Phytochemistry, Vol. 21, No. 7, pp. 1659–1661, 1982.
Printed in Great Britain.

0031–9422/82/071659–03$03.00/0

CARYOPHYLLANE DERIVATIVES FROM *PULICARIA SCABRA**

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(*Received* 16 *October* 1981)

Key Word Index—*Pulicaria scabra*; Compositae; Inuleae; sesquiterpenes; caryophyllane derivatives; sesquiterpenes etherified and esterified with sesquiterpenes.

Abstract—The investigation of *Pulicaria scabra* afforded in addition to known compounds seven new caryophyllane derivatives, three of them etherified with a caryophyllane derivative and one esterified with a caryophyllane derived alcohol. The structures were elucidated by high field ^{1}H NMR spectroscopy. The chemistry of this species is similar to that of *P. dysenterica* but differs from that of the other genera of the subtribe Inulinae.

INTRODUCTION

So far only a few species of the genus *Pulicaria* (Compositae, tribe Inuleae), which is placed in the subtribe Inulinae [1], have been investigated chemically. In addition to widespread polyacetylenes [2], thymol derivatives [2] and flavones [3], we have isolated recently from one species unusual caryophyllane derivatives [4]. We have now studied the consitituents of *Pulicaria scabra*. Again several caryophyllane derivatives were present and their structures are discussed in this paper.

RESULTS AND DISCUSSION

The aerial parts of *Pulicaria scabra* (Thumb.) Druce, which contained a flavonoid sulphate [3], afforded the thymol derivative **1**, the caryophyllane derivative **4** and seven other related compounds, which have not been isolated previously, these were the sesquiterpenes **3**, **5** and **6** as well as four more complicated compounds, the ether-linked caryophyllanes **7–9** and the ester **10**. Compound **6** was the 5,6-*cis*-isomer of **4** as shown in the ^{1}H NMR spectrum (Table 1) by the upfield shift of the H-5 signal. Also several other signals were shifted slightly, but the general pattern of the signals was nearly the same. The ^{1}H NMR spectrum of **3** (Table 1) showed that it was the corresponding alcohol of the acetate **4** as was deduced from the upfield shift of the H-14 signals, while the spectral data of **5** again indicated by the upfield shift of H-5 that this compound was the 5,6-*cis*-isomer of **3** (Table 1). In addition to this shift difference the couplings of H-8 were typically different in the *cis*- and *trans*-isomers. Also the H-15 signals were at slightly higher fields in the *cis*-series. The isomeric compounds **7–9** all showed a clear [M]$^+$ peak leading to the molecular formula $C_{30}H_{42}O_3$ and the fragmentation patterns were nearly identical for compounds **7–9**. Prominent ions were $C_{15}H_{21}O_2$ and $C_{15}H_{21}O$. The ^{1}H NMR spectra (Table 2) were in part very similar to those of **3** and **5**, respectively, indicating that one part of the obviously dimeric sesquiterpenes should be identical with these caryophyllane derivatives. The only possible linkage to the second moiety therefore was the oxygen function at C-14. The second moiety of **7** and **8** was again identical and the ^{1}H NMR signals were in part similar to those of 5, 13-dihydroxy-5, 6-dihydro-6, 14-dehydrocaryophyllen-7-one [4] although the oxygen function at C-13 was missing. Accordingly, the presence of a methylene ketone was indicated by two downfield olefinic signals which showed an allylic coupling with the proton under the oxygen function (H-5′). A pair of double doublets around δ 2.60 were assigned to the protons α to the keto group. Spin decoupling showed that they had to be assigned to H-8′ though the protons H-1′, H-9′ and H-10′ were overlapping multiplets. Compounds **7** and **8** differed only in the stereochemistry of the 5, 6-double bond, its assignment caused no problems as the chemical shifts of H-5 differed drastically. These results required an ether linkage between **3** and **5** respectively and 5-hydroxy-5, 6-dihydro-6, 14-dehydrocaryophyllen-7-one. The prominent fragments in the mass spectra of **7** and **8** could be explained if the ether linkage was broken first to produce two different allyl cations, *m/z* 233 and 217. The ^{1}H NMR spectrum of **9** differed from that of **8** mainly in the chemical shifts of some protons of the second moiety of the ether. In particular, the shifts and couplings of H-5′ and H-8′ were altered. This could be explained if a different stereochemistry at C-5 was proposed. Models showed that the system did not allow a definite proof. The molecular formula of **10** showed that this compound had one more oxygen ($C_{30}H_{42}O_4$), while the ^{1}H NMR spectrum (Table 2) showed that the second moiety of the molecule was the same as in **7–9**. However, the H-5′ signal was shifted downfield indicating that the ether linkage was replaced by an ester function.

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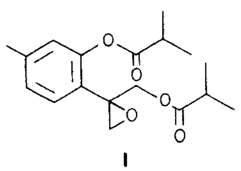
*Part 430 in the series "Naturally Occurring Terpene Derivatives". For Part 429, see Bohlmann, F. Singh, P. and Jakupovic, J. (1982) *Phytochemistry* 21 (in press).



