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THE STRUCTURE OF EURYOPSONOL

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Abstract—Euryopsonol, isolated from the resin of *Euryops floribundus*, has been shown to be 3α-hydroxy-9-oxofuranoeremophilane.

THE isolation of euryopsonol, $C_{15}H_{20}O_{31}$ m.p. 230–231°, from the unsaponifiable fraction of the resin of *Euryops floribundus* (Compositae) has been described,[1] and euryopsonol was shown to be doubly unsaturated, to contain a ketonic and an alcoholic group but the nature of the third oxygen atom remained unknown. Later supplies of plant failed to give more material and work was discontinued. The investigation has been renewed and evidence for the complete stereochemical structure of euryopsonol is now presented.

A closely related compound euryopsol, $C_{15}H_{22}O_4$, m.p. 173–174°, has been found to accompany europsonol. The content of europsonol is highest in the plant during midsummer and that of euryopsol during the autumn. They are readily separated by chromatography on alumina.

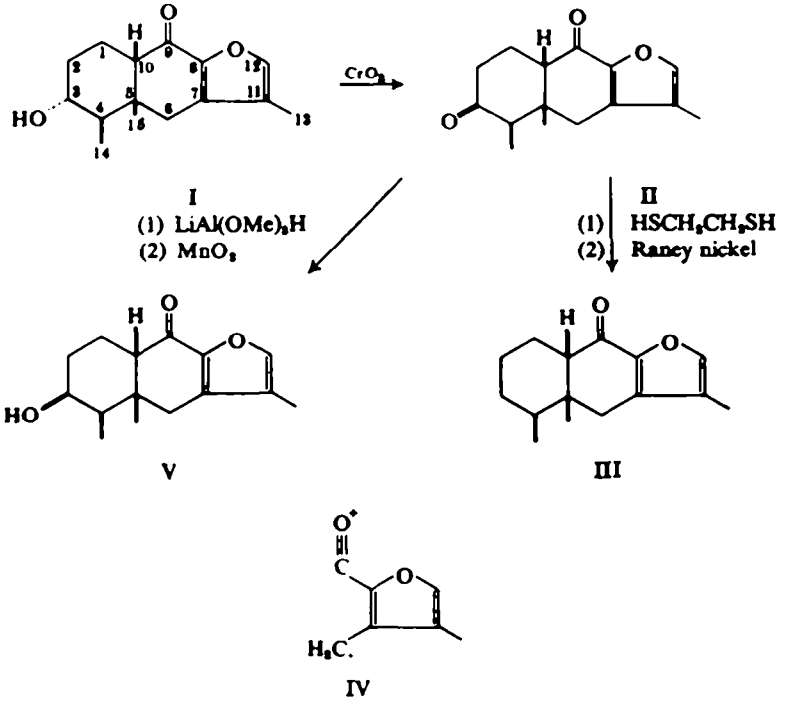
Of the three oxygen atoms in euryopsonol one could be attributed to an OH group (ν_{max} 3640 cm^{-1}) and one to a conjugated ketone (ν_{max} 1670 cm^{-1} and λ_{max} 280 mμ (log ε 4·16)). The third was probably present as a furan (ν_{max} 1540, 1130, 1080 and 880 cm^{-1}) even though euryopsonol gave no colour with Ehrlich's reagent (*p*-dimethylaminobenzaldehyde in HCl). This assignment is supported by its NMR spectrum; a Me signal on a furan ring at 7·98 τ (J = 1·2 c/s) and one proton on a furan ring at 2·57 τ (J = 1·1 c/s).

On catalytic hydrogenation in ethanol over Pd–C, euryopsonol consumed two moles of hydrogen to give an oily product, while with Adam's catalyst in ethanol or acetic acid hydrogenolysis occurred. Dehydrogenation of the LAH reduction product of euryopsonol gave a small amount of an undefined substituted naphthalene.

