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THE CHEMISTRY OF *EREMOPHILA* SP—VII†

AN EPOXYCEMBRADIENOL FROM *EREMOPHILA GEORGEI*

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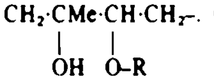
Abstract—The structure **5** is advanced for a macrocyclic diterpene from *Eremophila georgei*. The carbon skeleton was established by conversion to cembrane **11** and the absolute configuration follows from degradation to *R*-homoterpenyl methyl ketone. The configuration of C-3 has been related to C-1 by spectroscopic methods and the *Z*-configuration of the double bonds is based on NMR shifts in the keto lactone **12**.

Many *Eremophila* species are characterised by the presence of a resin coating on their leaves and terminal branches. In many cases these resins have been shown to be largely diterpenoid compounds and to date we have described compounds of the decipiane group (e.g. **1**) from *E. decipiens*,[1] members of the eremane series (e.g. **2**) from *E. fraseri*[2] and dihydroxyserrulatic acid **3** from *E. serrulata*.[3] *E. georgei* is a highly variable species which is widely distributed in the Murchison district of Western Australia where it grows to a height of 1 metre as a small shrub with viscid leaves. The volatile oil of this plant which contains a sesquiterpene (**4**) related to the zizaene series has been described recently[4] and we now wish to report the isolation and structure assignment of a diterpene dienol ether (**5**) from the neutral fraction. Spectral data indicated that the acidic fraction contained a series of related compounds but none were separable in a pure state. The dienol ether (**5**), $C_{20}H_{34}O_2$, was isolated in crystalline form after adsorption chromatography. The NMR spectrum of **5** showed singlets for three tertiary methyl groups at δ 1.02, 1.15 and 1.25 together with a singlet at δ 1.66 for two equivalent olefinic methyls. A broad triplet at δ 5.2 corresponded to two olefinic protons flanked by methylene groups and a doublet of doublets at δ 4.15 ($J = 4$, 11 Hz) was assigned to an oxymethine proton. The presence of hydrogen bonded hydroxyl was evident from the IR spectrum and its tertiary nature followed after acetylation which required forcing conditions. The acetate (**6**) showed no change in the signal for the oxymethine resonance which was accordingly assigned to an ether link. The presence of an ether bridge and two double bonds requires a monocyclic skeleton of which the most commonly occurring is cembrane (**11**).

The environment of the tertiary alcohol was explored by dehydration of the dienol (**5**) with phosporyl chloride which yielded the separable trienes (**7**) and (**8**). The NMR spectra of the trienes showed signals for only two tertiary methyl groups and the isomer **7** showed a total of three trisubstituted olefines bearing methyl whereas in the triene **8** one of these was replaced by an exocyclic methylene group. Significantly the resonance for the oxymethine proton was shifted downfield by 20 Hz in **8** and 40 Hz in **7** suggesting that it is allylic to the newly formed double bonds in **7** and **8** and consequently α to the tertiary hydroxyl as in the partial structure  $-\underset{\substack{|\\ OH}}{CH_2\cdot CMe}\cdot\underset{\substack{|\\ O\text{-}R}}{CH}\cdot CH_2-$. Catalytic hydrogenation of either triene resulted in some hydrogenolysis to give the saturated ether (**9**) and the tertiary alcohol (**10**) as mixtures of stereoisomers. The chemical shifts of the tertiary methyls in **5–10** suggest that they are all attached to carbon bearing oxygen. This assignment requiring a hydroxypropyl group in **10** was supported by the mass spectrum which showed the base peak at *m/e* 236 for the loss of C_3H_8O. A simple interrelation with cembrane (**11**) was then possible by dehydration of the cembranol **10** followed by hydrogenation. The stereoisomeric mixture thus obtained was found to have GLC, NMR and MS identical with an authentic sample.[5]

