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The Chemistry of the Natural Order Cupressales

45 *. The Structure and Configuration of Totarol and Totarolone **

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Totarolone, a constituent of the heartwood of *Tetraclinis articulata* has been reduced to the alcohol totaradiol and to totarol. The alcoholic hydroxyl group of the former compound is situated at C_3. Totarol has been degraded to the dicarboxylic acid (*10*) also obtained from dehydroabietic acid. The structure and absolute configuration of totarolone are therefore represented by formula (*1a*).

A totarol analogue of xanthoperol and some similar compounds have been prepared from totarol.

Totarolone, recently isolated from the heartwood of *Tetraclinis articulata* [1] gives totarol (*2a*) on Clemmensen reduction. Since the structure of totarol is known [2] this proves the nature of the carbon skeleton of totarolone.

Reduction of totarolone with potassium borohydride gives totaradiol *3a*. The molecular rotation shift between totaradiol (*3a*) and its diacetate (*3b*), $[M]_D + 43°$, is very similar to that between hinokiol (*7a*) and its diacetate (*7b*), $[M]_D + 47°$, suggesting that the environments of the asymmetric centres are similar in both series. The carbonyl function of totarolone and the secondary hydroxyl group of totaradiol, therefore, should be at C_3 in analogy with hinokione and hinokiol [3].

Reduction of totarolone benzyl ether (*1c*) with lithium aluminium hydride gave mainly totaradiol benzyl ether (*3c*) also obtained by direct benzylation of totaradiol (*3a*). The infrared absorption of the monobenzyl ether (ν_{max} 1030 cm^{-1}) indicated that the hydroxyl group was equatorial. When heated with phosphorus pentachloride the benzyl ether gave a resin which exhibited a weak band at 1670 cm^{-1} indicating that the usual retropinacol rearrangement had occurred with formation of compound *4*. The resin was therefore successively treated with osmium tetroxide and lead tetraacetate. Acetone was formed together with the A-trisnorcyclopentanone derivative *5* which contained *cis*-fused A/B-rings as the result of inversion at C_5 (*cf.* Ref.[4]). The ketone *5* exhibited the expected absorption at 1260 and 1740 cm^{-1}.

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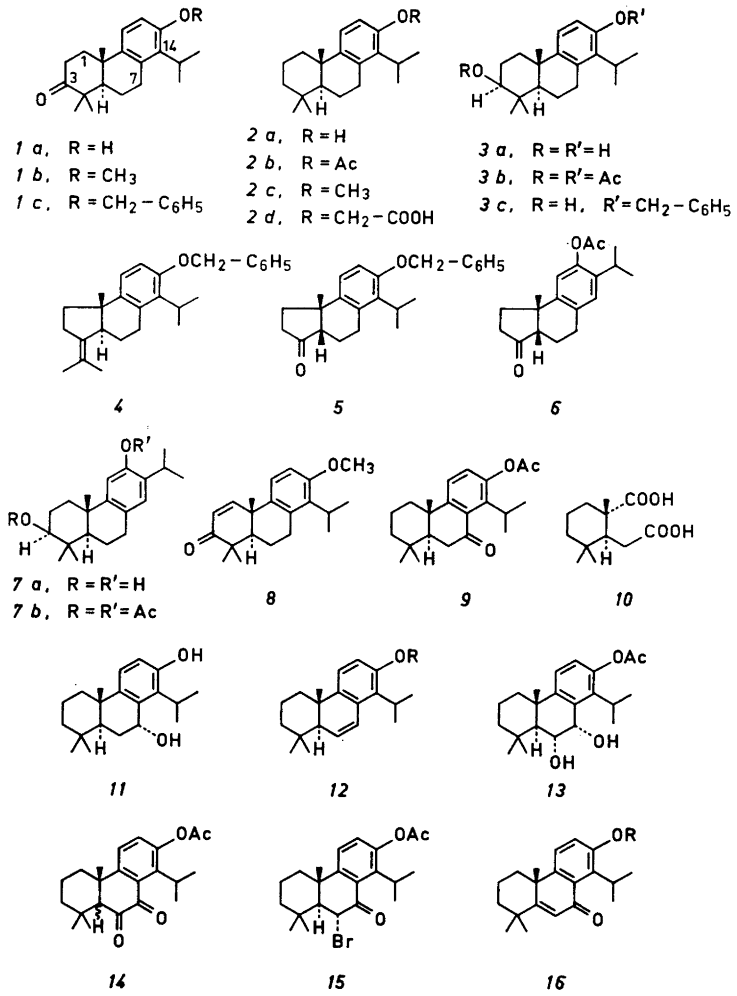

