proton magnetic resonance studies. The optical rotatory dispersion curves of some conjugated cyclopropyl ketones are discussed. The three membered rings contribute strongly to the Cotton effect but the contribution is of opposite sign to that predicted by the octant rule (*cf.* also Ref.[29]). The strong positive Cotton effects of the ketones (16) and (31) establish the absolute configuration of thujopsene (1a).

The structure of thujopsene (1a) and its corresponding acid, hinokiic acid (1b), has been determined [1–3]. Hydration of thujopsene (1a) with oxalic acid furnishes an alcohol shown to be identical with widdrol [4], the structure of which (2) has recently been elucidated [5–7] and proved by synthesis [8]. This paper provides details of previous results,[3] and supporting evidence, leading to the assignment of the configuration of thujopsene (1a). Recent conclusions [5,7] regarding the configuration of the common asymmetric centre of thujopsene (1a) and widdrol (2) agree with the present results.

Catalytic hydrogenation of thujopsene (1a) and hinokiic acid (1b) takes place by a conjugate addition.[3] The dihydrocompounds (3a) and (3b), respectively, have been subjected to degradation and evidence in favour of a *cis* ring junction for the compounds is given below.

Stepwise oxidative degradation of the dihydrocompounds (3a) and (3b) gave a ketone (4a),[3] monobromination of which followed by dehydrobromination of the resulting bromoketone (4b) with lithium bromide and lithium carbonate in refluxing dimethylformamide furnished the α,β-unsaturated ketone (5) in high yield. Ozonisation of the unsaturated ketone followed by oxidation with alkaline hydrogen peroxide gave the C_{12}-dicarboxylic acid (6). This acid readily formed the corresponding anhydride and could only be isolated as the free acid along with the anhydride. Sublimation of the crude acid at about 120° under water pump pressure gave the pure anhydride (7).

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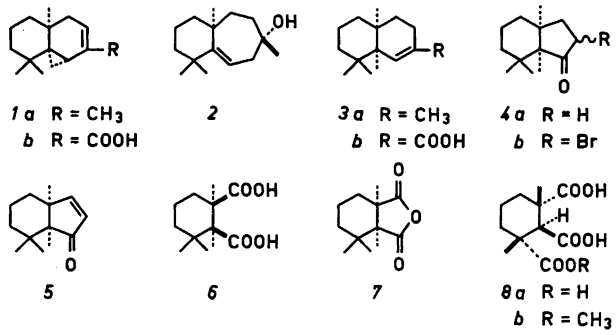
The ready anhydride formation of the C_{12}-dicarboxylic acid (6) can be compared with that of *cis*-1,2-cyclohexanedicarboxylic acid.[9] The asymmetric monomethylester (8b) of the tricarboxylic acid (8a), however, provides a more closely related cyclohexanedicarboxylic acid. The carboxyl groups are in this case in a *trans* relationship. The compound (8b) showed [10] only slight tendency to form an anhydride when heated to its melting point (about 160°) and contrary to the C_{12}-dicarboxylic acid (6), could readily be purified by recrystallisation from water. Thus the facile formation of the anhydride (7) must be explained by assuming a *cis* ring juncture in dihydrothujopsene (3a).



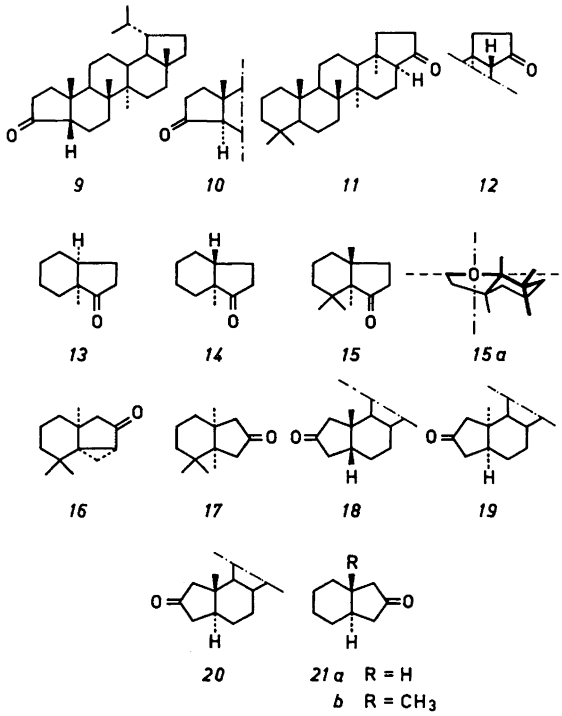
The ketone (4a) exhibits a remarkably low carbonyl stretching frequency for a five membered ring ketone (see Table 1). However, in the oxotrisnorlupane series (compounds 9 and 10) and oxotrisnorhopane series (compounds 11 and 12) it has been shown [11] that the carbonyl frequencies of the more stable *cis*-ketones (9 and 11) are much lower than those of the corresponding *trans*-ketones (10 and 12) (*cf.* Table 1). Moreover, there is a similar difference between the carbonyl bands of the *cis*- and *trans*-8-methylhexahydroindan-1-ones (13 and 14, respectively) as shown in Table 1. The low carbonyl frequency of the ketone (4a) strongly supports a *cis*-configuration.

