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The Chemistry of the Natural Order Cupressales

43 *. The Structure and Configuration of Hinokiol and Hinokione **

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The structures of hinokiol and hinokione have been revised. The oxygen atom of ring A is in the 3-position. The alcoholic hydroxyl group in hinokiol is β-oriented. The A/B-ring junction is the normal 5*a*,10β.

The phenolic diterpene alcohol hinokiol was first isolated from the wood of *Chamaecyparis obtusa* ("hinoki") by Yoshiki and Ishiguro [1a–c]. It has later been encountered in this laboratory in two *Athrotaxis* species [2a], in *Cupressus torulosa* [2b] and in *Tetraclinis articulata* [2c]. Hinokione is the corresponding ketone and a frequent congener of hinokiol [1a,b].

Structures *1a* and *1b* have been suggested for hinokiol and hinokione, respectively [3]. The carbon skeleton has been corroborated by an interrelation with ferruginol [4] but the configuration remained unknown and the location of the secondary hydroxyl group at C_2 rested on inconclusive evidence and appeared improbable to us. In this report we confirm the new structures *2a* and *2b* for hinokione and hinokiol, respectively.

Clemmensen reduction of hinokione afforded ferruginol (*2c*) of known structure and configuration [5]. This shows that rings A and B are *trans*-fused.

Bromination of hinokione acetate (*2d*) furnished a dibromo derivative (*3*). The optical properties of this compound indicated that both bromine atoms were attached to the carbon atom next to the carbonyl group [6]. Dehydrobromination with lithium bromide in dimethylformamide gave an amorphous product, which on boiling with activated zinc and alcohol gave 1,2-didehydro-2-bromohinokione (*4*) and finally the α,β-unsaturated ketone 1,2-didehydrohinokione (*5*) ***. Both (*4*) and (*5*) gave hinokione on mild catalytic reduction.

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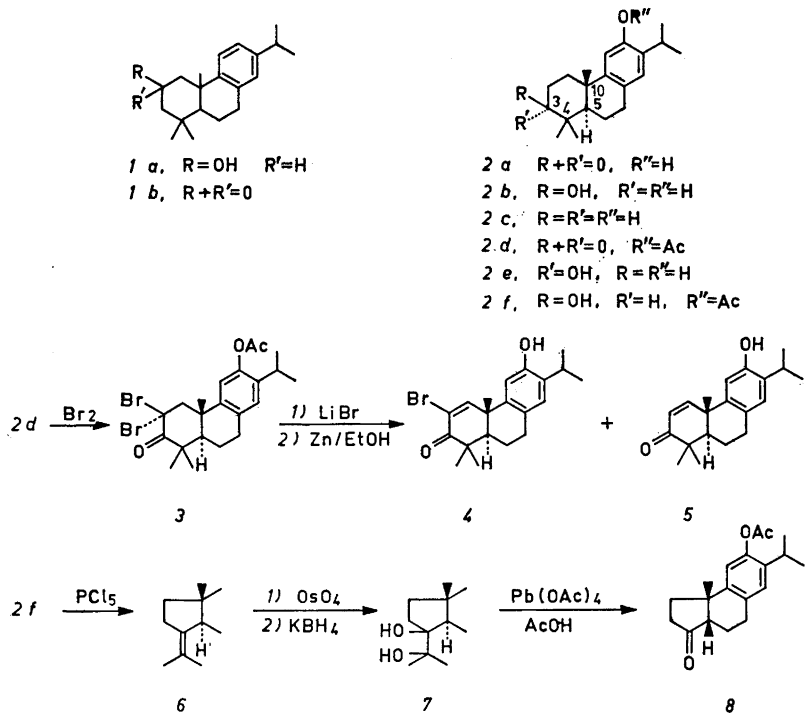
*** The debromination of *3* might involve the formation of a zinc-organic intermediate from which ZnBrOEt is released, the latter causing the observed deacetylation. Totarol acetate was not deacetylated under similar conditions.



The formation of an α,β-unsaturated ketone would be possible only if the alcoholic hydroxyl group were in position 1 or 3 but not in position 2. The A-ring of dibromohinokione is probably in the boat form, thus relieving the non-bonded interactions between Br at C_2 and the methyl groups at C_4 and C_{10} (*Cf.* Ref.[7]).

