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THE STRUCTURE OF EURYOPSOL, A FURANOEREMOPHILANE FROM *EURYOPS* SPECIES

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Abstract—Euryopsol, isolated from the resin of *Euryops spp.*, has been shown to be 1α,6β,10β-trihydroxyfuranoeremophilane. Euryopsol, $C_{15}H_{22}O_4$, m.p. 173–174°, occurs together with euryopsonol, $C_{15}H_{20}O_3$, m.p. 230–231°, in the unsaponifiable fraction of the resin of *Euryops floribundus* (Compositae).[1]* We have also obtained the former from *E. tenuissimus*.

BOTH its UV (λ_{max} 220 nm; ε 6800) and its IR spectrum (ν_{max} (KBr) 1560 and 885 cm^{-1}) as well as the positive test obtained with Ehrlich's reagent (*p*-dimethylaminobenzaldehyde in HCl) indicate that euryopsol contains a furan ring. The NMR spectrum† of euryopsol (in $CDCl_3$) shows that the furan ring contains a Me group (doublet at 2·04; J = 1 c/s) and one proton (doublet at 7·12; J = 1 c/s). Euryopsol contains three OH groups since after treatment with D_2O three deuteriums were incorporated into the molecular ion *m/e* 266. Unfortunately, the analysis of the amorphous acetate, obtained by treatment of euryopsol with acetic anhydride and pyridine at room temperature, was unsatisfactory.

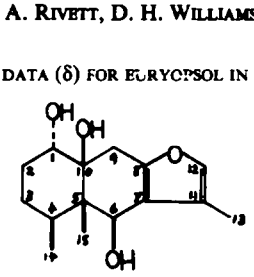
The NMR spectrum of euryopsol was determined at room temperature in various solvents (at 80° in $CDCl_3$ because of insufficient solubility at room temperature). The spectra are summarized in Table 1.

The spectrum obtained in DMSO-d_6 will now be discussed in detail. The 3-proton doublet (J = 5 c/s) centred at 0·68 shows considerable "filling-in" and is assigned to the 14-Me group, and the sharp three proton singlet at 1·06 to the 15-Me group. The proton at C-12 and the 13-Me protons appear as broadened singlets (probably due to weak allylic coupling between them) at 7·22 and 1·94 respectively. The two proton quartet at 2·6–2·8 (J = 18 c/s) is due to an isolated methylene group containing non-equivalent protons. From 3·60–5·10 there are five resonances equivalent to five protons. They are a one-proton multiplet at 3·65, one-proton doublets at 4·18 (J = 8 c/s), 4·39 (J = 8 c/s) and 4·43 (J = 5 c/s), and a one proton singlet at 5·06. On addition of deuterium oxide to the solution the resonances centred at 4·39, 4·43 and 5·06

* The *cis* fused structure assigned[1] to euryopsonol must be corrected to the *trans*. Dr. Novotný has informed us that this revision will be discussed in a forthcoming paper on kablicin in *Coll. Czech. Chem. Comm.*

† All chemical shifts are reported in ppm on the δ scale.

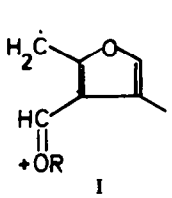
TABLE 1. NMR DATA (δ) FOR EURYOPSOL IN VARIOUS SOLVENTS



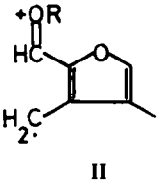
	DMSO-d_6	CD_3OD	$CDCl_3$	C_5D_5N	$\Delta^{CDCl_3}_{C_5D_5N}$
1-H	3·65	3·86	3·93	4·30	−0·37
6-H	4·18	4·36	4·44	4·66	−0·22
9-H	2·82	2·92	3·00	3·25	−0·25
	2·62	2·72	2·78	3·33	−0·55
12-H	7·22	7·12	7·12	7·22	−0·10
13-Me	1·94	1·99	2·04	2·12	−0·08
14-Me	0·68	0·75	0·79	0·77	+0·02
15-Me	1·06	1·17	1·23	1·46	−0·23

disappeared, the doublet at 4·18 collapsed to a singlet and the multiplet at 3·65 sharpened slightly. Accordingly three OH groups, one of which is tertiary (signal at 5·06) and two of which are secondary (signals centred at 4·39 and 4·43), must be present in euryopsol.