The presence of a five membered ether ring was established by oxidation of the dienol (**5**) with Jones reagent which resulted in cleavage to give the keto lactone (**12**), a process which has adequate precedent.[6] The NMR spectrum of **12** showed the presence of a methyl ketone (δ 2.11) and the IR spectrum had absorption for this group at 1710 cm^{-1} as well as for a γ-lactone (1770 cm^{-1}). Further degradation was achieved smoothly by osmium tetroxide-sodium periodate oxidation of the lactone (**12**) which gave (−)-homoterpenyl methyl ketone (**13**) which locates a double bond in **5** at the 11, 12 position. Further (+)-homoterpenyl methyl ketone is known[7] to have the *S* configuration which establishes the absolute configuration of C-1 as *R*. The position of the remaining double bond was shown to be 7,8 from the NMR spectrum of **7** which showed that the presence of the 4,5 double bond gave rise to doubly allylic signals centred at δ 3.1. Double resonance measurements confirmed that these were the M part of an AMXY spin system involving two olefinic and two doubly allylic geminal protons.

Double resonance measurements for the C-3 proton in **5** allow its configuration relative to the C-1 proton (*R*) to be assigned. As the 14-membered cembrane ring is flexible the conformation of the 5-membered ether ring is determined by steric interactions between its pendant groups. Hence the geminal methyls at C-15 must assume a conformation with a degree of staggering with the C-1 (14) bond.

The C-3 proton showed couplings of 13 Hz and 5 Hz to H-2a and H-2b respectively. H-2a also showed a large coupling (J 11 Hz) with H-1 which had a small coupling (J 4 Hz) with H-2b. Bearing in mind the limitation on ap-

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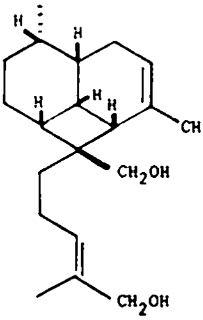
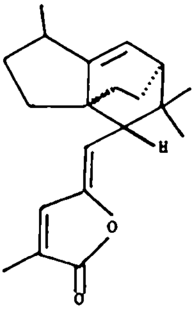
†Part VI. *Tetrahedron* 33, 1475 (1977).



(1)



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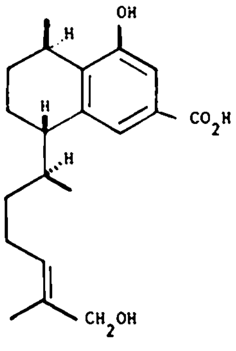

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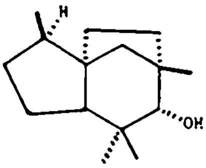

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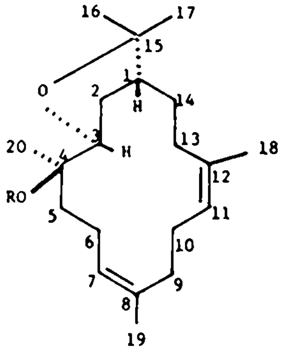
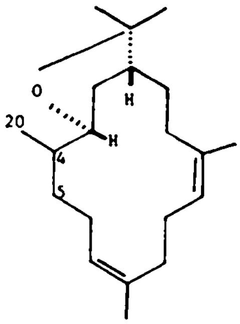


(5) R = H

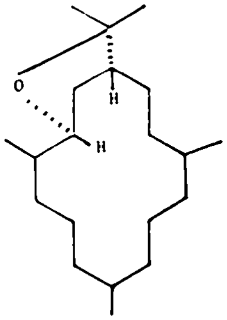
(6) R = $COCH_3$

(15) R = $COCF_3$

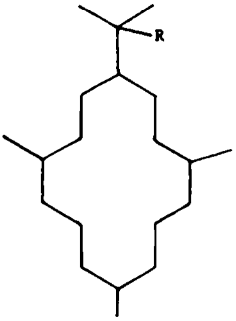


(7) Δ^4

(8) $\Delta^{4(20)}$

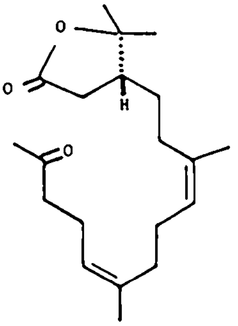


(9)