Oxidation with chromic acid in acetone afforded dehydroeuryopsonol (II) whose IR spectrum showed maxima at 1670 cm^{-1} (conjugated ketone), 1540 and 870 cm^{-1} (furan ring) and a new band at 1720 cm^{-1} (6-membered ketone). Since the UV absorption band at 280 mμ in euryopsonol was unchanged on oxidation to II the new keto group in dehydroeuryopsonol cannot be at C_6.

Dehydroeuryopsonol gave a positive Zimmermann test (negative with euryopsonol) and formed a monofurfurylidene derivative, indicating that an unhindered methylene group is adjacent to the newly formed keto group. Dehydroeuryopsonol formed a monooxime and a monothioketal. The thioketal showed only the band at 1670 cm^{-1} due to the conjugated keto group; the band at 1720 cm^{-1} in II had disappeared showing that it was the newly formed ketone which had reacted. Desulphurization of the thioketal afforded deoxydehydroeuryopsonol (III), kindly shown by

[1] D. H. S. Horn, J. R. Nunn and D. E. A. Rivett, *J. S. African Chem. Inst.* 7, 22 (1954).



Prof. Herout to possess an IR spectrum identical with that of 9-oxofuranoeremophilane.[2,3] Presumably they isolated the racemate from *Petasites* species since their material was optically inactive, whereas that obtained from euryopsonol had $[\alpha]_D$ −20°. The identity of III proves that the conjugated keto group in euryopsonol is at C-9; the UV spectrum euryopsonol had already suggested this position since 9-oxofuranoeremophilanes show λ_{max} 280–282 mμ and 6-oxofuranoeremophilanes λ_{max} 269 mμ.[4] The base peak, m/e = 122, in the mass spectrum of euryopsonol due to the carbonyl fragment IV supports the assignment of the CO group at C-9. Dehydroeuryopsonol is not a β-diketone because its UV spectrum is unchanged on addition of alkali and it gives no colour in ethanolic ferric chloride solution. Accordingly the other keto group cannot be at C-1. Since dehydroeuryolsonol, m.p. 217–218°, is clearly different from 2,9-dioxofuranoeremophilane,[4] m.p. 149°, the new keto group cannot be at C-2 and only C-3 remains.

Stereochemistry of the hydroxyl group

Brown and Deck[5] have recently shown that lithium trimethoxyaluminohydride is an excellent reagent for the stereospecific reduction of cyclic ketones to the less stable alcohol. When dehydroeuryopsonol was reduced in this way and the 9-OH group in the crude product oxidized to a ketone with manganese dioxide in refluxing benzene, epieuryopsonol (V), m.p. 216–217°, was obtained; no euryopsonol was formed. The

[2] L. Novotný, V. Herout and F. Sǒrm, *Tetrahedron Letters* 697 (1961).
[3] L. Novotný, J. Jizba, V. Herout and F. Sǒrm, *Coll. Czech. Chem. Comm.* **27**, 1393 (1962).
[4] L. Novotný, Ch. Tabačíkorá-Wlotzka, V. Herout and F. Sǒrm, *Coll. Czech. Chem. Comm.* **29**, 1922 (1964).
[5] H. C. Brown and H. R. Deck, *J. Am. Chem. Soc.* **87**, 5620 (1965).

absolute configuration of furanoeremophilane is known.[6] Euryopsonol is 3α-(equatorial) hydroxy-9-oxofuranoeremophilane (I) and epieuryopsonol is 3β-(axial) hydroxy-9-oxofuranoeremophilane (V) from the following evidence:

(1) From its method of formation from dehydroeuryopsonol the hydrogen atom at C-3 in epieuryopsonol would be expected to be sterically less hindered than that in euryopsonol.

(2) Epieuryopsonol is recovered unchanged under the mild conditions (pyridine and acetic anhydride at room temp) used to prepare euryopsonol acetate. This is due to steric interaction between the OH group and the 15-Me group.