If one assumes that euryopsol possesses a furanoeremophilane skeleton, the tertiary OH group must be at C-10; the only other possible position (C-4) is excluded by the doublet resonance for the 14-Me group. One of the two secondary OH groups must be situated at a C atom bearing a proton which is not coupled to any other protons, i.e. at C-6 or C-9. This proposal is supported by the mass spectrum of euryopsol with its base peak at *m/e* 124, corresponding to either of the fragment ions (I: R = H) or (II: R = H). The remaining OH group must therefore be at C-1, C-2 or C-3.



I



II

Additional evidence for the presence of two secondary OH groups is provided by the effect of trichloroacetyl isocyanate ($Cl_3C—CO—N=C=O$) on the NMR spectrum of euryopsol (in $CDCl_3$) when the resonances at 3·93 and 4·44 shift to 5·16 and 6·18 respectively (the signals corresponding to the urethane-N*H*- protons appear at 8·52 and 9·10 respectively). The magnitudes of the downfield shifts of these methine protons (1·23 and 1·74) are of the order expected (1·0–1·5) for protons adjacent to a secondary OH group.[2]

Oxidation of euryopsol with chromium trioxide in pyridine gave a crystalline diketone, $C_{15}H_{18}O_4$, m.p. 150–152°, ν_{max} 1717 (non-conjugated) and 1678 cm^{-1}

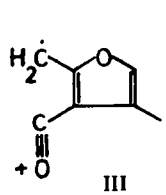
(conjugated) in poor yield. As with euryopsonol this diketone gives a negative Ehrlich test (positive with euryopsol) due to the electron-withdrawing effect of the conjugated CO group. The NMR spectrum of this oxidation product (in $CDCl_3$) shows only one proton in the region 3·7–5·2, a singlet at 4·14 which disappears on equilibration with deuterium oxide. This suggests that both secondary OH groups have been oxidized; the remaining resonance corresponds to the tertiary OH group at C-10. The NMR spectra of the diketone are summarized in Table 2.

TABLE 2. NMR DATA (δ) FOR OXIDATION PRODUCT FROM EURYOPSOL IN VARIOUS SOLVENTS

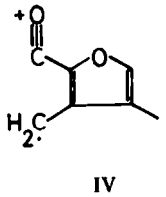
	$CDCl_3$	C_6D_6	C_5H_5N	$\Delta^{CDCl_3}_{C_6D_6}$	$\Delta^{CDCl_3}_{C_5H_5N}$
9-H	3·60	2·83	3·78	+0·77	−0·18
	2·84	2·37	2·96	+0·47	−0·12
12-H	7·12	6·70	—	+0·44	—
13-Me	2·22	2·14	2·23	+0·08	−0·01
14-Me	0·89	0·64	0·84	+0·25	+0·05
15-Me	0·98	0·96	1·20	+0·02	−0·22

The UV spectrum of the diketone (λ_{max} 270 nm; ε 3400) is compatible with the presence of a 6-keto group since it is known,[1,3,4] that 6-oxofuranoeremophilanes have λ_{max} 269 nm (ε ~ 4000) and 9-oxofuranoeremophilanes have λ_{max} 280–282 nm (ε ~ 20000). Accordingly euryopsol must possess a secondary OH group at C-6.

The base peak *m/e* 122 in the mass spectrum of the diketone corresponds to either of the fragment ions (III or IV), confirming the presence of a 6- or 9-CO group.

