Phytochemistry, 1976, Vol. 15, pp 777–780 Pergamon Press. Printed in England.

TRICYCLIC SESQUITERPENES FROM *EREMOPHILA GEORGEI*

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(*Received* 15 *November* 1975)

Key Word Index—*Eremophila georgei*; Myoporaceae; sesquiterpenes; tricyclo[6.2.1.$0^{1,5}$]undecanes.

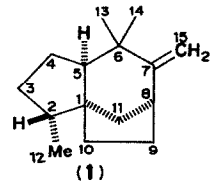
Abstract—The structures of three new tricyclic sesquiterpenes from *Eremophila georgei* are described. The absolute stereochemistry of these sesquiterpenes is shown to be antipodal to that of the zizane sesquiterpenes of vetiver oil.

INTRODUCTION

Recent investigations of the constituents of *Eremophila* species (Myoporaceae) have revealed a number of structurally novel sesquiterpenes and diterpenes [1–6]. In an extension of our work on this genus we have examined the sesquiterpenes of the steam volatile fraction from *Eremophila georgei* Diels. In this report evidence is presented for the structure of the four major components **1–4**, all containing the tricyclo[6.2.1.$0^{1,5}$]undecane skeleton. Sesquiterpenes based on this skeleton, the zizaene series, have previously been found only in vetiver oil [7]. Recently, a possible precursor of the zizaene sesquiterpenes *allo*-cedral, was isolated from *Biota orientalis* and *Juniperus rigida* [8]. Both *allo*-cedrol and the sesquiterpenes from *E. georgei* however belong to the series which is antipodal to that of the tricyclic sesquiterpenes in vetiver oil.

RESULTS AND DISCUSSION

Alumina chromatography of the steam volatile fraction of *Eremophila georgei* afforded the four sesquiterpenes **1**, **2**, **3** and **4**, in order of increasing polarity. The major component (**4**, 55% of the total fraction) was assigned a molecular formula of $C_{15}H_{26}O$ on the basis of elemental analysis and MS (M^+ 222) measurements. The NMR spectrum of **4** included signals for three tertiary methyl groups (δ 0.87, 1.02 and 1.22) and a secondary methyl group (δ 0.88, J 7Hz) but no signals downfield of δ 2.30. The IR spectrum showed absorption for a hydroxyl group at 3620 cm^{-1} and the absence of hydroxymethine signals in the NMR spectrum indicated it to be tertiary. The chemical shift for one of the tertiary methyls (δ 1.22) suggested that this methyl was geminal to the hydroxyl group. The evidence so far pointed to a tricyclic skeleton with 5 pendant groups. Dehydration of **4** with $POCl_3$ in pyridine yielded an alkene, $C_{15}H_{24}$, the NMR spectrum of which showed new signals for a vinyl methylene (δ 4.63) and for one allylic proton (apparent triplet, δ 2.78). Comparison of the NMR spectrum of the alkene with that published [7] for (+)-prezizaene showed them to be identical. A pure sample of the alkene had bp 80° (0.1 mm Hg) and optical rotation $[\alpha]_D^{CHCl_3}$ −54°. This shows that the alkene is the enantiomer of the naturally occurring prezizaene ($[\alpha]_D$ +55°) [7]. On the basis of this evidence the original alcohol could be assigned structure **4**. Given the propensity for rearrangement of these tricyclic systems it seemed important to establish that no rearrangement has occurred in the dehydration step. Treatment of the crude dehydration fraction with OsO_4 gave two isomeric diols in the ratio 6:1. The major product, $C_{15}H_{26}O_2$, showed a signal in its NMR spectrum attributable to a hydroxymethyl group (δ 3.52), consistent with structure **5** for this diol. The stereochemistry of the C-7 hydroxyl (α) is assigned on the basis of the expected approach of the OsO_4 from the less hindered side. Oxidation of the diol (**5**) with $NaIO_4$ afforded the nor-ketone (**6**, $C_{14}H_{22}O$, ν_{max} 1705 cm^{-1}) which on treatment with MeLi gave a tertiary alcohol identical with **4**, thus conclusively establishing the structure of **4** as a 7-hydroxy-(−)-prezizane. The stereochemistry of the 7-OH group is assigned as β from the following considerations. A comparison of the NMR spectra obtained for $CDCl_3$ and C_5H_5N solutions of **4** showed a deshielding effect of the pyridine on all three methyl groups suggesting that the 7-OH group is in a staggered conformation between the two vicinal methyl groups at C-6 and therefore must be in a β-configuration. The formation of the original alcohol exclusively in the transformation of **6** with MeLi supports the configurational assignment since MeLi would be expected to approach from the less hindered (α) side. Thus the major sesquiterpene from *E. georgei* can be formulated as 7β-hydroxy-(−)-prezizane. The more polar diol, obtained from OsO_4 treatment (mp 146–8°, $[\alpha]_D$ +0.4) of the crude prezizaene was assigned structure **7**. The NMR spectrum lacked signals for hydroxymethine protons although the IR spectrum showed ν_{max} at 3640 cm^{-1} due to hydroxyl absorptions. The formation of a diketone (**8**) (ν_{max} 1730 and 1705 cm^{-1}) on treatment of **7** with $NaIO_4$ confirmed the presence of two vicinal tertiary hydroxyl groups in the diol (**7**). The structure of the diol is thus best represented as 5β,6β-dihydroxy-(−)-zizane. The enantiomeric diol (mp 146–146.7°) has been obtained by OsO_4 treatment of the corresponding alkene [9]. The unexpected *endo*-addition of OsO_4 to the tetrasubstituted double bond of the tricyclo[6.2.1.$0^{1,5}$]-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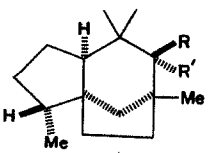
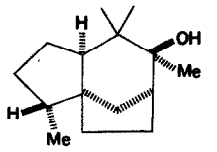

