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Phytochemistry, Vol. 27, No. 9, pp. 2994–2996, 1988.
Printed in Great Britain.

0031–9422/88 $3.00+0.00

AZULENES, LABDANES AND A FUROCURCUMENE FROM *IXIOLAENA LEPTOLEPIS*

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(*Received* 9 *December* 1987)

Key Word Index—*Ixiolaena leptolepis*; Compositae; diterpenes; labdanes; sesquiterpenes; furocurcumene; azulenes.

Abstract—The extract of the aerial parts of *Ixiolaena leptolepis* yielded, in addition to widespread compounds, manool, and four new labdane derivatives, three azulenes and a furocurcumene derivative. The structures were elucidated by high field ^{1}H NMR techniques.

INTRODUCTION

The small Australian genus *Ixiolaena* (Compositae, tribe Inuleae) is placed in the subtribe Gnaphaliinae in the *Helichrysum* group [1]. But the exclusively dysploid numbers of this genus are unusual and some other characters approach the *Helipterum* group. As the chemistry of the large genus *Helichrysum* has been studied in detail it was interesting to investigate *Ixiolaena leptolepis* (DC) Benth. as so far only one species has been studied for fatty acids [2].

RESULTS AND DISCUSSION

The aerial parts of *Ixiolaena leptolepis* afforded, in addition to tridecapentaynene, caryophyllen-1β,10α-epoxide and ferulic acid, a new type of bisabolene derivative, the furane **4**, the labdane derivatives (−)-manool and **5**–**9** as well as the azulenes **1** [3], **2** [4] and **3**.

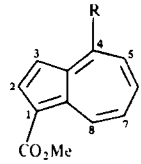
The structure of **3** clearly followed from the spectroscopic data. The molecular formula ($C_{14}H_{12}O_4$) and the ^{1}H NMR spectrum indicated that a dicarbomethoxy derivative of a highly unsaturated norsesquiterpene was present, while the colour required a substituted azulene. Spin decoupling showed that the carbomethoxy groups must be placed at C-1 and C-4. Accordingly, the data were close to those of the corresponding aldehyde, only some chemical shifts being slightly different. In the case of the aldehyde group at C-4 (**2**) the H-3 signal was shifted down field by 0.53 ppm. The absorption of visible light also differed by 6 nm.

The molecular formula of **4** ($C_{15}H_{16}O_2$) indicated the presence of a highly unsaturated sesquiterpene. The ^{1}H NMR spectrum showed an aldehyde singlet (δ 9.82) and a pair of broadened singlets (δ 6.28 and 7.91) which could be assigned to furane protons. A methyl singlet at δ 2.31, a pair of broadened two proton doublets at δ 7.06 and 7.09 and the remaining signals required a toluene derivative with a substituent in the *para*-position, and a CH(Me)CH_2 group. Thus all data agreed with the presence of a furocurcumene derivative. This was supported by spin decoupling which established the proposed assignments. Compound **4** has been named furoixiolal.

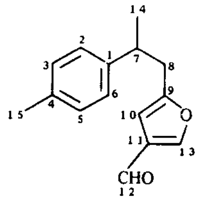
The ^{1}H NMR spectra of **5**–**8** (Table 1) clearly showed that we were dealing with *ent*-labda-7,14-diene-13-ol derivatives. Spin decoupling allowed the assignment of the position of additional functions. In the spectrum of **5** a 2β-hydroxy group showed a signal at δ 3.85 with couplings indicating an equatorial hydroxy group. In the spectrum of **6** this signal was shifted to δ 5.04. Typical signals of a senecioate indicated the presence of the corresponding 2β-senecioyloxy-*ent*-labdane. The spectra of **5** and **6** further showed by the fact that the signals for H-14 and H-16 were doubled that pairs of 13-*epi* compounds were present. The ^{1}H NMR spectrum of **7** required a further hydroxy group. Spin decoupling showed that a hydroxy group was at C-1 or C-3. NOE difference spectroscopy clearly indicated a 3β-hydroxy group which was supported by the observed small vicinal coupling between H-3 and H-2. The NOE between H-20 and H-2 allowed the assignment of the methyl singlets. Furthermore, a NOE between H-19 and H-3 established the C-3 position of the new hydroxy group. Also, clear effect was observed between H-18, H-3 and H-5.

The ^{1}H NMR spectrum of **8** (Table 1) showed that again a derivative of **5** had to be proposed. The spectra mainly differed by the replacement of one methyl singlet by a pair of doublets at δ 3.81 and 3.71. Accordingly, a primary hydroxy group was most likely located at C-20. This was established by the observed NOEs. Thus clear effects were observed between H-19, H-2 and H-20 as well as between H-18, H-6, H-5, H-3α and H-3β.