(3) The downfield position of the C-3 proton multiplet of euryopsonol as well as the magnitude of its displacement ($\Delta\tau = -1{\cdot}26$ ppm) on acetylation confirms that the OH group is attached to this carbon atom. Its upfield position (τ 6·50) realtive to that (τ 6·08) of the same proton in epieuryopsonol suggests that these protons are axial and equatorial respectively. In euryopsonol and its acetate this methine proton is responsible for the triplet (J = 10·8 c/s) broadened by secondary splitting (J = 4·8 c/s) into a sextet. Assuming a chair configuration of the cyclohexane ring[6] these triplets are due to two large diaxial and a smaller axial-equatorial vicinal coupling, similar to that observed in androst-4-en-11α-ol-3,20-dione,[7] indicating that the 14-Me group is in the equatorial position.[6] In the other possible chair conformation the 14-Me group is axial. If it is assumed that vicinal coupling constants have the same sign, the Karplus relationship predicts that the couplings of the 3-axial proton of euryopsonol will be significantly larger than the relatively small di-equatorial and two axial-equatorial couplings of the 3-equatorial proton of epieuryopsonol. The observed widths of the 3-proton signal in euryopsonol (25 c/s) and epieuryopsonol (6·0 c/s) are consistent with these considerations.

The downfield shift ($\Delta\tau = -0{\cdot}19$–$0{\cdot}25$) of the 15-Me group in epieuryopsonol relative to that in euryopsonol (τ 9·18) and dehydroeuryopsonol (τ 9·24) shows that there is 1,3-diaxial interaction between the OH group and the 15-Me group in epieuryopsonol, confirming that these compounds exist in the "steriod-like" conformation.[6,8]

The methylene protons at C-6 in I, II and V are magnetically non-equivalent and give rise to a quartet with the anticipated coupling constants (J = 15·0–16·0).

The NMR spectra of some of the furano-compounds obtained are summarized in Table 1.

The acid fraction from the saponfication of the resin has been shown[1] to contain anisic, isobutyric, angelic and tiglic acids. In common with related compounds, e.g. furanopetasin,[4] albopetasin,[9] euryopsonol is almost certainly present in the plant as the angelate although we have not yet succeeded in isolating the ester from the unsaponified resin.

Two further sesquiterpenoids containing the furanoeremophilane skeleton, furanoligularenone[10] from the roots of *Ligularia* species (Compositae) and warburgin[11]

[6] L. Novotný, J. Jizba, V. Herout, F. Sörm, L. H. Zalkow, S. Hu and C. Djerassi, *Tetrahedron* **19**, 1101 (1963).

[7] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* p. 82. Holden-Day, San Francisco (1964).

[8] H. Ishii, T. Tozyo and H. Minato, *Tetrahedron* **21**, 2605 (1965).

[9] L. Novotný, V. Herout and F. Sorm, *Coll. Czech. Chem. Comm.* **29**, 2189 (1964).

[10] F. Patil, J. M. Lehn, G. Ourisson, T. Tanahashi and T. Tanahashi, *Bull. Soc. Chim. Fr.* 3085 (1965).

[11] C. J. W. Brooks and G. D. Draffan, *Chem. Comm.* 393 (1966).

TABLE 1. NMR DATA (τ)

	Euryopsonol	Euryopsonol acetate	Epieuryopsonol	Dehydroeuryopsonol
13-Me	7·98(1·2)	7·98d(1·2)	8·01(1·0)	7·98d(1·0)
14-Me	8·88d(6·5)	9·02d(6·5)	8·86d(6·5)	8·94d(6·5)
15-Me	9·18s	9·12s	8·99s	9·24s
3-OH	8·09s		8·20s	
3-OAc		7·91s		
3-H	6·50m	5·24m	6·08m	
6-H_2	7·37q(16·0)	7·35q(16·0)	7·43q(16·0)	7·53q(15·0)
12-H	2·57q(1)	2·57q(1)	2·62q(1)	2·63q(1)

s = singlet, d = doublet, q = quartet, m = multiplet. The coupling constants (c/s) are shown in parentheses.

from the heartwood of *Warburgia ugandensis* (Canellaceae), have recently been described.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined in 95% EtOH, IR spectra and rotations in chf. NMR spectra were recorded on a Varian A-60 NMR spectrophotometer in $CDCl_3$ solns containing TMS as internal reference, and IR spectra on a Beckman IR-8 spectrophotometer. TLC were run on silica gel (Merck's kieselgel G) and the plates sprayed with a 30% soln of chlorosulphonic acid in AcOH and heated if necessary at 100° to bring out the spots. Neutral alumina refers to alumina (Riedel-de Haen) which had been acid-washed, neutralized and activated by heating at 170° for 18 hr.