(2) R, R' = O
(3) R, OH
R', H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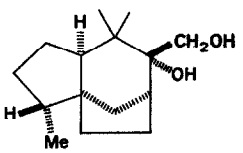
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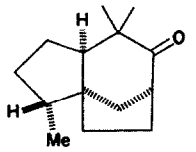
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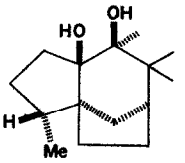
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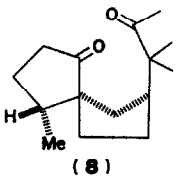
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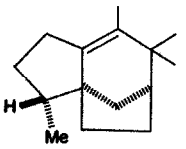
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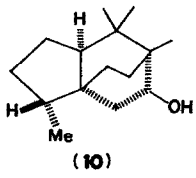
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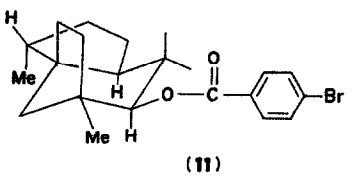
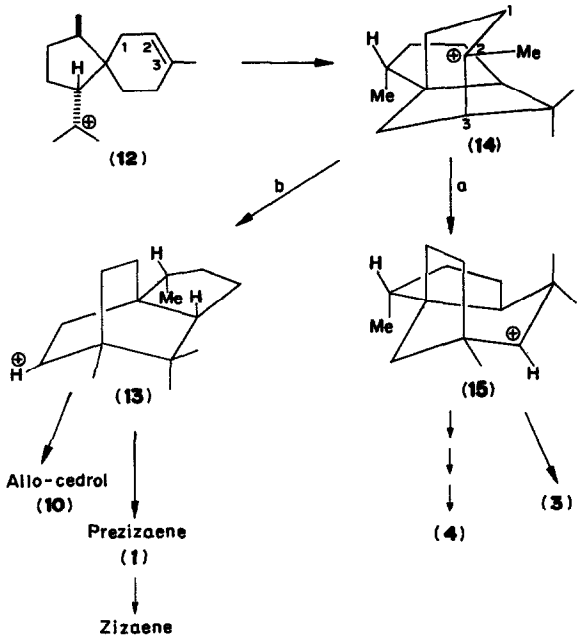

(11)