The optical rotatory dispersion curves of cyclopentanone derivatives have been studied by Klyne [14], who discussed the observed Cotton effects in terms

Table 1. Carbonyl stretching frequencies of some *cis*- and *trans*-hexahydroindan-1-one systems. (^{c} in CCl_4; ^{ch} in $CHCl_3$; ^{n} in "nujol"; ^{o} as liquid film).

Type	Compound	Carbonyl stretching frequency, cm^{-1}			Ref.
Cis-	9	1729^n	1738^c	1729^{ch}	11
	11	1725^n	1738^c	1729^{ch}	11
	13	1730^o			12
	4a	1725^n	1728^c	1725^{ch}	This work
Trans-	10	1752^n	1751^c	1733^{ch}	11
	12	1748^n	1744^c	1735^{ch}	11
	14	**1754^o**			13

of the octant rule. The octant diagram of the ketone (15), the possible *trans*-isomer of the ketone (4a), is shown in formula (15a). The contributions to the Cotton effect from the 9-methyl and 7-*gem*-dimethyl groups in this compound should all be positive and the amplitude should therefore be similar to or larger than that of the known (+)-*trans*-8-methylhexahydroindan-1-one (14) (a + 88 *) [13] which does not possess these substituents. In fact the amplitude of the ketone (4a) is much less (a + 33) and more consistent with the (+)-*cis*-8-methylhexahydroindan-1-one (13) (a + 20).[12]



As reported earlier [3] oxidative degradation of thujopsene (1a) gave the ketone (16). Reduction of this ketone with lithium in ammonia has now given in almost quantitative yield a fully saturated five membered ring ketone as shown from its infrared and ultraviolet spectra. The ketone exhibits strong infrared absorption at 1410 cm^{-1} due to the $-CO-CH_2-$ groupings. The apparent integrated intensity of this band (I = 45) is almost double those of the ketones (4a) and (16) (I = 22 and 23, respectively), which have only one such CH_2-grouping. The structure (17), proposed for the product, is supported by its proton magnetic resonance spectrum (see Experimental). Conclusive evidence for structure (17) follows from its degradation to the anhydride (7) by oxidation with nitric acid. This new lithium in ammonia reaction appears

* For nomenclature see Experimental.

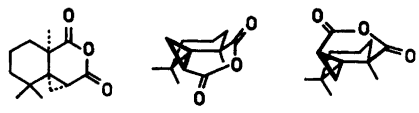
to be of value for the stereospecific opening of conjugated cyclopropane ring systems and further investigation of its application is in progress.

The ketone (17) exhibits a negative Cotton effect (a −103) which is in agreement with that expected for a *cis*-hexahydroindan-2-one derivative (*cf.* a 2-oxo-5β-A-norsteroid (18), a − 150,[13] and a 2-oxo-19α-A-norsteroid (19), a − 113 [15]). *trans*-Hexahydroindan-2-ones are distinguished [14] by their much larger amplitudes (*e.g.* a 2-oxo-5α-A-norsteroid (20), a + 234,[16] (−)-*trans*-hexahydroindan-2-one (21a), a − 222,[17] and (−)-*trans*-8-methylhexahydroindan-2-one (21b), a − 219 [13]). The optical rotatory dispersion data for the ketone (17) thus serves as supporting evidence for a *cis*-configuration in dihydrothujopsene (3a).

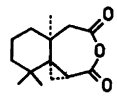
The proton magnetic resonance spectrum of dihydrothujopsene (3a) has been reported in a previous communication.[2] A sharp resonance signal at τ 8.61 was assigned to CH_2-groups of the rings. Musher and Richards [18] have investigated the proton magnetic resonance spectra of some *cis*- and *trans*-decalin systems and have found that the ring hydrogens of the *cis* compounds give only one sharp resonance signal, whereas those of the corresponding *trans* forms exhibit broad resonance. In a detailed investigation of the spectra of the various isomers of 10-methyldecalol-2, Musher [19] found a similar difference in the appearance of the ring hydrogen signals between *cis*- and *trans*-fused isomers. Furthermore, the spectra of *cis*- and *trans*-Δ^2-octalins [20] show a similar characteristic difference. The sharp ring hydrogen signal of dihydrothujopsene (3a) may therefore serve as an indication for a *cis*-ring juncture in this compound.