Similar to the crystalline, semipure compound *6* from hinokiol [3], the cyclopentanone *5* showed a positive Cotton effect resembling that of the A/B *cis*-fused 3-keto-A-norcholanic acid [4]. The rotation below 290 mμ was masked by the strong absorption of the aromatic ring.

The rotatory dispersion curves of totarolone and hinokione were very similar showing a positive Cotton effect similar to that of lanost-8-en-3-one [5].

The structure and absolute configuration of totarolone must therefore be represented by *1a*. The α,β-unsaturated totarolenone [1] which accompanies totarolone in *Tetraclinis articulata* and which is hydrogenated to totarolone must consequently have structure *8* (OH instead of OCH_3).

During attempts to relate totarol to dehydroabietic acid totarol acetate (*2b*) was oxidised to 7-ketototarol acetate (*9*) [1]. Attempts to cleave this com-

pound between the carbonyl group and the aromatic ring with hydrazoic acid in trichloroacetic acid failed, the starting material being recovered unchanged. This is obviously due to steric hindrance from the isopropyl group since 7-ketodehydroabietic acid is cleaved under these conditions [7].

On oxidation with trifluoroperacetic acid, however, 7-ketototarol acetate gave an acid product in about 25 % yield. It could not be obtained crystalline but the infrared absorption of the crude product showed, in addition to the hydroxyl peaks in the 3000 cm^{-1} region, a sharp peak at 1730 cm^{-1} attributable to a nonconjugated carboxyl group. The crude acid was therefore ozonised followed by oxidation with alkaline hydrogen peroxide. A complex mixture of acids resulted from which, with considerable difficulty, a small amount of the dicarboxylic acid *10* was isolated. It was identified by mixed melting point with an authentic specimen [7] and by comparison of infrared spectra. This confirms that totarol has the usual steroid configuration (5α,10β).

The phenolic hydroxyl group of ferruginol is said to be resistent to methylation [8]. However, totarolone could be methylated with methyl iodide and potassium carbonate in acetone.

Reduction of the methyl ether (*2c*) as well as the phenoxy acetic acid (*2d*) with lithium-ammonia failed. (An analogous compound without the isopropyl group has been successfully reduced by this method [2].) Attempts to oxidise totarol with potassium nitrosodisulphonate [9] to an orthoquinone suitable for further degradations were also unsuccessful.

Since Δ^6-dehydroferruginol and xanthoperol are found in Nature [10], it was of some interest to prepare similar compounds of the totarol type.

Lithium aluminium hydride reduction of 7-ketototarol acetate gave a mixture of epimeric 7-hydroxytotarols from which the main component (m.p. 215—217.5°) was isolated. This compound must be 7α-hydroxytotarol (*11*) for the following reasons: (1) inspection of molecular models shows that the quasi-equatorial hydroxyl group is more hindered than the quasi-axial due to the presence of the isopropyl group in position C_{14} and (2) because the compound is smoothly dehydrated by oxalic acid in dry toluene to Δ^6-totarol (*12*, R = H). This compound was easily hydrogenated to totarol.