Isolation of euryopsonol and euryopsol. Euryops fluoribundus. N.E.Br. was collected on the farm "Sondagsrivier Hoek", about 25 miles to the west of Graaff-Reinet, during October 1962 to November 1964. In a typical experiment, undried stems (16·8 kg) collected during December 1963 were steeped in cold acetone (110 l.) for 2 days. The solvent was removed by flash evaporation and the residual aqueous resin extracted with ether (3 l.). The ether soln was washed with water and evaporated. The residual gum (400 g) was refluxed with 25% ethanolic KOH (500 ml) for 6 hr, water (500 ml) added and the EtOH removed under reduced press. The residue was extracted with ether (8 × 400 ml), the ether soln washed with water (5 × 200 ml), dried (Na_2SO_4), and concentrated to 300 ml whereupon a crystalline solid (12·0 g), m.p. 195–210°, separated. From the intensity of its absorption at 280 mμ this material contained about 75% euryopsonol. A soln of the solid (12·0 g) in THF (150 ml) was poured onto a column of neutral alumina (325 g) prepared in ether. Four 300 ml fractions of ether, four 300 ml fractions of 1% EtOH in ether and three 300 ml fractions of 5% EtOH in ether were collected.

Fractions 1–7 (8·0 g) on recrystallization from benzene afforded euryopsonol (5·4 g), m.p. 222–226°. Fractions 8–11 (3·6 g), after recrystallization from EtOH, gave euryopsol (2·0 g), m.p. 173–174°. Analytically pure euryopsonol crystallized from EtOH as large almost colourless prisms, m.p. 230–231°, $[\alpha]_D^{18} -36°$ (*c*, 1·2), λ_{max} 280 mμ (ε 14600), ν_{max} 3640, 1670, 1540, 1130, 1080, 880 cm^{-1}. (Found: C, 72·6; H, 8·1; M (by mass spectrometry), 248. Calc. for $C_{15}H_{20}O_3$: C, 72·55; H, 8·1%; M, 248.)

Analytically pure euryopsol crystallized from EtOH as fine colourless needles, m.p. 173–174°, $[\alpha]_D^{17}$ (in EtOH) +14° (*c*, 1·1), λ_{max} 220 mμ (ε 6800), ν_{max} (KBr) 3400, 3020, 1660, 1560, 1340, 1280, 1125, 1078, 1050, 1038, 1000, 885 cm^{-1}. (Found: C, 67·6; H, 8·3; M (by mass spectrometry), 266. $C_{15}H_{22}O_4$ requires: C, 67·65; H, 8·3%; M, 266.)

Both euryopsonol and euryopsol gave intense wine-red solns changing to green when dissolved in Ac_2O containing a few drops of conc H_2SO_4.

Acetylation of euryopsonol with acetic anhydride-pyridine. A soln of euryopsonol (90 mg) in Ac_2O (4 ml) and pyridine (0·3 ml) was left at room temp for 20 hr. The solvent was removed and the residue crystallized from MeOH to give euryopsonol acetate,[1] m.p. 197–198° (reported 196–198°), λ_{max} 280 mμ (log 4·17), ν_{max} 1735 and 1675 cm^{-1}. Hydrolysis of this acetate with refluxing ethanolic KOH resulted in regeneration of euryopsonol.