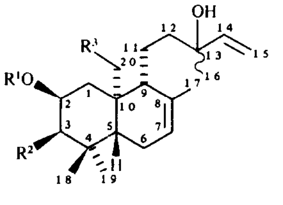
The labdanes **9a** and **9b** could not be separated. The broadened singlets at δ8.70 and 7.77 indicated the presence of hydroperoxides. Most signals were close to those in the spectrum of compound **5**. However, in one isomer an olefinic methyl signal was replaced by a pair of broadened singlets (δ 5.21 and 4.85). In the second one a 8,9-double bond must be proposed. (Table 1). Furthermore, two new low field signals were visible, a broadened doublet at δ 4.24 and a double doublet at δ 4.51, respectively. Spin decoupling allowed the assignment of nearly all signals of the two sets. All data only agreed with the presence of the proposed hydroperoxides **9a** and **9b** which most likely were formed by reaction of compound **5** with singlet oxygen. As the presence of *ent*-labdanes in the related genus *Rutidosis* has been established [5] it is probable that *ent*-labdanes are also present in this case, especially as (−)-manool was isolated.



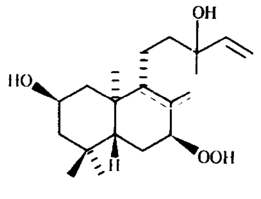
1 R = Me
2 R = CHO
3 R = CO$_2$Me



4



	5	**6**	**7**	**8**
R^1	H	Sen	H	H
R^2	H	H	OH	H
R^3	H	H	H	OH



9a Δ^8
9b $\Delta^{8(17)}$

The isolation of the azulenes **1**–**3** may be an indication of a relationship between *Ixioaena* and *Helichrysum*, so far the only genus from which this type of azulene has been reported [3, 4]. The isolation of *ent*-labdanes is less characteristic as these diterpenes are reported from many genera of the subfamily Asteroideae. They have been isolated from six *Helichrysum* species [6–8], and *Achyrocline* [9], *Denekia* [3], *Gnaphalium* [10] and *Rutidosis* species [5] which are all placed in the same subtribe as *Ixiolaena* [1]. Further results are needed to establish a clearer understanding of relationship.

Table 1. ^{1}H NMR spectral data of compounds **5**–**9** (400 MHz, CDCl$_3$, δ-values)

H	**5**	**6**	**7**	**8**	**9a**†	**9b**‡
1α	*	*	1.84 *dd*	2.47 *dd*	2.16 *ddd*	2.03 *br d*
1β	*	*	1.44 *dd*	0.86 *dd*	1.09 *dd*	1.00 *dd*
2α	3.85 *tt*	5.04 *tt*	4.01 *ddd*	3.87 *tt*	3.94 *tt*	3.87 *tt*
3α	*	*	3.45 *d*	1.73 *dd*	1.82 *ddd*	1.76 *ddd*
3β	*	*	—	1.17 *dd*	1.16 *dd*	1.14 *dd*
5	*	*	1.52 *dd*	1.32 *dd*	1.39 *br d*	1.44 *dd*
7	5.38 *br s*	5.39 *br s*	5.39 *br s*	5.47 *br s*	4.24 *br d*	4.51 *dd*
14	5.92, 5.91 *dd*	5.92, 5.90 *dd*	5.91 *dd*	5.91 *dd*	5.91 *dd*	5.91 *dd*
15t	5.21 *dd*	5.21 *dd*	5.21 *dd*	5.22 *dd*	5.22 *dd*	5.26 *dd*
15c	5.06 *dd*	5.07 *dd*	5.07 *dd*	5.07 *dd*	5.09 *dd*	5.13 *dd*
16	1.28, 1.285 *s*	1.29, 1.285 *s*	1.29 *s*	1.30 *s*	1.29 *s*	1.28 *s*
17	1.67 *br s*	1.68 *br s*	1.66 *br s*	1.73 *br s*	1.70 *br s*	5.21 *br s* 4.85 *br s*
18	0.91 *s*	0.99 *s*	1.00 *s*	0.98 *s*	0.95 *s*	0.91 *s*
19	0.91 *s*	0.92 *s*	0.91 *s*	0.94 *s*	0.91 *s*	0.81 *s*
20	0.79 *s*	0.86 *s*	0.80 *s*	3.81 *d* 3.71 *d*	1.01 *s*	0.68 *s*

*Obscured; † H-6β 2.23 *br d*, H-6α 1.48 *ddd*, OOH 7.77 *br s*;‡ H-6β 1.98 *ddd*, H-6α 1.54 *ddd*, OOH 8.70 *br s*.

J[Hz]: 14,15t = 17.5; 14,15c = 11; 15t,15c = 1; compounds **5** and **6**: 1β,2 = 2,3β = 12; 1α,2 = 2,3α = 4; compound **7**: 1α,1β = 1β,2 = 12.5; 1α,2 = 5; 2,3 = 2.5; 5,6β = 5; 5,6α = 10; compound **8**: 1α,1β = 1β,2 = 2,3β = 3α,3β = 12; 1α,2 = 2,3α = 4; 5,6β = 5.5; 5,6α = 12; compounds **9a** and **9b**: 1α,1β = 1β,2 = 2,3β = 3α,3β = 12; 1α,2 = 2,3α = 4; 1α,3α = 2; 5,6α = 6α,6β = 14; (compound **9a**: 1α,3α = 1α,7α ~ 0.5; 6α,7 = 3; compound **9b**: 6β,7 = 2.5; 6α,7 = 3.5).