The proton magnetic resonance spectrum of the C_{13}-anhydride (22) has also been reported in connection with the structure elucidation of thujopsene and hinokiic acid.[2] The single proton on the cyclopropane ring in a position α to one of the carbonyl groups has its resonance position at a comparatively low field (X-part of an ABX-spectrum centered at τ 7.78). In the two possible forms of the anhydride, (22a) and (22b) with the two six membered rings *trans*- and *cis*-fused, respectively, this proton lies very near to the trigonal plane of the carbonyl group (the C—C—O-plane), in which the diamagnetic anistotropy of this group will cause maximal shift towards lower field.[21] Similarly the anisotropy of the other carbonyl group accounts for the low resonance frequency (τ 8.45) assigned to the protons of the angular methyl group. The signals due to the various methyl groups in the C_{13}-anhydride (22) and related compounds are listed in Table 2. The ketone (4a) and the C_{12}-anhydride (7) also have angular methyl groups in positions α to a carbonyl group but their resonance frequencies (*cf.* Table 2) do not appear at such low field as that of the C_{13}-anhydride (22). It is therefore considered that the angular methyl group of the latter compound is situated near the trigonal plane of the adjacent carbonyl group. Inspection of models (*cf.* formula 22a and 22b) shows that such a steric arrangement is only possible for the *cis*-configuration (22b).

With the *cis*-A/B-ring fusion of thujopsene (1a) established by the above evidence, an approach to determine the absolute configuration was a study of possible isomerisations of the ketone (16) in the hope of obtaining an octalone derivative, *e.g.* the ketone (24), which then could be related to a possible degradation product of the di- and triterpene series. However, the ketone



22 22a 22b



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(16) was found to be remarkably stable to acids while prolonged treatment under vigorous conditions gave a complex mixture of products.

As the two ketones (4a) and (17) of *cis*-hexahydroindanone type may invert between various conformations and, at present, too little is known about such *cis*-fused ring systems, no certain conclusions regarding their absolute configuration can be drawn from their optical rotatory dispersion data. However, in the structure elucidation of widdrol (2), recently carried out by Enzell [7] in this Laboratory, the octalone derivative (25) and the decalone (26) were obtained. The optical rotatory dispersion curves exhibited by these compounds showed that their angular methyl groups were α-oriented. It follows therefore that the angular methyl groups of widdrol (2) and thujopsene (1a) are α-oriented.

Djerassi *et al.*[22] have pointed out that the optical rotatory dispersion curves of ketones are strongly affected by conjugated cyclopropane rings, giving rise to characteristic Cotton effects. The ketone (16) shows a similar characteristic positive Cotton effect where the maximum occurs at remarkably low wavelength for a five membered ring ketone (Fig. 1). The application of the octant rule [23] to the ketone (16), for a tentative assignment of the absolute configuration of thujopsene, suggested that the CH_2-group of the cyclopropane ring was in a positive octant.[1,3] However, further work on this problem has now shown that, for the application of the octant rule to this type of ketones, the cyclopropane ring cannot be considered as an ordinary alkyl group.

Table 2. Methyl group shifts of C_{13}-anhydride (22) and related compounds. (In carbon tetrachloride solutions and with tetramethylsilane as internal standard on a Varian A-60 instrument, 60 Mc/s).

Compound	Shifts in τ-units	
	Angular methyls	*Gem*-dimethyls
C_{13}-Anhydride (22)	8.45	8.88; 9.33
C_{14}-Anhydride (23)	9.31 *	8.81; 9.21 *
Ketone (16)	9.42	8.86; 9.01
Ketone (4a)	8.85; 8.94 *	9.09 * (6 protons)
C_{12}-Anhydride (7)	8.75; 8.78	8.96 (6 protons)

* Tentatively assigned.