Catalytic hydrogenation of hinokione gave isohinokiol (*2e*) and a small amount of hinokiol, whereas reduction with potassium borohydride gave hinokiol in good yield. This indicates that the alcoholic hydroxyl group in hinokiol is equatorial and that in isohinokiol axial [8,9].

Comparison of the molecular rotation of hinokiol and isohinokiol derivatives with those of the corresponding ferruginol derivatives shows that the shifts in rotation are positive for hinokiol and negative for isohinokiol (*cf.* Table 1). By analogy with the similar effects known from 3-hydroxy-triterpenes having

Table 1. Molecular rotation shifts (Molecular rotations, in ethanol within brackets).

Hinokiol diacetate (272) — Ferruginol acetate (188) = + 84°
Isohinokiol diacetate (109) [1b] — Ferruginol acetate (188) = —79°
Hinokiol methylether * acetate (283) — hinokiol methylether * (188) = + 95°
Isohinokiol methylether * acetate (42) — isohinokiol methylether * (144) = —102°

* Phenolic hydroxyl methylated.

$a_{\blacktriangle}^{\blacksquare}5\alpha,10\beta$-absolute configuration [10], this indicates that the alcoholic hydroxyl group in hinokiol is 3β and in isohinokiol 3α.

Treatment of the mono (phenol) acetate of hinokiol (*2f*) with phosphorus pentachloride gave a product possessing an I.R. absorption indicating that dehydration had occurred and that the acetyl group was still present. It therefore appeared that the molecule had undergone the retropinacol rearrangement (*2f—6*) frequently observed in the 3β-hydroxy triterpene series [8,11]. The product was therefore treated with osmium tetroxide and the osmate cleaved with potassium borohydride. The material obtained was subjected to a re-acetylation with acetic anhydride and pyridine to ensure that the phenolic hydroxyl was protected and the product (*7*) oxidised with lead tetraacetate. A high yield (63 %) of acetone was obtained. It is obvious, therefore, that the reaction had proceeded normally and this was confirmed by the fact that the non-volatile fission product exhibited the I.R. absorption expected for a cyclopentanone derivative. The product was re-acetylated and purified by sublimation giving a crystalline semi-pure product (*8*) in small yield which showed a positive Cotton effect similar to that of *cis*-oxotrisnorlupane [11]. (Inversion at C_5 occurred during the oxidation). It is obvious from these results that the alcoholic hydroxyl group in hinokiol is in position 3 and that it is β-oriented. The location of this hydroxyl group has been definitely established by a synthesis of D,L-hinokiol methyl ether recently carried out by one of us [12].

Having the conventional steroid absolute configuration, hinokione should exhibit a positive Cotton effect in analogy with lanost-8-en-3-one [13]. As seen from Table 2 there appears to be a positive peak at 302 mμ but the trough is masked.

Table 2. Specific rotations at different wavelengths.

Hinokione	+ 160°	(450)	+ 1430°	(302)	+ 1375°	(300)
Lanost-8-en-3-one	+ 74°	(589)	+ 610°	(300)	+ 498°	(277.5)
Hinokiol	+ 132°	(450)	+ 332°	(312)		
Ferruginol acetate	+ 118°	(450)	+ 310°	(312)		
Totarolone	+ 167°	(400)	+ 1130°	(312)	+ 130°	(300)

EXPERIMENTAL

Hinokione from the heartwood of *Tetraclinis articulata* had m.p. 191—192°, $[\alpha]_D$ + 111.9° (in EtOH), ν_{max}^{CO} 1695 and ν_{max}^{OH} 3440 cm^{-1}. λ_{max} 208 mμ (ε 16 900); 219 (7480), 284 (2440) (in ethanol); 226 mμ (16 900), 242 (7100), 306 (4600) (in 0.1 N NaOEt-EtOH).

Reduction of hinokione. (a) *With potassium borohydride.* A solution of hinokione (575 mg) in methanol (40 ml) was added to a suspension of potassium borohydride (190 mg) in a mixture of methanol (10 ml), water (1 ml) and 2 N sodium hydroxide solution (8 drops). The mixture was left at room temperature for 10 h. On dilution with water (50 ml) and neutralisation with 2 N sulphuric acid crystals of hinokiol separated (yield 530 mg). After three recrystallisations from benzene the melting point was 240—242°, undepressed on admixture with an authentic specimen of hinokiol.