Osmylation of Δ^6-dehydrototarol acetate and subsequent hydrolysis of the osmate with hydrogen sulphide gave a mixture of two diol acetates, from which the main component was isolated in a pure state. Osmium tetroxide will attack the ethylenic linkage from the less hindered α-side and the predominant product should therefore be 6α,7α-dihydroxytotarol acetate (*13*). Mild oxidation of the mixture of the diol acetates with chromium trioxide and sulphuric acid in acetone gave yellow 6,7-diketototarol acetate (*14*). In spite of repeated recrystallisations the product melted over a wide range as does xanthoperol [10] and other related compounds [11].

Bromination of 7-ketototarol acetate (*9*) readily gave a monobromo derivative which, according to the I.R. absorption [12], should be the expected 6α-bromo-7-ketototarol acetate (*15*). Treatment with lithium bromide-lithium carbonate in dry dimethylformamide gave Δ^5-dehydro-7-ketototarol acetate (*16*, R = Ac) in excellent yield. Mild alkaline hydrolysis of this compound gave Δ^5-dehydro-7-ketototarol (*16*, R = H).

EXPERIMENTAL

Clemmensen reduction of totarolone(1a). A mixture of totarolone (230 mg), amalgamated zinc filings (1.5 g) acetic acid (10 ml) and conc. hydrochloric acid (4 ml) was refluxed for 2 h. Amalgamated zinc filings (500 mg) and conc. hydrochloric acid (2 ml) were added and heating continued for 5 h. The hot solution was decanted and on cooling white crystals (150 mg) were obtained, m.p. 120–125°. Recrystallisation from light petroleum gave a crystalline product, m.p. 125–128° (mixed m.p. with authentic totarol 127–128°), $[\alpha]_D$ + 42.5° (in EtOH). The I.R. spectrum was identical with that of totarol.

Totaradiol(3a). A mixture of totarolone (120 mg), 2 N sodium hydroxide solution (5 drops), potassium borohydride (120 mg) and methanol (30 ml) was allowed to stand for 2 h. Water (40 ml) was added and the mixture acidified. Further addition of water (60 ml) gave a crystalline product which was recrystallised from benzene, m.p. 100–102°; resolidifying at 105° (crystal solvent?). It gradually remelted between 169–178°; resolidified at 179° and was completely molten at 183°, $[\alpha]_D$ + 40° (EtOH), ν_{max} 1002, 1180, 1280, 1585, 3380, 3610 cm^{-1}. (Found: C 80.0; H 9.9. Calc. for $C_{20}H_{30}O_2$: C 79.4; H 10.0).

Recrystallisation from carbon tetrachloride gave crystals, m.p. 170–173°, which on sublimation *in vacuo* gave a sample, m.p. 180.5–181.5°.

Totaradiol diacetate (3b) (pyridine-acetic anhydride) gave colourless crystals, m.p. 119–121.5°, from light petroleum. $[\alpha]_D$ + 41° (EtOH), ν_{max} at 1202, 1248, 1725, 1765 cm^{-1}. (Found: C 74.6; H 8.7. Calc. for $C_{24}H_{34}O_4$: C 74.6; H 8.9).

Totaradiol monobenzyl ether (3c). A solution of totarolone benzyl ether (380 mg) in ether (100 ml) was added to a suspension of lithium aluminium hydride (250 mg) in ether (100 ml). The mixture was heated under reflux for 3 h. The excess hydride was destroyed and 0.5 N sulphuric acid added. Extraction with ether gave colourless crystals (400 mg), m.p. 189–193°. The product was crystallised three times from methanol and then sublimed, m.p. 192–193°, $[\alpha]_D$ + 33° (EtOH); ν_{max} 1030, 1264, 1500, 1582, 1590 and 3420 cm^{-1}; λ_{max} 210 mμ (ε 33 880), 277 (1640), 285 (1630). (Found: C 82.3; H 9.1. Calc. for $C_{27}H_{36}O_2$: C 82.6; H 9.2).