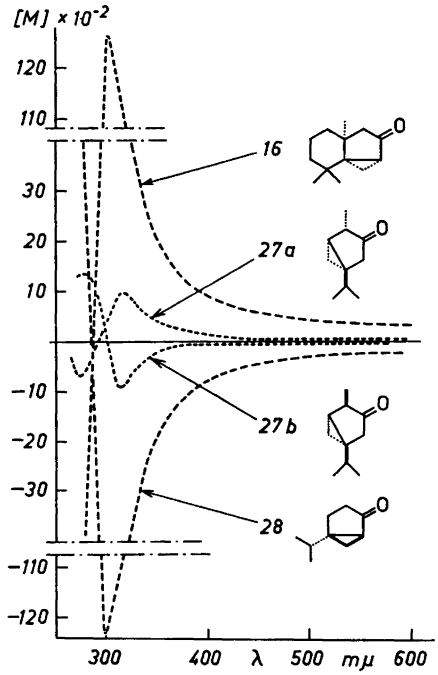
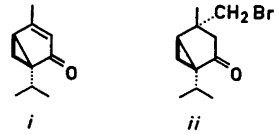


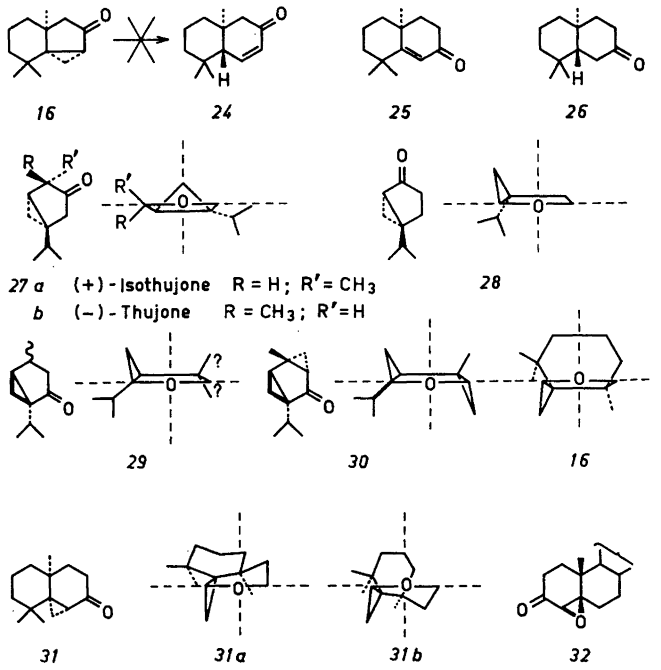
Fig. 1. Optical rotatory dispersion curves (in methanol) of ketone (16), (+)-isothujone (27a), (−)-thujone (27b), and sabinaketone (28).

The rigid bicyclo [3,1,0] hexanones in the thujane group provide suitable model systems for the study of the Cotton effects of ketones with conjugated cyclopropane rings. However, when this work was started the absolute configuration of the thujane group was not known. This point was established during the course of this work by a degradation of a thujane derivative to a compound of known absolute configuration [24] and also at the same time by Walborsky *et al.*[25] by a partial asymmetric synthesis of (+)-*cis*-umbellularic acid. A comparison of the optical rotatory dispersion curves of the two epimeric thujones (27a) and (27b), whose relative configurations are now known,[26] with that of sabinaketone (28) (Fig. 1) clearly illustrates that the large Cotton effect of the latter is associated with the asymmetrically arranged cyclopropane ring whereas ordinary alkyl substituents give minor contributions to the observed Cotton effect. The octant diagrams of the epimeric thujones (27a) and (27b), sabinaketone (28), β-dihydroumbellulone (29) and the tricyclic ketone (30) * are shown in the formula scheme. According to the octant rule

* The tricyclic ketone (30) (Eastman, R. H. *J. Am. Chem. Soc.* **76** (1954) 4115) is formed by a Michael addition of diethyl malonate to umbellulone (i) followed by hydrolysis, decarboxylation, and Hunsdiecker degradation to the ketone (ii), which is finally ringclosed by alkali. The configuration of the additional cyclopropane ring has been assigned on the basis that the Michael addition occurs from the less sterically hindered side.



i *ii*



the cyclopropane rings of sabinaketone (28), β-dihydroumbellulone (29) and the tricyclic ketone (30) are all in *positive octants*. However, sabinaketone (28) exhibits a strong *negative Cotton effect* (Fig. 1) as does also β-dihydroumbellulone (29) (a — 68) and the tricyclic ketone (30) ($a < -180$), the curves of which have been recorded by Djerassi *et al.*[22] The cyclopropane ring of the ketone (16), which shows a strong *positive Cotton effect* (Fig. 1) ($a > +260$), must therefore be in a *negative octant* (*cf.* octant diagram (16) in the last formula scheme).

The ketone (31), a degradation product of thujopsene (1a),[27,28] shows a similar strong positive Cotton effect ($a < +202$)[28] to that of the ketone (16). Ketone (31) may exist in one of the two conformations shown on the octant diagrams (31a) and (31b). In both cases the cyclopropane ring is in a negative octant causing the strong positive Cotton effect. A more extensive investigation concerning the optical properties of various cyclopropyl and epoxi ketones, which at present has been carried out,[29] fully confirm the above results from both an empirical and theoretical point of view. As epoxide rings are shown to possess optical properties similar to those of cyclopropane rings, the strong positive Cotton effect of the ketone (31) can be compared with that of a 4β,5β-epoxi-3-oxosteroid (32)[29] providing further evidence for the assigned absolute configuration of thujopsene (1a).