undec-5-ene skeleton has been established by X-ray crystallographic analysis [9]. The diol (**7**) must have originated from the corresponding tetra-substituted alkene (**9**) and the formation of the latter most probably arises from a rearrangement of the initially formed carbonium ion during dehydration of **4**. This alternative finds support in the known [9] isomerisation of prezizaene and zizaene to a number of isomers of which the alkene corresponding to **9** is the thermodynamically more stable. Under our conditions dehydration of **4** always gave a mixture of the two alkenes **1** and **9**. This was also reflected in the low value for the optical rotation of the alkene fraction ($[\alpha]_D$ − 38°) obtained by dehydration of **4**. Purification of (−)-prezizaene (**1**) could be achieved either by careful distillation or by reaction of the crude alkene fraction with less than the molar equivalent of OsO_4 required. The unreacted olefin showed increased $[\alpha]_D$ values and its NMR spectrum was identical to that reported for prezizaene. The low $[\alpha]_D$ value reported previously by Tomita and Hirose [8] for (−)-prezizaene ($[\alpha]_D$ −40°) may also reflect a similar mixture of the two alkenes **1** and **9**. These authors also report the isolation of a tricyclic alcohol ($[\alpha]_D$ −46.2°), following solvolysis of the *p*-bromobenzenesulfonate of *allo*-cedrol (**10**), to which they assigned structure **4** without stereochemical definition at C-7, on the basis of its dehydration to (−)-prezizaene. It now appears likely that the tricyclic alcohol described by them has the same stereochemistry at C-7 as the naturally occurring alcohol **4** ($[\alpha]_D$ −48.3°). (−)-Prezizaene (**1**) was also isolated from the steam volatile fraction (5% of the total fraction) and was identical with the sample obtained by dehydration of **4**. The origin of this alkene cannot be clearly stated although some of it is likely to arise by dehydration of **4** during isolation since its rotation ($[\alpha]_D$ −47°) and the formation of the two diols **5** and **7** on OsO_4 treatment, shows it to be contaminated by the alkene **9**.

The second sesquiterpene alcohol (**3**; 25% of the total fraction) isolated from *E. georgei* showed M^+ 222.19837 consistent with a formula of $C_{15}H_{26}O$. The NMR spectrum of **3** showed signals for three tertiary methyl groups (δ 0.92, 1.03, 1.07), a secondary methyl group (δ 0.86, *J* 7Hz) and a hydroxy methine proton (*brs*, δ 3.18) which appeared at δ 4.95 in the NMR spectrum of the *p*-bromobenzoate derivative (**11**). Jones oxidation of **3** afforded a cyclohexanone (ν_{max} 1700 cm^{-1}) which was shown to be identical with the ketone **2**, also obtained from the chromatography of the steam volatile fraction (2% of the total fraction). Treatment of either sample of ketone with $NaBH_4$ generated the alcohol **3**. An examination of the effect of increasing amounts of $Eu(dpm)_3$ on the NMR spectrum of **2** failed to indicate the presence of hydrogens α- to the carbonyl group [10] although all three tertiary methyl groups were significantly deshielded as expected from the observed pyridine induced shift. This, together with the unreactivity of the ketone under conditions of α-bromination, indicated that the ketone was fully substituted in the α-position. On this evidence the alcohol was tentatively assigned structure **3** and the ketone structure **2**. Due to lack of material and the availability of the *p*-bromobenzoate derivative **11** in a suitable crystalline form the structural assignment was confirmed by a single crystal X-ray diffraction analysis [11] which yielded the structure and absolute configuration for **11** as shown. Application of Brewster's rule [12] for the determination of the configuration of the C-7 hydroxyl also predicts the correct configuration. Thus the $\Delta[M]_D$ value ($=[M]_D^{\text{p-bromobenzoate}} - [M]_D^{\text{alcohol}}$) − 26.5° is consistent with the 7*R* configuration.

The occurrence of the sesquiterpene alcohols **3** and **4** is interesting in the light of growing speculation on the biosynthetic sequence leading to the tricyclo system of the zizaene sesquiterpenes [8]. The cyclization of β-acoradiene, the accepted precursor, can be considered, *a priori*, to occur either by attack of C-2 or C-3 on the carbonium ion **12** or its equivalent (Scheme 1). Tomita and Hirose [8] on the basis of the formation of *allo*-cedrol on formic acid treatment of β-acoradiene, and of prezizaene (**1**) and the alcohol (**4**), *inter alia*, from solvolysis of the *p*-bromobenzoate derivative of *allo*-cedrol, suggest that the cyclization of the carbonium ion occurs at C-3 to yield the secondary carbonium ion **13**. This can either be hydroxylated to give *allo*-cedrol or rearrange in two ways leading to the prezizane skeleton or to a new skeleton represented by **3**, whose occurrence they anticipated.