EXPERIMENTAL

The air-dried plant material was extracted and worked-up as reported elsewhere [11]. The extract of the aerial parts of *Ixiolaena leptolepis* (430 g, collected in SE Australia in August 1986, voucher RMK 9615, deposited in the US National Herbarium, Washington, U.S.A.) afforded by CC four crude fractions: Fr. 1: petrol; Fr. 2: Et_2O–petrol (1:3); Fr. 3: Et_2O–petrol (1:1) and Fr. 4: Et_2O–MeOH (9:1). TLC of fraction 1 gave 6 mg tridecapentaynene while fraction 2 gave 5 mg caryophyllene-$1\beta,10\alpha$-epoxide, 3 mg **1** and by repeated TLC (Et_2O–petrol, 1:9, two developments) 20 mg **4** (R_f 0.40). TLC of fraction 3 gave 6 mg (−)-manool, 11 mg ferulic acid, 6 mg **2** and a mixture which gave by HPLC (MeOH–H_2O, 9:1, RP 8, *ca* 100 bar) 5 mg **6** (R_t 17.4 min) and 8 mg **3** (R_t 7.0 min). TLC of fraction 4 (Et_2O–petrol, 1:1, three developments) gave 60 mg **5** (R_f 0.50) and two mixtures (4/1 and 4/2). HPLC of 4/1 (MeOH–H_2O, 3:1) afforded 4 mg **9a**/**9b** (R_t 8.2 min) and HPLC of 4/2 (MeOH–H_2O, 7:3) gave 60 mg **7** (R_t 28.7 min) and 40 mg **8** (R_t 22.2 min).

1,4-*Dicarbomethoxyazulene* (**3**). Violet coloured oil; UV $\lambda_{max}^{Et_2O}$ 556 nm; MS *m/z* (rel. int.): 244.074 $[M]^+$ (76) (calc. for $C_{14}H_{12}O_4$: 244.074), 213 $[M-OMe]^+$ (100), 183 $[213-CH_2O]^+$ (9), 170 (9), 135 (20), 126 (21); ^1H NMR ($CDCl_3$): δ8.47 (*d*, H-2), 7.64 (*d*, H-3), 7.75 (*br d*, H-5), 7.84 (*br dd*, H-6), 7.63 (*br dd*, H-7), 9.77 (*d*, H-10), 3.96 and 4.08 (OMe); (*J* [Hz]: 2,3 = 4.5; 5,6 = 6,7 = 7,8 = 10).

Furoixiolal (**4**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2720, 1690 (CHO); MS *m/z* (rel. int.): 228.115 $[M]^+$ (2) (calc. for $C_{15}H_{16}O_2$: 228.115), 119 [dimethyltropylium]$^+$ (100); ^1H NMR: δ7.06 (*br d*, H-2, H-6), 7.09 (*br d*, H-3, H-5), 3.10 (*tq*, H-7), 2.92 and 2.83 (*dd*, H-8), 6.28 (*br s*, H-10), 7.91 (*br s*, H-13), 9.82 (*s*, H-12), 1.26 (*d*, H-14), 2.31 (*s*, H-15); (*J* [Hz]: 2,3 = 8; 7,8 = 7,8′ = 7,14 = 7; 8,8′ = 15).

2β,13-*Dihydroxy*-ent-*labda*-7,14-*diene* (**5**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3590 (OH), 925 ($CH{=}CH_2$); CIMS *m/z* (rel. int.): 289 $[M+1-H_2O]^+$ (52), 271 $[289-H_2O]^+$ (100).

13-*Hydroxy*-2β-*senecioyloxy*-ent-*labda*-7,14-*diene* (**6**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1720 ($C{=}CCO_2R$); CIMS *m/z* (rel. int.): 371 $[M+1-H_2O]^+$ (5), 289 $[M+1-SenOH]^+$ (6), 271 $[371-SenOH]^+$ (100).

$2\beta,3\beta$,13-*Trihydroxy*-ent-*labda*-7,14-*diene* (**7**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH); CIMS *m/z* (rel. int.): 305 $[M-H_2O+1]^+$ (56), 287 $[305-H_2O]^+$ (100), 269 $[287-H_2O]^+$ (20), 203 $[C_{15}H_{23}]^+$ (16).

2β,13,20-*Trihydroxy*-ent-*labda*-7,14-*diene* (**8**). Colourless oil; IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH); CIMS *m/z* (rel. int.): 305 $[M-H_2O+1]^+$ (100), 287 $[305-H_2O]^+$ (80), 269 $[287-H_2O]^+$ (25).

2β,13-*Dihydroxy*-7β-*hydroperoxylabda*-8 [*and* 8(17)],14-*diene* (**9a**/**9b**). Colourless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (OH); CIMS *m/z* (rel. int.): 321 $[M-H_2O+1]^+$ (49), 303 (100), 287 $[321-H_2O_2]^+$ (75), 285 (76), 269 (81).

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