Although no direct correlation of thujopsene (1a) or widdrol (2) to a compound of known absolute configuration has been carried out, the results pre-

sented above leave no doubt that the configuration of thujopsene is represented by the stereoformula (1a).

Biogenetic routes to sesquiterpenes were initially suggested by Ruzicka [30] and have been further developed on configurational and electronic bases by Hendrickson.[31] Considering the configurations of thujopsene, widdrol, α-cedrene,[32] and cuparene,[33] these compounds can be shown to be "biogenetically" closely related, and derived from a common 2,3-*cis*-farnesyl cation properly orientated. It is therefore not surprising that these compounds have been found to occur together in several genera of the order Cupressales (*e.g. Cupressus*,[34], *Juniperus* [35] and *Thujopsis* [36]). These biogenetic relationship will be further discussed elsewhere.

EXPERIMENTAL

Melting points are uncorrected and taken on a Kofler micro hot stage. Alumina used for chromatography is supplied by Merck A.G., Darmstadt, Germany, and the degree of activity is according to Brockmann. Light petroleum refers to a fraction b.p. 40–60°. The infrared (IR) spectra are recorded on a Perkin-Elmer No. 21 instrument (NaCl-prisms; solutions in 1 mm NaCl-cell). The ultraviolet (UV) spectra are measured in alcohol (95 %) on a Beckman DK 2 spectrophotometer. The rotations are taken in chloroform. The optical rotatory dispersion (ORD) curves are recorded in methanol and the data are given as molecular rotations, $[M]$. The amplitudes quoted in the text are according to the nomenclature used by Klyne [14], $a = [M] \times 10^{-2}$. The proton magnetic resonance (PMR) spectra are obtained with *ca.* 10–15% carbon tetrachloride solutions on a Varian A-60 instrument (60 Mc/s) equipped with an electronic integrator. Tetramethylsilane is used as internal standard. The chemical shifts are given in τ-units [37]. The PMR spectra of dihydrothujopsene (3a), ketone (16), C_{13}-anhydride (24), and C_{14}-anhydride (25), previously reported by us,[2] have been determined in the same way. The shifts obtained for these four compounds agreed closely with those previously reported.

Stepwise oxidative degradation of dihydrothujopsene (3a) gave [3] the *ketone* (4a) which exhibits IR carbonyl absorption at 1725 cm^{-1} ("nujol"), 1728 cm^{-1} (*ca.* 1 % carbon tetrachloride solution) and 1725 cm^{-1} (*ca.* 1 % chloroform solution), and the following ORD data: $[M]_{500}$ + 200°; $[M]_{325}$ + 2000° (max.); $[M]_{280}$ −1300° (min.); $[M]_{270}$ −1000°.

The PMR spectrum of the ketone (4a) shows a multiplet (integrated area, 2 H) centered at τ 7.80 and a similar multiplet (2 H) at τ 8.45. These two multiplets are assigned to the CH_2-groups in positions α and β to the carbonyl group, respectively. A broad signal group at τ 8.61 (6 H) is assigned to the CH_2-groups of the six membered ring. A sharp signal at τ 8.85 (3 H) may be assigned to the angular methyl group adjacent to the carbonyl group, and two signals at τ 8.94 (3 H) and τ 9.09 (6 H) are assigned to the other angular methyl group and the *gem*-dimethyl group. The signal at τ 9.09 may tentatively be assigned to the latter group.

Bromoketone (4b). Bromine (0.320 g) in acetic acid (1 ml) containing one drop of hydrobromic acid (50 %) was added to a solution of the ketone (4a) (0.388 g) in acetic acid (3 ml). The reaction mixture was left for 12 h when the colour had disappeared. The solution was poured into ice-water and extracted with ether. The ether phase was washed with saturated aqueous sodium bicarbonate and water, dried and evaporated. The oily residue crystallised after addition of small amounts of methanol. Recrystallisation from methanol gave the *bromoketone* (4b) (0.325 g), m.p. 64–65°, $[\alpha]_D$ + 92° (*c* 1.0), $\lambda_{max}^{CCl_4}$ 1743 cm^{-1}. (Found: C 57.0; H 7.8; Br 29.0. $C_{13}H_{21}OBr$ requires C 57.1; H 7.7; Br 29.3).