Further addition of water gave a second crop of crystals (5 mg), m.p. 200—209°. This product was slightly impure isohinokiol. However, chromatography on silica gel failed to give a purer product.

(b) *By catalytic hydrogenation.* Hinokione (100 mg) in glacial acetic acid (20 ml) was hydrogenated in the presence of a platinum oxide catalyst (5 mg) for 4.5 h. After filtration and evaporation of the solvent in a vacuum, a solid, m.p. 205—230°, was obtained. On cooling a hot benzene solution of this product a first crop of crystals was obtained

which, after recrystallisation from benzene, gave pure hinokiol (22 mg). From the mother liquor crude isohinokiol was obtained, which after three crystallisations from benzene melted at 206–209°. (Lit.[1a] 204°.) Yield 50 mg. (ν_{max} 1003, 3240 and 3510 cm^{-1}.)

Clemmensen reduction of hinokione. A mixture of hinokione (320 mg), amalgamated zinc, acetic acid (10 ml) and concentrated hydrochloric acid (3 ml) was refluxed for 5 h, 0.5 ml concentrated hydrochloric acid being added after each hour. The product was dissolved in benzene and purified by filtration through a column of silica gel. The resinous product (270 mg) was acetylated, yielding a resin which on sublimation followed by recrystallisation afforded ferruginol acetate, m.p. 82–84°, $[\alpha]_D$ + 55.1° ($CHCl_3$) identified by direct comparison with an authentic sample.

2,2-Dibromohinokione acetate. A solution of bromine (600 mg) in acetic acid (7 ml) was added drop by drop over 2 h to a cooled solution of hinokione acetate (400 mg) in acetic acid (20 ml containing 2 drops of acetic acid saturated with hydrogen bromide). After 30 min the mixture was poured into water and excess bromine destroyed with sodium thiosulphate. The product (590 mg, m.p. 174–179°) was recrystallised from methanol. Repeated recrystallisations did not change the melting point. (Found: C 54.4; H 6.0; Br 33.8. $C_{22}H_{26}Br_2O_3$ requires: C 52.8; H 5.6; Br 31.95.) ν_{max} 1724 and 1765 cm^{-1}. ν_{max} 208 mμ (ε 3000), 268 (1220), 277 (1230), 313 (97).

Dehydrobromination of 2,2-dibromohinokione acetate. The substance (550 mg), lithium carbonate (1 g) and lithium bromide (1 g) in dimethylformamide (20 ml, redistilled) was heated on the steam bath with stirring under dry nitrogen for 16 h. The solution was poured into 100 ml of cold water, giving a white precipitate. ν_{max} 1210, 1691 and 1762 cm^{-1}. A mixture of this material (460 mg), zinc dust activated with acetic acid (500 mg), and methanol (60 ml) was refluxed for 20 h. The filtrate was evaporated and the residue extracted with cyclohexane. On evaporation a solid (360 mg) was obtained. It was dissolved in benzene and chromatographed on silica gel (30 g), with benzene-ether (19:1) as eluent. On evaporation a solid (180 mg) was obtained which was recrystallised twice from benzene-cyclohexane and sublimed to give 2-bromo-1,2-didehydro-hinokione, m.p. 208–210°, $[\alpha]_D$ + 142° (EtOH). ν_{max} 1668 and 3460 cm^{-1}. λ_{max} 206 mμ (ε 32 300), 258 (11 100) and 283 (5600). (Found: C 64.0; H 6.9. $C_{20}H_{25}O_2Br$ requires: C 63.7; H 6.7.) With Brady's reagent an oil was obtained.

The column was now washed with benzene-ether, giving white crystals (166 mg). These were recrystallised once from benzene and twice from cyclohexane, yielding pure 1,2-didehydro-hinokione, m.p. 175–178°, $[\alpha]_D$ + 163° (EtOH). ν_{max} 1655 and 3280 cm^{-1}. λ_{max} 205 mμ (ε 23 600), 225 (18 900), 284 (3800). (Found: C 80.2; H 8.9; $C_{20}H_{26}O_6$ requires: C 80.5, H 8.8.)