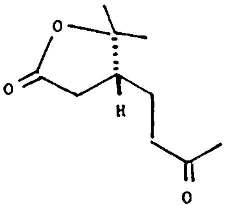


(10) R = OH

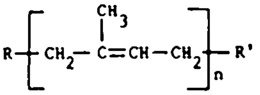
(11) R = H



(12)



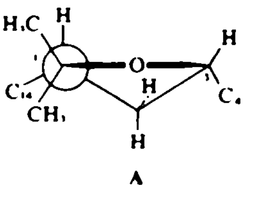
(13)



$$R\left[CH_2-\overset{\overset{\displaystyle CH_3}{|}}{C}=CH-CH_2\right]_n R'$$

(14)

plication of Karplus relationships in 5-membered rings the large values observed nevertheless point to a *trans*-anti-parallel arrangement of the H-1, H-2a and H-3 protons. This condition is satisfied only if C-3 has the *R*-configuration and the 5-membered ring the conformation shown in structure **A**. The stereochemistry of the two trisubstituted double bonds was tentatively assigned as *cis*- after comparing the chemical shifts of the olefinic methyls (δ 1.67) in the keto lactone (**12**) with the values recorded[8] for the structurally similar *cis*- and *trans*-polyprenols of the type **14** in CCl_4 solutions (δ 1.66 and 1.58 respectively). Since the carbonyl group of the keto lactone should complex with benzene, shifts recorded in this solvent are likely to be unreliable.



A

There is now a substantial number of cembrane based diterpenes described and many have configurations securely based on X-ray crystallographic studies. Among these *cis*- double bonds occur rarely, consistent with biosynthetic schemes based on formations of the rings from all *trans*-geranylgeranyl pyrophosphate. The origin of the *cis*-double bonds in (**5**) requires elucidation.

The stereochemistry of the tertiary alcohol at C-4 was not determined and to assign this centre and to confirm the above assignments the X-ray diffraction method was used. The parent compound (**5**) and its trifluoroacetate derivative (**15**) gave suitable crystals but **5** proved more amenable to solution. The X-ray crystallographic study is reported in the following publication.[9]

EXPERIMENTAL

General experimental details are as described previously.[10]

Isolation of 3,15-*epoxy-4-hydroxycembra*-7,11-*diene* (**5**). Fresh leaves and terminal branches of *E. georgei* (12 kg), collected 33 miles east of Yalgoo, Western Australia, were decoated by washing briefly in acetone and the recovered resin (1.0 kg) separated into neutral and acidic components. Treatment of the former with activated charcoal followed by chromatography on alumina (activity I) gave the dienol (**5**, 50 g) which crystallised from n-pentane, as prisms, m.p. 114–5°, $[\alpha]_D$ - 3.4° (*c* 0.6). (Found: C, 78.2; H, 11.4; M$^+$ 306. $C_{20}H_{34}O_2$ requires: C, 78.4; H, 11.2%; M$^+$ 306), δ ($CDCl_3$) 1.02, 1.15 and 1.25 (3H, s, tertiary methyls); 1.66 (6H, s, olefinic methyls); 4.15 (1H, d of d, J = 4, 11 Hz, oxymethine); 5.2 (2H, m, vinyl protons): ν_{max} (CS_2) 3580, 3450 and 3025.