α,β-Unsaturated ketone (5). The bromoketone (4b) (0.265 g), dry lithium carbonate (0.40 g) and anhydrous lithium bromide (0.40 g) in freshly distilled dimethylformamide (15 ml) was heated under reflux for 2 h. The cooled reaction mixture was diluted with water and extracted with ether. The washed and dried ether extract gave on evaporation of the solvent a white solid (0.190 g) with strong camphorous smell. The product was purified by chromatography on alumina (activity I, 8 g). Ether/petroleum ether (5 %)

eluted the *α,β-unsaturated ketone* (5) (0.173 g). The analytical sample was sublimed under reduced pressure and had m.p. 183—185° (sealed tube), $[\alpha]_D$ + 85° (*s* 1.1), and the following ORD data: $[M]_{500}$ + 300°; $[M]_{380}$ + 500 (inflex.); $[M]_{350}$ + 1200° (max.); $[M]_{300}$ + 250° (min.); $[M]_{270}$ + 2000°. The IR spectrum showed characteristic bands at 1700, 1600, and 835 cm^{-1} ("nujol"; *α,β*-unsaturated 5-membered ring ketone with *cis*-disubstituted double bond), and the UV spectrum a maximum at 226 mμ (ε 6300). (Found: C 81.3; H 10.5. $C_{13}H_{20}O$ requires C 81.2; H 10.5).

C_{12}-Dicarboxylic acid (6) *and its anhydride* (7). The *α,β*-unsaturated ketone (5) (0.120 g) was dissolved in ethyl acetate (5 ml) and methanol (2 ml). The solution was treated with ozone at −70° until a blue colour appeared. Excess ozone was removed by passing nitrogen through the reaction mixture. Water (15 ml) was added and the organic solvents were evaporated on a water bath. Aqueous sodium hydroxide (10 %, 10 ml) and hydrogen peroxide (30 %, 2 ml) were added to the hot oily water phase and the reaction mixture was kept at water bath temperature for 3 h. The cooled reaction mixture was extracted with ether and the alkaline water phase acidified with cold dilute sulphuric acid (2 N). Extraction several times with ether and evaporation of the washed and dried (Na_2SO_4) ether phase at room temperature under water pump pressure gave the crude crystalline *C_{12}-dicarboxylic acid* (6) (0.105 g). Attemted recrystallisation from aqueous acetic acid gave a mixture of the acid and the corresponding anhydride as shown from its IR spectrum. A saturated solution of the mixture in aqueous methanol when allowed to slowly evaporate at room temperature gave large crystals of the dicarboxylic acid (6) which, however, according to its IR spectrum still contained some anhydride. Following the description by Barton and Schmeidler[18] for the purification of the monomethylester (8b) by recrystallisation from water also gave a mixture of the anhydride and the acid. The above acid-anhydride mixtures gave on sublimation under reduced pressure (10 mm Hg) at about 120° the pure anhydride (7) as a white solid with m.p. 214—216° (sealed tube), $[\alpha]_D$ + 48° (*c* 1.4), IR bands at 1840 and 1775 cm^{-1} ("nujol"; 5-membered ring anhydride). (Found: C 68.5; H 8.6. $C_{12}H_{18}O_3$ requires C 68.5; H 8.6).

The PMR spectrum of the anhydride (7) shows one broad signal group at τ 8.60 and three smaller broad signals at τ 8.86, 8.88, and 9.05. The combined integrated areas of these four signals correspond to 6 H. These signals are assigned to the CH_2-groups of the six membered ring. Two sharp signals at τ 8.75 and 8.78, each corresponding to 3 H, are assigned to the angular methyl groups. One sharp signal at τ 8.96 (6 H) is assigned to the *gem*-dimethyl group.

Ketone (17). Lithium (0.20 g) was added to liquid ammonia (50 ml) with stirring. The ketone (16) (0.75 g) in dry ether (4 ml) was added to the lithium in ammonia solution and the stirring was continued for 2 h. Ammonium chloride was added to destroy excess lithium. Ether (50 ml) was added and the ammonia allowed to evaporate. The product, worked up in the usual way, was chromatographed on alumina (activity I, 30 g.). Ether/petroleum ether (10 %) eluted the *ketone* (17) (0.70 g). The analytical sample was sublimed under reduced pressure giving a white solid with m.p. 174—175° (sealed tube), $[\alpha]_D$ −106° (*c* 1.5). The ketone (17) had the following ORD data: $[M]_{500}$ −250°; $[M]_{315}$ −4950° (min.); $[M]_{280}$ + 5340° (max.); $[M]_{275}$ + 4300°. The IR spectrum (CCl_4) of the ketone (17) showed bands at 1740 cm^{-1} (5-membered ring ketone) and 1410 cm^{-1} (CH_2-groups next to the carbonyl group). The apparent integrated intensity (I = 43) of the latter band was compared those of the same type of bands of the ketone (16) (I = 23) and the ketone (4a) (I = 22). The UV spectrum of the ketone (17) did not show any maximum above 200 mμ. (Found: C 80.5; H 11.4. $C_{13}H_{22}O$ requires C 80.4; H 11.4).