2-Bromo-1,2-didehydro-hinokione was refluxed with zinc and methanol as above for 24 h. A quantitative yield of 1,2-didehydro-hinokione was obtained.

Hydrogenation of 2-bromo-1,2-didehydro-hinokione and of 1,2-didehydro-hinokione. 2-Bromo-1,2-didehydro-hinokione (10 mg) and palladium on charcoal (1 mg) in ethanol was shaken under hydrogen for 24 h. Hinokione (5 mg) was obtained. In the same manner 1,2-didehydro-hinokione also furnished hinokione.

Hinokiol monoacetate. (a) *From hinokiol.* A suspension of hinokiol (1 g) in a mixture of dry benzene (400 ml), acetic anhydride (7 ml) and pyridine (30 drops) was shaken at room temperature for 40 h. The solution obtained was shaken successively with dilute solutions of sodium carbonate, sulphuric acid and finally with water and evaporated. The solid residue was dissolved in benzene and chromatographed on silica gel (50 g). Benzene containing 0–2 % ether eluted a small amount of hinokiol diacetate. With 4 % ether the monoacetate (470 mg) was obtained. It was recrystallised from ether and sublimed, giving pure hinokiol monoacetate (2 *f*), m.p. 186–189°, $[\alpha]_D$ + 59.9° (in EtOH). ν_{max} 1025, 1220, 1730 and 3460 cm^{-1}. (Found: C 76.3; H 9.25. $C_{22}H_{32}O_3$ requires: C 76.7; H 9.4.) Pure ether, finally, eluted hinokiol (190 mg).

(b) *From hinokione acetate.* Hinokione acetate (30 mg) was dissolved in methanol (5 ml), water (2 drops) was added and the solution added to a suspension of potassium borohydride (25 mg) in methanol (2 ml) at room temperature. After 40 min, water (1 ml) and several drops of 2 N sulphuric acid were added with cooling in ice. Further addition of water (7 ml) precipitated a solid (23 mg) which when chromatographed as above furnished 11 mg hinokiol monoacetate (*2f*) and 8 mg of hinokiol.

Action of phosphorus pentachloride etc. on hinokiol monoacetate. A solution of hinokiol monoacetate (155 mg) in light petroleum (150 ml) was evaporated to 120 ml and cooled

in an ice bath to give a fine suspension. Phosphorus pentachloride (420 mg) was added with vigorous shaking. The mixture was kept in an ice box for one hour and then for 3 h at room temperature with occasional shaking. It was then washed successively with 5 % sodium carbonate solution and water. The organic phase was dried and evaporated. The residue was acetylated with acetic anhydride and pyridine. The product was chromatographed on a column of neutral alumina (5 g). Elution with benzene gave a resin (104 mg), $\nu_{max}^{CCl_4}$ 1205 and 1755 cm^{-1}.

A mixture of the above resin (70 mg), osmium tetroxide (100 mg), pyridine (1.5 ml) and dry ether (15 ml) was left in a dark place for 8 days. After removal of the solvents the residue was treated with potassium borohydride (250 mg) in methanol (10 ml) for 10 h. Dilution of the reaction mixture with water, neutralisation with 2 N sulphuric acid and extraction with ether gave a dark coloured extract which was dried and filtered through a silica column to give a purple solid (45 mg) from 250 ml of ether eluent. This solid was acetylated with acetic anhydride and pyridine at room temperature for 10 h, giving 45 mg of a glassy material exhibiting strong absorption at 1210, 1750 and 3400 (broad) cm^{-1}.

The product was treated with lead tetra-acetate (200 mg) in redistilled acetic acid (2 ml) for 12 h. The reaction mixture was warmed to effect solution. The acetone formed was collected by distillation and identified as the 2,4-dinitrophenylhydrazone. (Yield 17 mg).

The residue from the distillation was extracted with ether giving a non-crystalline solid which was acetylated with pyridine and acetic anhydride. The product was chromatographed on neutral alumina using benzene as eluent to give a non-crystalline solid. $\nu_{max}^{CCl_4}$ 1210, 1740 and 1755 cm^{-1} as expected for a compound of structure *8*. The solid gave a red colour and then an oily precipitate with Brady's reagent and on sublimation gave ill-defined crystals, m.p. 104—112°.

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