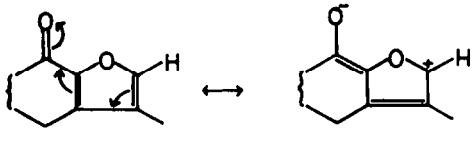


III



IV

Further evidence for the presence of a CO group at C-6 rather than at C-9 in the diketone is provided by the identical value (7·12) for the chemical shift of the C-12 proton (in $CDCl_3$) in both euryopsol and the diketone; 6-oxofuranoeremophilane possesses a similar value (7·06).[4] The introduction of a CO group at C-9 would cause an increase in electron-withdrawal from C-12 (see A ⟷ B, and this would be expected to cause greater deshielding of the C-12 proton as observed in euryopsonol (δ = 7·43), *cis* fused (7·29) and *trans* fused 9-oxofuranoeremophilane (7·33).[5]



A B

The position of the second CO group, and hence the position of the third OH group in euryopsol, was determined by deuterium-exchange of the diketone in the presence of a trace of alkali. This was expected to give incorporation at the C atoms adjacent to the unconjugated CO group and also at C-9. Indeed, the NMR spectrum of the deuterated diketone showed extensive incorporation and the complete disappearance of the C-9 methylene AB quartet. The mass spectrum of the deuterated product, determined after back exchange with water to convert the C-10 OD to OH, showed the incorporation of a maximum of four deuteriums and a base peak at *m/e* 124 as compared with *m/e* 122 in the undeuterated diketone. Accordingly, the second CO group must be at C-1. A CO group at C-2 would give a maximum incorporation of six deuteriums, and a CO at C-3 a maximum of five deuteriums as well as causing the 14-Me doublet to collapse to a singlet in the NMR spectrum of the deuterated diketone. In fact the 14-Me resonance was unchanged.

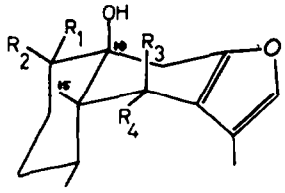
In agreement with the above evidence for the presence of a *vic*-diol grouping in euryopsol, it reacted with periodate but consumption of reactant was continuous and we were unable to isolate a homogeneous product.

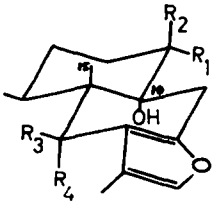
In the NMR spectrum of euryopsol in pyridine-d_5 containing deuterium oxide the C-1 proton gives a fairly well resolved quartet, suggestive of the X-portion of an ABX system while in the other solvents employed this resonance is unresolved even after the OH proton has been exchanged with deuterium. This observation can be explained by virtual coupling[6] which arises because the difference in chemical shift between the C-2 and C-3 protons is small compared with their coupling constants. In pyridine the C-2 protons will undergo an appreciable downfield shift (0·20 ppm) relative to the C-3 protons[7] and this will reduce the effect of virtual coupling. If the C-1 proton forms the X-portion of an ABX system then $J_{AX} + J_{BX} = 16$ c/s. Accordingly the C-1 proton is axial and the C-1 OH group equatorial.

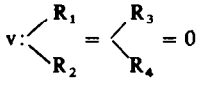
The 14-Me doublet in the NMR spectrum of euryopsol was poorly resolved in all the solvents used. This is also probably due to virtual coupling caused by the small difference in chemical shift between the protons at C-3 and C-4.