Totaradiol (130 mg), anhydrous potassium carbonate (130 mg), and redistilled benzyl bromide (850 mg) in acetone (60 ml) were refluxed for two days. The reaction mixture was diluted with water and the products were extracted with ether. Recrystallisation of the residue from the ether solution with methanol gave totaradiol monobenzyl ether, m.p. 192–193°.

The *acetate* (pyridine-acetic anhydride) formed colourless crystals, m.p. 212–215°, $[\alpha]_D$ + 39° ($CHCl_3$). (Found: C 80.2; H 8.8. Calc. for $C_{29}H_{38}O_3$: 80.1; H 8.8).

Retropinacole rearrangement of totaradiol monobenzyl ether. To a solution of totaradiol monobenzyl ether (200 mg) in light petroleum (200 ml), phosphorus pentachloride (1 g) was added with shaking. The mixture was set aside at room temperature for 18 h with occasional shaking. The solution was then treated with 10 % sodium hydroxide solution and finally with water. The residue from the organic phase was adsorbed on a column of basic alumina (20 g). Light petroleum eluted a colourless resin (140 mg) exhibiting no hydroxyl absorption in the infrared.

This resin, and osmium tetroxide (140 mg), were dissolved in a mixture of ether (20 ml) and pyridine (2 ml). After 3 days the solvents were evaporated *in vacuo* and the residue heated with a solution of sodium sulphite (900 mg) in ethanol (30 ml) and water (15 ml) for a few seconds. The reaction product was extracted with ether. The residue (ν_{max} 3610, 3650 cm^{-1}) was dissolved in acetic acid (10 ml) and lead tetraacetate (400 mg) added. After 12 h water (7 ml) was added. The mixture was heated and the first ml of distillate was collected. Addition of Brady's reagent gave acetone 2,4-dinitro-phenylhydrazone, m.p. and mixed m.p. 128–130°. Yield 50 mg (68 %).

The residual liquid was diluted with water and extracted with ether. The ether solution was then evaporated and the residue chromatographed on silica (15 g). Light petroleum-benzene (1:1, 150 ml) eluted 58 mg of a resin which was distilled in a high vacuum. On trituration with light petroleum a small amount of a crystalline product, m.p. 135–141°, was obtained. ($\nu_{max}^{CCl_4}$: 1260 and 1740 cm^{-1}). The crude material was treated with Brady's reagent giving a yellow product which would not crystallise: λ_{max} 363 mμ (ε 20 200).

Degradation of 7-ketototarol acetate (9). A methylene chloride solution (20 ml) of trifluoroacetic anhydride (4 ml) was added to an ice cooled agitated mixture of 80 % hydrogen peroxide (1 ml) in methylene chloride (10 ml). This peracid solution was slowly (one hour) added to a stirred suspension of 7-ketototarol acetate (3 g) and anhydrous disodium hydrogen phosphate (6.5 g) in methylene chloride. The reaction mixture was stirred for 16 h, heated under reflux for 3 h, then poured into water. The organic layer was washed with 10 % sodium carbonate solution and gave unreacted starting material. From the aqueous layer 810 mg of a solid, acid product was obtained which showed the typical absorption of a carboxylic acid in the 3000 cm^{-1} region and a strong band at 1730 cm^{-1}.

The solid was dissolved in 45 ml of methylene chloride and ozonised for 2.5 h at −20°. The residue from the evaporation of the solvent was oxidised with 30 % hydrogen peroxide (20 ml) in methanol (25 ml) and 2 N sodium hydroxide (15 ml). The acid fraction obtained was chromatographed on silica gel (25 g) using benzene followed by ether as eluents. The fraction eluted with 160 ml of ether gave crystals (30 mg), m.p. 120—158°. Two recrystallisations from methanol-water and one from acetone-cyclohexane gave *trans*-1,3,3-trimethyl-1-carboxycyclohexyl-2-acetic acid (*10*), m.p. and mixed m.p. with an authentic sample 164—168°. $[\alpha]_D$ −4.5° (EtOH). The IR-spectra of the two specimens were superimposable.