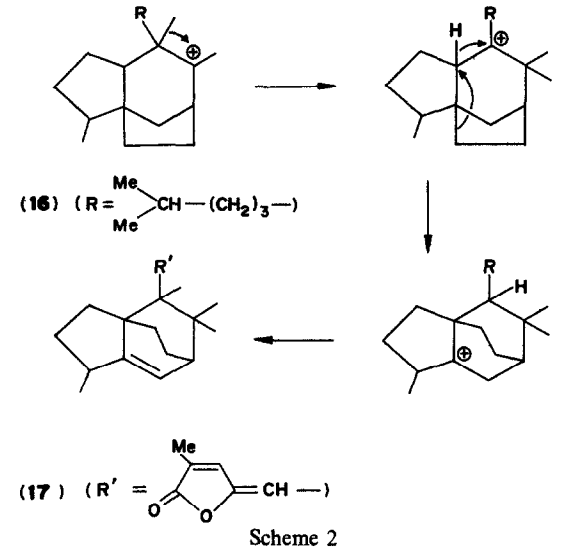
With respect to the biosynthesis however cyclization of **12** to C-2 cannot yet be excluded. Such cyclization would lead to the tertiary carbonium ion **14** which could rearrange to yield either **3** (path a) or *allo*-cedrol (path



Scheme 1

b). Rearrangement of **15** can also lead to the carbonium ion precursor of **4**. A decision on the sequence leading to prezizaene and zizaene and whether the *allo*-cedryl cation **13** or the secondary carbonium ion **15** is the intermediate in the formation of **4** must however await results from biosynthetic studies.

Of some interest is the similarity between the tricyclic sesquiterpenes of *E. georgei* and the novel diterpene eremolactone **17** from *E. fraserii* [4] and *E. freelingii* [5]. Indeed the skeleton of eremolactone can be considered to arise by a similar pathway as the alcohol **4** through the carbonium ion **16**, followed by further rearrangement as shown in Scheme 2.



Scheme 2

EXPERIMENTAL

General details have been described [13]. MS were measured by direct insertion with energies of 10–70 eV and temps from 60–180°. NMR spectra were measured at 60 MHz and 90 MHz for CCl_4 solns unless otherwise stated. Analytical GLC was carried out using 1.5 m × 1.5 mm metal columns containing 3% SE-30 on varaport 30 (100/120) with oven temp of 135°.

Isolation of the sesquiterpenes from E. georgei. Leaves and terminal branches (12 kg) of the plant, collected 74 miles east of Mt. Magnet, W.A. were extracted with Me_2CO. Solvent was removed and residue taken up into Et_2O and washed with 5% NaOH. The remaining neutral fraction (480 g) was adsorbed on a column of alumina (Act. I) and eluted with petrol–$CHCl_3$. Combined non-polar fractions (180 g) were then steam distilled to give an oil (48 g). A portion of this oil (11.0 g) was adsorbed on a column of neutral alumina (Act III, 500 g) and eluted with a polarity gradient of *n*-hexane–$CHCl_3$ in increments of 5%. The fractions collected were grouped on the basis of TLC and NMR comparisons to give four major components: (a) (−)-*prezizaene* (**1**), R_f (hexane) 0.90, $[\alpha]_D$ − 47° (*c*, 0.1). NMR: δ 0.87 (*d J* 7Hz, 12-H_3), 1.05, 1.08 (*s*, 13-, 14-H_3) 2.78 (apparent triplet, 8-H) and 4.63 (*br s*, $W_{1/2}$ 3Hz, 15-H_2). MS *m/e* (%): 204 (M^+, 30), 189(30), 175(20), 161(30), 133(100); (b) (−)-7-*oxo*-2,6,6,8-*tetramethyltricyclo*[6.2.1.$0^{1,5}$]*undecane* (2), R_f (hexane) 0.85. IR ν_{max} cm^{-1} 1700. NMR ($CDCl_3$, 90 MHz): δ 0.92 (*d J* 7Hz, 12-H_3), 1.12 (6H), 1.16 (13-, 14-, 15-H_3). MS *m/e* (%): 220 (M^+, 55), 205(10), 192(60), 177(15), 161(10), 121(100), 108(80), 147(50); (c) (−)-7β-*hydroxy*-2,6,6,8-*tetramethyltricyclo*[6.2.1.$0^{1,5}$]*undecane* (**3**), mp 39-42°, R_f (hexane) 0.80, $[\alpha]_D$ − 32° (*c*, 1.1) $[M]_D$ − 71°. (M^+ 222.19837, $C_{15}H_{26}O$ requires 222.19835). IR ν_{max} cm^{-1}: 3640. NMR ($CDCl_3$, 90 MHz): δ 0.86 (*d*, *J* 7Hz, 12-H_3), 0.92, 1.03, 1.07 (*s*, 13-, 14-, 15-H_3), 3.18 (*br s*, $W_{1/2}$ 2.5 Hz, 7α-H); (C_5H_5N): δ 0.86 (12-H_3), 1.09, 1.13, 1.19 (13-, 14-, 15-H_3) 3.25 (7α-H). MS *m/e* (%): 222(50), 207(20), 191(60), 135(40), 121(100); (d) 7β-*hydroxy*-(−)-*prezizaene* (**4**), R_f (hexane) 0.75, bp 100° (0.1 mm), $[\alpha]_D$ −48.3° (*c* 0.1). (Found: C, 80.77; H, 11.80. $C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%). IR ν_{max} cm^{-1}: 3620. NMR (90 MHz): for $CDCl_3$ soln see text, (C_5D_5N): δ 0.89 (12-H_3), 1.00, 1.23, 1.39 (13-, 14-, 15-H_3). MS *m/e* (%): 222 (M^+, 15), 204(10), 179(80), 161(20), 137(40), 135(40), 109(100).