3,15-*Epoxy-4-acetoxycembra*-7,11-*diene* (**6**). A solution of the dienol (**5**, 150 mg) and fused sodium acetate (100 mg) in acetic anhydride (10 ml) was heated under reflux for 3 h before water was added to decompose excess anhydride. The product, isolated with ether, crystallised from aqueous methanol as prisms, m.p. 114–5°, $[\alpha]_D$ −53° (*c* 0.74). (Found: C, 75.4; H, 10.4; M$^+$ 348. $C_{22}H_{36}O_3$ requires: C, 75.8; H, 10.4% M$^+$ 348), δ (CCl_4) 1.00, 1.22 and 1.35 (3H, s, tertiary methyls); 1.67 (6H, s, olefinic methyls); 1.94 (3H, s, acetate); 4.15 (1H, d of d, J = 4, 11 Hz, oxymethine); 5.2 (2H, m, vinyls): ν_{max} (CS_2) 1725.

3,15-*Epoxycembra*-4,7,11-*triene* (**7**) *and* 3,15-*epoxycembra*-4(10),7,11-*triene* (**8**). The dienol (**5**, 3.18 g) in pyridine (50 ml) containing $POCl_3$ (10 ml) was left at ambient temperature for 24 h, poured onto ice and the product recovered with ether. This oil (2.49 g) was chromatographed on alumina impregnated with $AgNO_3$ (10% W/W). Elution with light petroleum gave the *triene* (**7**, 1 g) as an oil, b.p. 140–50°/0.1 mm, $[\alpha]_D$ + 29° (*c* 0.723). (Found: C, 83.2; H, 11.0; M$^+$ 288. $C_{20}H_{32}O$ requires: C, 83.3; H, 11.2%; M$^+$ 288), δ ($CDCl_3$) 1.02 and 1.25 (3H, s, tertiary methyls); 1.66 (9H, s, olefinic methyls); 2.24 and 3.15 (A and M protons of AMXY spin system, $J_{AY} = J_{AX} = 5$ Hz, $J_{MX} = J_{MY} = 11.3$ Hz, $J_{AM} = 14.1$ Hz); 4.85 (1H, d of d, J = 4, 11 Hz oxymethine); 5.0–5.4 (3H, m, vinyls): ν_{max} (CS_2) 3020.

Further elution with light petroleum gave the other isomer (**8**, 0.8 g) as an oil, b.p. 145–55°/0.1 mm, $[\alpha]_D$ −44° (*c*, 1.70). (Found: C, 83.4; H, 10.9; M$^+$ 288. $C_{20}H_{32}O$ requires: C, 83.3; H, 11.2%; M$^+$ 288), δ ($CDCl_3$) 1.22 (6H, s, tertiary methyls); 1.72 (6H, br.s, w/2 = 3 Hz, olefinic methyls); 4.5 (1H, t, J = 7.5 Hz, oxymethine); 4.9 and 5.11 (1H, br.s, w/2 = 3 Hz, C-20 methylenes); 5.24 (2H, m, vinyls): ν_{max} (CS_2) 3060, 3020.

3,15-*Epoxycembrane* (**9**) *and* 15-*hydroxycembrane* (**10**). The triene (**8**, 500 mg) in ethanol (50 ml) containing 10% palladium/charcoal (80 mg) was stirred under a hydrogen atmosphere for 6 h and the recovered oil (480 mg) chromatographed on alumina (Act I). Elution with light petroleum gave the ether (**9**, 200 mg) as an oil, b.p. 140–5°. (Found: C, 81.8; H, 12.9; M$^+$ 294. $C_{20}H_{38}O$ requires: C, 81.6; H, 13.0%; M$^+$ 294), δ ($CDCl_3$) 0.80 to 1.05 (9H, m, secondary methyls); 1.15 (6H, s, tertiary methyls); 3.85 (1H, m, w/2 = 20 Hz, oxymethine): ν_{max} (CS_2) 1150 (ether). Elution with light petroleum–chloroform gave the alcohol (**10**, 170 mg) as an oil, b.p. 140–5°/0.1 mm. (Found: C, 81.2; H, 13.5; M$^+$ 296. $C_{20}H_{40}O$ requires: C, 81.0; H, 13.6%; M$^+$ 296), δ ($CDCl_3$) 0.90 (9H, d, J = 5 Hz, secondary methyls), 1.2 (6H, s, tertiary methyls): ν_{max} (CS_2) 3590 (OH).