Dehydrogenation of euryopsonol. Euryopsonol (2·0 g) was reduced with excess LAH in THF and

the product worked up in the usual way. The resultant oil (1·8 g) was dehydrogenated with 30% Pd–C in a N atm and the mixture chromatographed on alumina in hexane to give finally 9 mg of a trinitrobenzene complex, m.p. 104·5–106°, depressed on admixture with the corresponding complex of eudalene, m.p. 111°. (Found: C, 60·6; H, 4·9; N, 10·5. $C_{20}H_{19}O_6N_3$ requires: C, 60·45; H, 4·8; N, 10·6%.) Decomposition of the complex on alumina afforded a hydrocarbon whose UV spectrum (λ_{max} 228 and 282 mμ (log ε 5·037 and 3·797)) indicated that it was a substituted naphthalene.

Dehydroeuryopsonol (II). To a soln of euryopsonol (1·00 g) in dry, purified acetone (70 ml) at 5–10° was added dropwise with stirring 8N chromic acid (1·6 ml) until an orange-brown tint persisted.[13] The mixture was kept for 5 min, EtOH (2 ml) and water (100 ml) added and the acetone removed under reduced press. After leaving overnight at 5° the *dehydroeuryopsonol* (0·87 g), m.p. 215–217°, was filtered off. Recrystallization from MeOH and sublimation at 150°/10^{-3} mm afforded a pure sample, m.p. 224–225°, $[\alpha]_D^{18}$ −69° (*c*, 1·2), λ_{max} 280 mμ (ε 14,400), ν_{max} 1720, 1670, 1540, 1140, 1090, 870 cm^{-1}. (Found, C, 73·0, H, 7·5. $C_{15}H_{18}O_3$ requires: C, 73·2; H, 7·4%.)

The *mono-oxime*, prepared by refluxing dehydroeuryopsonol with hydroxylamine hydrochloride and AcONa in ethanol for 2 hr, crystallized from aqueous MeOH as fine colourless needles, m.p. 199–200°. (Found: C, 69·0; H, 7·6. $C_{15}H_{19}O_3N$ requires: C, 68·9; H, 7·3%.)

The *furfurylidene derivative* was prepared by keeping a soln of furfural (0·2 ml), 30% aqueous NaOH (0·4 ml), dehydroeuryopsonol (120 mg) and EtOH (15 ml) at room temp for 5 hr, concentrating the soln to 4 ml and leaving overnight at 5°. The yellow crystalline product (111 mg) was recrystallized from EtOH, m.p. 212–214·5°, λ_{max} 326 and 285 mμ (ε 22000 and 18500) due to an α,β,γ,δ-unsaturated ketone and an α,β-unsaturated furfurylidene ketone. (Found: C, 73·6; H, 6·2. $C_{20}H_{20}O_4$ requires: C, 74·0; H, 6·2%.)

The *mono-thioketal* was obtained by keeping a mixture of dehydroeuryopsonol (300 mg), AcOH (8 ml), ethanedithiol (0·5 ml) and BF_3-etherate (0·2 ml) at room temp for 45 hr. The mixture was diluted with water (40 ml), a soln of KOH (13 g) in water (25 ml) carefully added with ice-cooling, and the resulting ppt (300 mg) collected. The time of reaction was varied and the products obtained examined by TLC in AcOEt–benzene (1:1). About 40 hr was required for the reaction to be complete. Recrystallization of the crude product (obtained after reaction for 40 hr, 300 mg) from EtOH gave the *mono-thioketal* (230 mg), m.p. 184–186°. A pure sample was obtained by sublimation at 110°/10^{-3} mm, m.p. 186–187°, ν_{max} 1670 cm^{-1}. (Found: C, 63·5; H, 6·9. $C_{17}H_{22}O_2S_2$ requires: C, 63·3; H, 6·9%.)

Deoxydehydroeuryopsonol. A mixture of the ethylene monothioketal of dehydroeuryopsonol (123 mg) and freshly prepared Raney Ni (2 g) in MeOH–acetone (1:1, 18 ml) was refluxed for 9 hr, filtered and evaporated. The crystalline residue (87 mg) was chromatographed over neutral alumina (5 g) with elution by benzene–hexane (1:1) to afford a product (41 mg), which showed one spot, R_f 0·70, on TLC in benzene–AcOEt (3:2). Crystallization from benzene–hexane followed by sublimation at 90°/10^{-3} mm furnished *deoxydehydroeuryopsonol* (17 mg), m.p. 145°, $[\alpha]_D^{17}$ −20° (*c*, 1·0), λ_{max} 280 mμ (ε 14800), ν_{max} 1666, 1540, 1125, 1075, 876 cm^{-1}, possessing the same IR spectrum as 9-oxofuranoeremophilane. (Found: C, 78·0; H, 8·8. Calc. for $C_{15}H_{20}O_2$: C, 77·55; H, 8·9%.)