The cyclohexylamine salt of the acid was recrystallised from isopropyl alcohol, m.p. 180—183°.

Totarolone methyl ether (1b). A mixture of totarolone (120 mg), anhydrous potassium carbonate (125 mg) and methyl iodide (2 ml) in acetone (15 ml) was heated under reflux for two days. The reaction product was triturated with hot light petroleum (30 ml). The undissolved material was totarolone. The filtrate was evaporated and the residue dissolved in ethanol (3 ml). On cooling the methyl ether crystallised. It was recrystallised from ethanol and sublimed, m.p. 88—100°, $[\alpha]_D$ + 99° (EtOH); ν_{max} 1260, 1705 cm^{-1}. (Found: C 78.8; H 9.3. Calc. for $C_{21}H_{30}O_2$: C 80.2; H 9.6).

Totarol glycolic acid ether (2d). The potassium salt of totarol was prepared by heating and stirring a mixture of totarol (5.16 g) and potassium (850 mg) in benzene (150 ml). To the resulting suspension, a solution of ethyl bromoacetate (3.64 g) in dry benzene was added slowly (mechanical stirring, reflux). At the end of the addition a clear solution was obtained. Heating was continued for another hour. The reaction mixture was shaken with water and the neutral and acidic products isolated. From the acid fraction totarol glycolic acid ether (440 mg) was isolated and gave colourless crystals from methanol-water, m.p. 193—196°, $[\alpha]_D$ + 42.3° (EtOH).

From the neutral fraction the ethyl ester was obtained, (m.p. 73—76°) which on alkaline hydrolysis gave the above acid, m.p. 194—196°. (Found: C 76.4; H 9.6. Calc. for $C_{22}H_{32}O_3$: C 76.7; H 9.4).

7α-Hydroxytotarol (11). A solution of 7-ketototarol acetate (200 mg) in ether (35 ml) was added dropwise to a suspension of lithium aluminium hydride (112 mg) in ether (107 ml). The mixture was heated under reflux for 30 min. The reaction product was isolated in the usual manner and crystallised from benzene, m.p. 215—217.5°, $[\alpha]_D$ + 21.6° ($CHCl_3$), + 30.6° (EtOH); ν_{max} 990, 1275, 1590, 3350 and 3600 cm^{-1}. (Found: C 79.4; H 9.8. Calc. for $C_{20}H_{30}O_2$: C 79.4; H 10.0).

Δ^6-Dehydrototarol acetate (*12*, R = Ac), 7-Hydroxytotarol (3.2 g) and anhydrous oxalic acid (6 g) in dry toluene (100 ml) was distilled with recycling of the toluene for 4 h. The trapped water was removed from time to time. The toluene layer was washed with 2 N sodium hydroxide and water and the toluene removed by distillation. The residue was chromatographed on silica (100 g). Benzene-light petroleum (1:1) eluted an oil (3 g) which did not crystallise. (ν_{max} 690, 1270 cm^{-1}). On hydrogenation with Pd/C in ethanol totarol was obtained.

The oil was acetylated with acetic anhydride and pyridine and the product was crystallised once from light petroleum and twice from ethanol and then sublimed, m.p. 138—140°, $[\alpha]_D$ −114.4° ($CHCl_3$). λ_{max} 267 mμ (ε 9270), 228 shoulder (21 000), 222 (25 900) and 217 shoulder (22 600); ν_{max} 685, 1760 cm^{-1}. (Found: C 80.4; H 9.1. Calc. for $C_{22}H_{30}O_2$: C 80.9; H 9.3.)