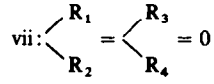
With the exception of furanoligularenone,[8] the ring junction of all naturally occurring furanoeremophilane-type sesquiterpenoids (referred to by the descriptive term "furanoeremophilanoides" in a recent review[9]) is *cis*.* Accordingly the ring junction in euryopsol can reasonably be expected to be *cis* since the absence of a C-10 proton and of a CO group at C-1 or C-9 precludes isomerization by alkali[12] during isolation from the plant. This assumption is supported by the large negative pyridine-induced solvent shift ($\Delta^{CDCl_3}_{C_5H_5N} = -0{\cdot}22$ ppm) of the 15-Me singlet in the diketone which arises mainly from association of pyridine with the C-10 OH group because the C-10 OH and 15-Me groups subtend an angle $\sim 60°$ (V).[7] There will also be a small negative contribution arising from association of pyridine with the CO group at C-6.[13] When the rings are *trans*-fused (VII) the C-10 OH and the 15-Me groups subtend an angle of $\sim 180°$, which would be expected to give a small value of $\Delta^{CDCl_3}_{C_5H_5N}$ ($-0{\cdot}00$ to $-0{\cdot}05$ ppm).[7] Furthermore, the contribution from the 6-CO group would be expected to be small and probably slightly positive.[13]

* Since *cis* fused eremophilanes exist in the preferred steroid-like conformation[1,4,10,11] the stereochemistry of euryopsol will be discussed using this conformation. As will be apparent all the evidence is in favour of this assumption.

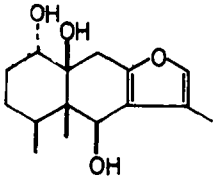




v: 

vii: 

vi: $R_1 = R_3 = OH, R_2 = R_4 = H$ viii: $R_1 = R_3 = OH, R_2 = R_4 = H$



IX

Further evidence in support of the *cis* ring junction is provided by the magnitude of the pyridine-induced solvent shift ($\Delta^{CDCl_3}_{C_5D_5N} = -0{\cdot}37$ ppm) of the C-1 proton in euryopsol which is rather larger than the value expected ($-0{\cdot}15$ to $-0{\cdot}25$ ppm)[7] for a proton on a carbon bearing a OH group. For a *cis* ring junction (VI) the dihedral angle between the C-1 proton and the C-10 OH group is $\sim 60°$ and for a *trans* (VIII) it is $\sim 180°$. In the former case additional deshielding would be expected to be appreciable ($-0{\cdot}15$ to $-0{\cdot}20$ ppm)[7] but negligible in the latter.

If the rings are *cis* fused, the C-6 OH group must be β for the following reasons. A C-6α OH group would be in a quasi 1,3-diaxial relationship with the 14-Me group and hence the δ-value for the chemical shift of the 14-Me protons would be expected to be appreciably greater than that actually observed (0·79 ppm in $CDCl_3$). This is shown by the difference in chemical shift of the 14-Me protons in 6α-hydroxy (0·88 ppm) and in 6β-hydroxyfuranoeremophilane (1·04 ppm).[4] The pyridine-induced solvent shift for the 14-Me protons would be expected to be appreciably negative for a C-6αOH group,[7] whereas it is in fact slightly positive (+0·02 ppm).

All the evidence discussed supports the structure IX for euryopsol. Euryopsol is the first furanoeremophilanoid with a substitutent (OH) attached at the ring junction (C-10).

In order to provide further chemical evidence for the structure of euryopsol, its reaction with acid was investigated. Euryopsol is very sensitive to acid and this has proved a serious handicap in many degradative experiments, but it was thought that treatment with acid under mild conditions might cause elimination of water and formation of a Δ^9-double bond conjugated with the furan ring. Euryopsol was converted after standing for a short time in methanolic HCl into a crystalline product, $C_{16}H_{24}O_4$, m.p. 119–123°. The NMR spectrum of this compound in DMSO shows the presence of two OH protons, a doublet centred at 4·38 (J = 4 c/s) and a singlet

at 4·58. Olefinic protons are absent, the characteristic AB quartet for the C-9 protons remain and there is a sharp proton singlet at 3·28. These results suggest that the product contains one secondary and one tertairy OH group and an aliphatic OMe group. A one-proton singlet at 4·05 and a one-proton multiplet at 3·99 are observed in $CDCl_3$; on addition of trichloroacetyl isocyanate the latter suffers a large downfield shift (1·20 ppm) while the former is unaffected, thus indicating that one of the methine protons adjacent to oxygen is no longer adjacent to a free OH group.[2] The base peak at *m/e* 138 in the mass spectrum of the methylated product corresponds to the fragment ion (I: R = Me). Accordingly the product obtained by the action of methanolic HCl on euryopsol is the 6-OMe derivative.