The *2,4-dinitrophenylhydrazone* of the ketone (17) had m.p. 122—124° (needles) from aqueous methanol and m.p. 126—127° (plates) after solidifying and remelting.

The PMR spectrum of the ketone (17) shows two quartets characteristic for two AB-spectra with combined integrated area corresponding to 4 H. One of the quartets was centered at τ 7.83 (J = 17.5 cps) and the other at τ 7.98 (J = 17.5 cps). These two AB-spectra must be assigned to the two CH_2-groups next to the carbonyl group. A broad signal group centered at τ 8.55 (6 H) is assigned to the CH_2-groups of the six membered ring. Four sharp signals at τ 8.80, 8.94, 8.98 and 9.15 (each corresponding to 3 H) are assigned to the geminal and angular methyl groups.

The ketone (17) was oxidised with nitric acid using vanadium pentoxide catalyst according to a method previously described.[10] An ice-cooled mixture of fuming nitric acid (*d* 1.52, 0.5 g) and concentrated nitric acid (*d* 1.40, 1.5 g) containing vanadium pentoxide

(≈ 1 mg) was added in portions to the ketone (17) (0.60 g). When the first vigorous reaction had stopped the reaction mixture was heated to about 50°, when further reaction occurred, and finally heated under reflux for 2 h. The cooled reaction mixture was poured into ice-water and extracted with ether. The washed ether phase was extracted with aqueous sodium hydroxide (10 %). The ether washed alkaline phase was acidified and extracted with ether. The dried and evaporated ether extract gave an oil, which was distilled in a gradient tube under reduced pressure. The product in the colder part of the tube solidified and was sublimed once more to yield a white solid (0.05 g) with m.p., mixed m.p. and IR spectrum identical with those of the *C_{12}-anhydride* (7).

Acid isomerisations of the ketone (16). (i) The ketone (0.205 g) was dissolved in dry ether (10 ml) and the solution was saturated with dry hydrogen chloride gas at room temperature and then left for 1 h. The reaction mixture was poured into ice-water and worked up in the usual way to yield a crystalline solid which on recrystallisation from methanol gave unchanged material (0.180 g).

(ii) The ketone (0.105 g) in formic acid (98 %, 4 ml) was heated under reflux for 3 h. Working up with ether in the usual way gave an oil which was chromatographed on alumina (neutral, activity I, 6 g). The main product (0.058 g) was eluted with petroleum ether/ether (1:4), and was shown to be unchanged starting material. Other fractions eluted with petroleum ether/ether mixtures and with ether were shown to be complex mixtures by vapour phase chromatography (stationary phase 100–115 mesh Silocel C 22 brick powder impregnated with 10 % "polyethylene alkatene", a polyester supplied by Perkin-Elmer Co; temperature 140° on a Pye Argon Chromatograph Cat. No 12 000).

(iii) The ketone (0.103 g) in acetic acid (3 ml) and hydrobromic acid (66 %, 0.5 ml) was heated under reflux for 1.5 h. The reaction mixture was worked up with ether in the usual way and the product chromatographed on alumina (neutral, activity I, 6 g). The main fraction (0.076 g) was eluted by petroleum ether/ether (1:5) and found to be unchanged starting material. Other fractions eluted by petroleum ether/ether mixtures and with ether were shown to be complex mixtures by vapour phase chromatography (for conditions see under ii).

(iv) The ketone (0.200 g) in acetic acid (4 ml) and hydroiodic acid (66 %, 1 ml) was heated under reflux for 3 h. Considerable amounts of free iodine were formed and the reaction mixture was therefore worked up with ether and aqueous thiosulphate. The product (0.215 g) was chromatographed on alumina (neutral, activity I, 12 g). The only homogeneous fraction (0.025 g) which could be isolated was eluted by petroleum ether/ether (1:1). This solid fraction had m.p. 240° (sealed tube) and $[\alpha]_D$ −136°. The compound gave a yellow 2,4-dinitrophenyl hydrazone, m.p. 162–164° (needles from methanol), but has not been further investigated. The other fractions from the chromatography were shown to be complex mixtures by vapour phase chromatography (for conditions see under ii).