Dehydration of 7β-*hydroxy*-(−)-*prezizane* (**4**). The alcohol (**4**; 0.8 g) in C_5H_5N (20 ml) was treated with $POCl_3$ (3 ml) and the mixture was left at room temp. for 30 hr. The product (0.75 g) was adsorbed on alumina (neutral, Act II, 10 g). Elution with petrol and $CHCl_3$ gave two fractions, the more polar starting material (**4**, 300 mg) and a colourless oil (400 mg), $[\alpha]_D$ − 38°, whose spectral characteristics were comparable to those of prezizaene (**1**). Distillation of the oil gave (−)-*prezizaene* (**1**), bp 80° (0.1 mm), $[\alpha]_D$ − 54° (*c*, 0.06). (Found: C, 88.51; H, 11.80. $C_{15}H_{24}$ requires: C, 88.60, H, 11.84%). MS *m/e* (%): 204 (M^+, 30), 189(30), 175(20), 161(30), 133(100). The NMR was identical to that published for (+)-prezizaene. The alkene was shown to be identical with the sample of (−)-prezizaene described above.

OsO_4 oxidation of the alkene fraction from the dehydration of **4**. The hydrocarbon fraction (400 mg), from the dehydration of (**4**), in C_5H_5N (10 ml) was stirred with OsO_4 (500 mg) overnight. A soln of $NaHSO_3$ (0.8 g) in H_2O (20 ml) was added and stirring continued for 2 hr. Recovery of the product yielded an oil (450 mg) which was separated by PLC to give two compounds. The less polar component (380 mg) crystallized from Et_2O–pentane as needles of 7α,15-*dihydroxy*-(−)-*prezizane* (**5**) mp 93–4°, $[\alpha]_D$ − 32° (*c*, 0.01) (Found: C, 75.15; H, 11.02, $C_{15}H_{26}O_2$ requires: C, 75.58; H, 11.00%). IR ν_{max} cm^{-1}: 3550. NMR: δ 0.86 0.95 (*s*, 13-, 14-H_3) and 3.52 (*s*, 15-H_2). MS *m/e* (%): 238 (M^+ 10), 207(40), 189(100), 143(100). The more polar component (60 mg) crystaliized from Et_2O–*n*-pentane as needles of 5β,6β-*dihydroxy*-(−)-*zizane* (**7**), mp 146–8°, $[\alpha]_D$ + 0.4° (*c*, 0.02) (Found: C, 75.65: H, 10.78. $C_{15}H_{26}O_2$ requires C, 75.78: H, 11.00%). IR ν_{max} cm^{-1}: 3640. NMR ($CHCl_3$): δ 0.92 (*d*, *J* 7Hz, 12-H_3), 1.00, 1.05 and 1.27 (*s*, 13-, 14-, 15-H_3); (C_5H_5N): 0.93 (12-H_3), 1.03 (6H), 1.52 (13-, 14-, 15-H_3). MS *m/e* (%): 238 (M^+, 5), 220(10), 205(15), 189(30), 177(50), 133(60), 121(5), 109(80), 107(80), 95(100). Similar treatment of a sample of prezizaene obtained from the

steam volatile fraction also gave two diols which were shown to be identical to **5** and **7**.