EXPERIMENTAL

M.Ps are uncorrected. UV spectra were determined in 95% EtOH, IR spectra and rotations in $CHCl_3$. NMR spectra were recorded on a Varian Associates HA-100 spectrometer at normal probe temps except for euryopsol in $CDCl_3$ (determined at 80° because of its insolubility) and with TMS as internal standard. Mass spectra were determined on AEI MS9 and MS12 instruments.

Oxidation of euryopsol with chromium trioxide-pyridine. In a typical experiment a soln of euryopsol (500 mg) in pyridine (5 ml) was added to a well-stirred, ice-cold mixture of CrO_3 (1·1 g) in pyridine (14 ml). Stirring was continued for a further ½ hr and the reaction mixture left at room temp overnight. The mixture was diluted with water, the soln extracted with ether (4 × 25 ml), the combined ethereal extracts washed with water, dried ($MgSO_4$) and evaporated to afford a crystalline residue (60–80 mg). Recrystallization from aqueous MeOH and sublimation at 120°/0·1 mm gave colourless crystals (20–30 mg), m.p. 148–152°. An analytical sample, prepared by filtration in benzene through a small column of alumina, and vacuum sublimation had m.p. 150–152°, λ_{max} 270 nm (ε 3400), ν_{max} 3465, 2925, 1717, 1678, 1420 cm^{-1}. (Found: C, 69·0; H, 7·1; M (by mass spectrometry), 262. $C_{15}H_{18}O_4$ requires: C, 68·7; H, 6·9%, M, 262).

Deuterium exchange of diketone from euryopsol. The diketone (10 mg) was heated with D_2O (1 ml) and a trace of KOH for 36 hr on a steam bath. The soln was diluted with water, extracted with benzene, the benzene extract washed with water, dried ($MgSO_4$) and evaporated to afford a crystalline residue which was pure by TLC. The NMR spectrum of this product indicated that considerable deuterium exchange had occurred; the mass spectrum of the highest peak *m/e* 266 showed a max incorporation of four D atoms.

Periodate oxidation of euryopsol. When solns of euryopsol (1 mmole) and $NaIO_4$ (2–8 mmoles) in aqueous EtOH were left to stand the uptake of periodate varied from 1·0 (½ hr) to 2·2 (70 hr) moles periodate per mole euryopsol.

A soln of euryopsol (1 mmole) and $NaIO_4$ (1 mmole) in MeOH (30 ml) and water (12 ml) was left to stand overnight. The product, extracted in the usual way with AcOEt, was an oil, which TLC showed to consist chiefly of one component, and had ν_{max} 3400, 1720, 1620 and 895 cm^{-1} but failed to react with the usual carbonyl reagents.

Methylation of euryopsol with methanolic hydrochloric acid solution. Conc HCl (1·4 ml) was added to a soln of euryopsol (100 mg) in MeOH (20 ml) and the soln allowed to stand ½ hr while a blue colour developed. The soln was poured into $NaHCO_3$aq, the mixture concentrated under reduced press and extracted with ether. The crystalline residue obtained on evaporation of the dried ($MgSO_4$) ethereal extract contained a trace of euryopsol as indicated by TLC. Accordingly the product was triturated with benzene and filtered to remove euryopsol which is insoluble. Evaporation of the filtrate and recrystallisation of the residue from aqueous MeOH followed by vacuum sublimation afforded colourless crystals (35 mg), m.p. 119–123°, λ_{max} 223 nm (ε 5300). (Found: C, 68·3; H, 8·7; M (by mass spectrometry), 280. $C_{16}H_{24}O_4$ requires: C, 68·55; H, 8·6%; M, 280).

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