Similar hydrogenation/hydrogenolysis of the triene **7** gave the same two products **9** and **10**.

Cembrane (**11**). The alcohol (**10**, 100 mg) in pyridine (5 ml) containing $POCl_3$ (1 ml) was left at ambient temp. for 24 h, poured onto ice and the product recovered with ether. Hydrogenation of this oil with palladium/charcoal (10%) gave cembrane (**11**, 60 mg), identical in all respects with and authentic sample.[5] (M$^+$ 280. $C_{20}H_{40}$ requires: M$^+$ 280), δ ($CDCl_3$) 0.88 (15H, d, J = 5.5 Hz, secondary methyls).

6,10 - *Dimethyl* - 14 - *oxo* - 3(1 - *hydroxy* - 1 - *methyl* - *ethyl)pentadeca* - 6,10 - *dien* - *oic acid γ-lactone* (**12**). A stirred solution of the dienol (**5**, 1.85 g) in acetone (60 ml) was treated at ambient temperature with excess Jones reagent for 20 min before quenching with methanol. Dilution with water and extraction with ether gave the crude product which after filtering through an alumina column (35 g, Act II) gave the γ-lactone (**12**, 1.011 g) as an oil, b.p. 200°/0.1 mm. (Found: C, 75.0; H, 10.1; M$^+$ 320. $C_{20}H_{32}O_3$ requires: C, 75.0; H, 10.1%; M$^+$320), δ ($CDCl_3$) 1.25 and 1.44 (3H, s, tertiary methyls); 1.67 (6H, s, olefinic methyls); 2.11 (3H, s, methyl ketone); 5.1 (2H, m, w/2 = 18 Hz, vinyls). In CCl_4 both olefinic methyls resonate at δ 1.67 whereas in benzene they are at 1.60 and 1.66: ν_{max} (CS_2) 3025, 1775 and 1720.

6 - *Oxo* - 3 - (1 - *hydroxy* - 1 - *methylethyl)heptanoic acid γ-lactone* (**13**) [*homoterpenyl methyl ketone*]. A solution of the lactone (**12**, 800 mg) in 20% aqueous methanol (100 ml) containing sodium periodate (3 g) and osmium tetroxide (10 mg) was stirred at room temp. for 12 h, diluted with water and the products extracted with ether. Purification by preparative TLC gave the γ-lactone (**13**, 40 mg) as an oil δ ($CDCl_3$) 1.28 and 1.45 (3H, s, tertiary methyls); 2.18 (3H, s, methyl ketone): ν_{max} (CS_2) 1775, 1720.

The semicarbazone derivative crystallised from methanol as needles, m.p. 194–7°, $[\alpha]_D$ 50° (*c* 0.22 $CHCl_3$) [lit.,[7] 195–6, +49.9°].

The NMR and IR spectra were identical to those obtained for an authentic sample prepared from (±)α-terpineol by ozonolysis, with an oxidative work up.

3,15-*Epoxy-4-trifluoroacetoxycembra*-7,11-*diene* (**15**). A solution of the dienol (**5**, 2.5 g) and trifluoroacetic anhydride (5 ml) in pyridine (20 ml) was left for 3 h, diluted with water, and extracted with ether. Crystallisation of the recovered product from n-pentane gave the trifluoroacetate (**15**, 2.8 g) as prisms (monohydrate), m.p. 118–20°, $[\alpha]_D$ −40° (*c* 2.38 in $CHCl_3$) (M$^+$ 402.23695). $C_{22}H_{33}O_3F_3$ requires: 402.23818), δ ($CDCl_3$) 1.06, 1.30 and 1.55 (3H, s, tertiary methyls); 1.67 (6H, s, olefinic methyls); 4.42 (1H, d of d, J = 4, 12 Hz, oxymethine); 5.25 (2H, m, w/2 = 20 Hz, vinyls): ν_{max} (Cs_2) 1770.

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