$NaIO_4$ oxidation of the diols (**5**) *and* (**7**). The diol (**5**, 380 mg) in dioxan (30 ml) was treated with a soln of $NaIO_4$ (400 mg in 10 ml of H_2O) and the mixture was stirred for 2 hr. Recovery of the product gave 7-*oxo*-15-*nor*-(−)-*prezizane* (**6**, 300 mg) as an oil, bp 70° (0.1 mm) (Found: C, 81.81; H, 10.84. $C_{14}H_{22}O$ requires: C, 81.50; H, 10.75%). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1705. NMR: δ 0.93 (*d*, *J* 7Hz, 12-H_3) and 1.03 (*s*, 13-, 14-H_3). MS *m/e* (%): 206 (M^+, 100), 191(80), 163(30), 150(20), 135(60), 107(100). The diol (**7**, 60 mg) was treated in a similar way to yield the diketone (**8**, 50 mg). IR ν_{max} cm^{-1}: 1730, 1705. NMR (90 MHz, $CDCl_3$): δ 0.95 (*d*, *J* 7Hz, 12-H_3), 0.98, 1.08 (*s*, 14-, 15-H_3) and 2.15 (*s*, 13-H_3). MS *m/e* (%): 236 (M^+, 10), 234(6), 203(11), 193(23), 175(70), 125(45), 95(95), 91(100).

Treatment of **6** *with MeLi.* The nor-ketone (**6**, 300 mg) in Et_2O was treated with a soln of MeLi in Et_2O (0.1 M) for 1 hr. Recovery of the product gave an oil (250 mg) which was homogeneous on TLC. Distillation of this oil gave 7β-hydroxy-(−)-prezizane, bp 100° (0.1 mm), $[\alpha]_D$ − 43.9°, identical with the naturally occurring compound.

Interrelationship of **2** *and* **3**. The alcohol (**3**, 100 mg) in ME_2CO was titrated with Jones reagent. Recovery of the product in the usual way afforded a compound identical with the ketone **2**. Treatment of either ketones (90 mg) in EtOH (30 ml) with $NaBH_4$ (920 mg) for 12 hr yielded the same alcohol identical with the naturally occurring alcohol (**3**).

p-*Bromobenzoate derivative of* **3**. The alcohol (**3**, 200 mg) in C_5H_5N (50 ml) was treated with *p*-bromobenzoyl chloride (500 mg) for 24 hr. The product recovered (350 mg) crystallized from Me_2CO–*n*-pentane as prisms of the p-*bromobenzoate* (**11**), mp 122°, $[\alpha]_D$ − 11° (*c*, 0.5) $[M]_D$ −44.6° (Found: C, 65.33; H, 7.26. $C_{22}H_{29}O_2Br$ requires: C, 65.18, H, 7.21%). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720. NMR: δ 0.93, 0.97, 1.02 (s, 13-, 14-, 15-H_3), 4.95 (*br s*, 7-H) and 7.92, 7.54, (AA'BB' system, aromatic H). MS *m/e* (%): 406, 404 (M^+, 10), 221(10), 204(100), 185(50), 183(50), 121(60).

REFERENCES

1. Hegarty, B. F., Kelly, J. R., Parks, R. J. and Sutherland, M. D. (1970) *Australian J. Chem.* **23,** 107.
2. Massy-Westropp, R. A. and Reynolds, G. D. (1966) *Australian J. Chem.* **19,** 303.
3. Chetty, G. L., Zalkow, L. H. and Massy-Westropp, R. A. (1969) *Tetrahedron Letters* 307.
4. Jefferies, P. R., Knox, J. R. and Middleton, E. J. (1962) *Australian J. Chem.* **15,** 532.
5. Birch, A. J., Subba Rao, G. S. R. and Turnbull J. P. (1966) *Tetrahedron Letters* 4749.
6. Ghisalberti, E. L., Jefferies, P. R. and Sheppard, P. (1975) *Tetrahedron Letters* 1775.
7. Andersen, N. H. and Falcone, M. S. (1971) *Chem. Ind.* No. 2, 61.
8. Tomita, B. and Hirose, Y. (1973) *Phytochemistry* **12,** 1409 (and references therein).
9. Andersen, N. H., Smith, S. and Ohita, Y. (1973) *Chem. Commun.* 447.
10. Kristiansen, P. and Ledaal, T. (1971) *Tetrahedron Letters* 2817.
11. Ghisalberti, E. L., White, A. H. and Willis, A. C. (1976) *J. Chem. Soc.* (*Perkin II trans*) (in press).
12. Brewster, J. H. (1961) *Tetrahedron* **13,** 106.
13. Ghisalberti, E. L., Jefferies, P. R., Payne, T. G. and Worth, G. K. (1973) *Tetrahedron* **29,** 403.