Sabinaketone (28). Sabinene (3.0 g), $[\alpha]_D$ + 102°, n_D^{25} 1.4662, was ozonised according to the description by Schmidt [38]. The product was chromatographed on alumina (neutral, activity I, 60 g). Ether eluted the *sabinaketone* (28) (1.35 g) which was distilled under reduced pressure. The compound was homogeneous according to gas liquid chromatography (stationary phase, 100–115 mesh Silocel C 22 brick powder impregnated with 2,4-dinitrophenyl-2-naphthyl ether and dibenzyl pyridine as described by Groth [39], temperature 150° on a Pye Argon Chromatograph Cat. No 12 000), and had m.p. ≈ 14° (*lit.*[38] m.p. 17°). The ORD curve of sabinaketone (28) is shown in Fig. 1.

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REFERENCES

1. Erdtman, H. and Norin, T. *Chem. Ind. (London)* **1960** 622.
2. Forsén, S. and Norin, T. *Acta Chem. Scand.* **15** (1961) 592.
3. Norin, T. *Acta Chem. Scand.* **15** (1961) 1676.
4. Nagahama, S. *Bull. Chem. Soc. Japan* **33** (1960) 1467.
5. Enzell, C. *Acta Chem. Scand.* **15** (1961) 1191.
6. Ito, S., Endo, K., Takeshita, H., Nozoe, T. and Stoter, J. B. *Chem. Ind. (London)* **1961** 1618.
7. Enzell, C. *Acta Chem. Scand.* **16** (1962) 1553.
8. Enzell, C. *Tetrahedron Letters* **1962** 185.
9. Baeyer, A. *Ann.* **258** (1890) 145.
10. Barton, D. H. R. and Schmeidler, G. A. *J. Chem. Soc.* **1948** 1197.
11. Baddeley, G. V., Halsall, T. G. and Jones, E. R. H. *J. Chem. Soc.* **1960** 1715.
12. Acklin, W. and Prelog, V. *Helv. Chim. Acta* **42** (1959) 1239.
13. Djerassi, C., Riniker, R. and Riniker, B. *J. Am. Chem. Soc.* **78** (1956) 1239.
14. Klyne, W. *Tetrahedron* **13** (1961) 29.
15. Klyne, W. *Personal communication.*
16. Djerassi, C., Riniker, B. and Riniker, R. *J. Am. Chem. Soc.* **78** (1956) 3163.
17. Bourn, P. M. and Klyne, W. *J. Chem. Soc.* **1960** 2044.
18. Musher, J. I. and Richards, R. E. *Proc. Chem. Soc.* **1958** 230.
19. Musher, J. I. *J. Am. Chem. Soc.* **83** (1961) 1146.
20. Oberhänsli, P. and Whiting, M. C. *Personal communication.*
21. Jackman, L. M. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, London 1959, p. 119.
22. Djerassi, C., Riniker, R. and Riniker, B. *J. Am. Chem. Soc.* **78** (1956) 6377.
23. Mofitt, W., Woodward, R. B., Moscowitz, A., Klyne, W. and Djerassi, C. *J. Am. Chem. Soc.* **83** (1961) 4013.
24. Norin, T. *Acta Chem. Scand.* **16** (1962) 640.
25. Walborsky, H. M., Sugita, T., Ohno, M. and Inouye, Y. *J. Am. Chem. Soc.* **82** (1960) 5255.
26. Norin, T. *To be published.*
27. Kobayashi, H., Nagahama, S. and Akiyoshi, S. *Bull. Chem. Soc. Japan* **34** (1961) 1123.
28. Nozoe, T., Takeshita, H., Ito, S., Ozeki, T. and Seto, S. *Chem. Pharm. Bull. (Tokyo)* **8** (1960) 936.
29. Djerassi, C., Klyne, W., Mislow, K., Moscowitz, A., Norin, T., Ohloff, G. and Klein, E. *To be published.*
30. Ruzicka, L. *Proc. Chem. Soc.* **1959** 341.
31. Hendrickson, I. B. *Tetrahedron* **7** (1959) 82.
32. Stork, G. and Clarke, Jr., F. H. *J. Am. Chem. Soc.* **83** (1961) 3120.
33. Enzell, C. and Erdtman, H. *Tetrahedron* **4** (1958) 361.
34. Barreto, H. S. and Enzell, C. *Acta Chem. Scand.* **15** (1961) 1313.
35. Pettersson, E. and Runeberg, J. *Acta Chem. Scand.* **15** (1961) 713.
36. Nagahama, S. and Norin, T. *To be published.*
37. Tiers, G. V. D. *J. Phys. Chem.* **62** (1958) 1151.
38. Schmidt, H. *Z. angew. Chem.* **42** (1929) 126.
39. Groth, A. B. *Svensk Papperstid.* **61** (1958) 315.

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