6α,7α-Dihydroxytotarol acetate (13). A mixture of the above acetate (590 mg), osmium tetroxide (500 mg), ether (20 ml) and pyridine (1 ml) was kept in a dark place for three days. The solvents were evaporated and the residue dissolved in benzene. This solution

was saturated with hydrogen sulphide and the precipitate obtained was removed by filtration. The benzene solution was washed with water and the solvent evaporated. The residue (510 mg) was recrystallised from benzene-light petroleum giving colourless crystals, (340 mg), m.p. 220–222°, $[\alpha]_D$ + 47.7° (EtOH); ν_{max} 1185, 1760, 3370 (broad) and 3480 cm^{-1}. (Found: C 72.9; H 8.8. Calc. for $C_{32}H_{32}O_4$: C 73.3; H 8.9.)

6,7-Diketototarol acetate (14). To a cold solution of 6,7-dihydroxytotarol acetate (200 mg) in acetone (15 ml) a solution of chromium trioxide (112 mg) in 1 N sulphuric acid (3 ml) was added slowly, with shaking. After 30 min at room temperature the solution was diluted with water and extracted with ether. The yellow solution gave a product (107 mg) which was chromatographed on silica (10 g). The product eluted with ether: benzene (3:97) gave yellow crystals which were recrystallised several times from cyclohexane, m.p. 185–204°; ν_{max} 850, 1585, 1683, 1733, 1762, 3540, 3360 cm^{-1}; λ_{max} 325 mμ (3000), 285 (4950), 208 (14 500).

The compound gave a deep yellow colour reaction with aqueous ferric chloride. (Found: C 72.0; H 7.6. Calc. for $C_{32}H_{38}O_4$, 0.5 H_2O: C 72.3; H 8.00).

6α-Bromo-7-ketototarol acetate (15). To a solution of 7-ketototarol acetate (2.3 g) in acetic acid (75 ml) and one drop of hydrobromic acid, bromine (0.12 g) in acetic acid (12 ml) was added dropwise at room temperature. Decolourisation was instantaneous. An excess of 1 ml was added and after one minute a further addition of water and sodium bisulphite. The precipitate was crystallised from methanol three times to give slightly yellowish needles, m.p. 176–178°, $[\alpha]_D$ −53.1° (EtOH); ν_{max} 1205, 1690 and 1763 cm^{-1}; λ_{max} 208 mμ (ε 13 400), 257 (4860), 293 (1800). (Found: C 62.3; H 6.9; Br 19.6. Calc. for $C_{32}H_{39}O_3Br$: C 62.7; H 6.9; Br 19.0).

Δ^5-Dehydro-7-ketototarol acetate (*16*, R = Ac). A mixture of 6α-bromo-7-ketototarol acetate (550 mg), freshly fused lithium bromide (1.1 g), dry lithium carbonate (250 mg) and dry dimethylformamide (20 ml) was heated to 100° for 40 h with stirring. The reaction mixture was then poured into ice-water. The precipitate was collected and recrystallised from light petroleum, m.p. 163–165°, $[\alpha]_D$ −20.6° (EtOH); ν_{max} 1195, 1595, 1624, 1655 and 1764 cm^{-1}; λ_{max} 259 mμ (ε 12 300), 270 (11 900), 310 shoulder (2600). (Found: C 77.6; H 8.1. Calc. for $C_{32}H_{38}O_3$: C 77.6; H 8.3.)

Δ^5-Dehydro-7-ketototarol (*16*, R = H). Δ^5-Dehydro-7-ketototarol acetate was hydrolysed with sodium hydroxide in methanol. Addition of water gave a precipitate which crystallised from benzene. Pale-yellow crystals, m.p. 243–245°, $[\alpha]_D$ −39.3° (EtOH); ν_{max} 1290, 1607, 1630 and 3300 cm^{-1}; λ_{max} 207 mμ (ε 14 300), 227 (14 300), 249 (10 200), 278 (9600) and 340 (2500).

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