The 2,4-*dinitrophenylhydrazone*, prepared in diglyme by Shine's method,[13] crystallized from AcOEt as fine orange needles, m.p. 283° (dec). (Found: N, 14·0. $C_{21}H_{24}O_5N_4$ requires: N, 13·6%.)

Epieuryopsonol. A soln of dehydroeuryopsonol (1·50 g, 6·1 mmoles) in dry THF (120 ml) was added dropwise with magnetic stirring at 0° during ½ hr to 60 ml of a 0·28M soln of lithium trimethoxyaluminohydride (35% excess), prepared as described.[6] The mixture was stirred a further hr at 0° and residual hydride decomposed by the slow addition of water (2 ml). Ether (250 ml) and sat aqueous sodium potassium tartrate (30 ml) were added, the ethereal layer separated and the aqueous layer extracted with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to afford an oil (1·50 g), which from the intensity of absorption at 280 mμ contained 0·1% unchanged dehydroeuryopsonol. This oil was refluxed in benzene[14] (250 ml) with active MnO_2[15] (15 g). At intervals samples were removed from the soln and examined by TLC in AcOEt–benzene (1:1). The spot at R_f 0·45 due to epieuryopsonol was fully developed after refluxing for 3 hr; the plate showed

[13] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.* 2549 (1953).

[14] A. J. Shine, *J. Org. Chem.* **24**, 252 (1959).

[14] O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.* **75**, 5930 (1953).

[15] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.* 1094 (1952).

no spot at R_f 0·39 due to euryopsonol The MnO_2 was filtered off after the soln had been refluxed for 3 hr and the filtrate concentrated to 10 ml when colourless prisms (0·66 g), m.p. 213–215°, of *epieuryopsonol* formed. An analytical sample was recrystallized from aqueous EtOH, m.p. 216–217°, $[\alpha]_D^{23}$ −8° (*c*, 1·1), λ_{max} 280 (ϵ 14700), ν_{max} 3620, 1670, 1540, 1130, 1085, 863 cm^{-1}. (Found: C, 72·5: H, 8·0. $C_{18}H_{30}O_3$ requires: C, 72·55; H, 8·1%.)

Reduction of II with LAH and subsequent oxidation with MnO_2 also furnished epieuryopsonol but in much poorer yield.

The 2,4-*dinitrophenylhydrazone*, prepared by Shine's method,[18] crystallized from AcOEt as fine orange needles, m.p. 302° (dec). (Found: C, 59·1; H, 6·0; N, 13·1. $C_{31}H_{34}O_6N_4$ requires: C, 58·9; H, 5·65; N, 13·1%.) The 2,4-dinitrophenylhydrazone of euryopsonol melts at 288·5–289° (dec).[1]

Epieuryopsonol was recovered unchanged on standing overnight at room temp in a mixture of pyridine and Ac_2O but a compound analysing correctly for the acetate could be prepared as follows, although on alkaline hydrolysis at room temp it failed to regenerate epieuryopsonol. A soln of epieuryopsonol (50 mg) in Ac_2O (3 ml) and pyridine (0·5 ml) was refluxed for 2 hr, the solvent removed under reduced press and the residue sublimed at 130°/0·1 mm. Recrystallization from benzene–hexane afforded colourless plates of the *acetate*, m.p. 171–172°, ν_{max} 1670 and 1725 cm^{-1} and no band at 3620 cm^{-1}. (Found: C, 70·25; H, 7·9. $C_{17}H_{28}O_4$ requires: C, 70·3; H, 7·6%.)

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