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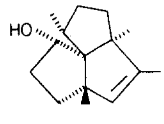

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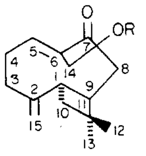
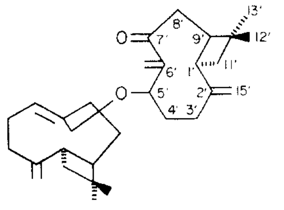


3 R=H
4 R=Ac
5 R=H; 5,6 *cis*
6 R=Ac; 5,6 *cis*



7
8 5,6 *cis*
9 5,6 *cis* 5'β-H

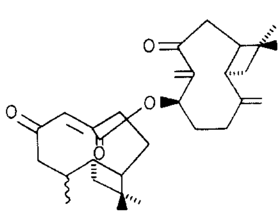


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Table 1. ^{1}H NMR spectral data of compounds **3**, **5** and **6** (400 MHz, CDCl$_3$, TMS as int. standard)

	3	**5**	**6**
H-1	2.38 *ddd br*	2.51 *ddd br*	2.46 *ddd br*
H-3	2.66 *dd br* 2.27 *ddd br*	2.64 *m* 2.39 *m*	2.55–2.35 *m*
H-4	2.55 *m*	2.23 *ddd br*	
H-5	6.40 *dd br*	5.91 *dd br*	5.85 *dd br*
H-8	2.92 *dd* 2.32 *dd*	2.86 *dd* 2.60 *dd*	2.77 *dd* 2.60 *dd*
H-9	1.73 *dd br*	1.75 *dd br*	1.85 *m*
H-10	1.85 *dd* 1.56 *dd*	1.87 *dd* 1.67 *dd*	1.89 *dd* 1.69 *dd*
H-12	1.02 *s*	1.06 *s*	1.05 *s*
H-13		1.01 *s*	1.02 *s*
H-14	4.23 *d br*	4.15 *s br*	4.75 *dt*
H-14′	4.10 *d*		4.54 *d*
H-15	5.04 *s br*	4.89 *s br*	4.91 *s br*
H-15′	4.95 *s br*	4.85 *s br*	4.86 *s br*
OAc	—	—	2.02 *s*

J(Hz): Compound **3**: 1, 9 = 1, 10 = 1, 10′ = 9; 3, 3′ = 12; 3, 4 = 6; 3, 4′ = 1.5; 3′, 4 = 8; 3′, 4′ = 10; 4, 5 = 12; 4′, 5 = 4; 8, 8′ = 14; 8, 9 = 12; 8′, 9 = 1.5; 14, 14′ = 12; compound **5** and **6**: 1, 9 = 10; 1, 10 = 10; 1, 10′ = 7.5; 10, 10′ = 11; 4, 5 = 12.5; 4′, 5 = 5; 8, 8′ = 17.5; 8, 9 = 10; 8, 9′ = 1.5; (compound **6**: 4, 14 = 1; 14, 14′ = 12).

Accordingly, the signals of the first moiety were changed more drastically. A singlet at δ 6.30 was that of H-5. The absence of the typical H-8 signal further showed that the 7-keto group was most probably located at C-4. Furthermore, the signals of the C-15 methylene protons were missing and replaced by an additional methyl signal (1.36 *d*) indicating a hydrogenated 2, 15-bond. Though some signals were overlapping multiplets, spin decoupling studies supported the proposed structure, which was reasonable from biogenetic considerations. The stereochemistry at C-2 could not be assigned. We have named compound **7** puliscarbrin and **10** 4,14-di-oxy-2,15-dihydropuliscabrin. The roots afforded tridecapentaynene, stigmasterol and the rare seseqiterpene alcohol **2**, which had previously been reported from *Pulicaria dysentrica* [4]. The isolation of complicated caryophyllane derivatives from a *Pulicaria* species may show that these compounds could be of chemotaxonomic importance. Sesquiterpene lactones were reported [5] from *P. crispa* Sd. Bip. (= *Francoeuria crispa* Cass.). However, more species need investigation to obtain a clear picture of this genus and its relationship to other genera in the tribe Inuleae.

EXPERIMENTAL

The air-dried plant material, collected in Transvaal (voucher 81/27, deposited in the Botanic Research Institute, Pretoria) was extracted with Et$_2$O–petrol (1:2) and the resulting extracts were separated by CC (Si gel) and repeated TLC (Si gel). Known compounds were identified by comparing the ^{1}H NMR spectra with those of authentic material. The aerial parts (90 g) gave 5 mg **1**, 20 mg **3** (Et$_2$O–petrol, 7:3), 18 mg **4**, 20 mg **5** (same solvent), 4 mg **6** (Et$_2$O–petrol, 1:1), 8 mg **7** (Et$_2$O–petrol, 1:4), 5 mg **8** (same solvent), 2 mg **9** (same solvent) and 2 mg **10** (Et$_2$O–CH$_2$Cl$_2$–C$_6$H$_6$, 1:5:5), while the roots (15 g) gave 1 mg tridecapentaynene, 5 mg stigmasterol and 20 mg **2**.

14-*Hydroxy-caryophyllen-7-one* (**3**). Colourless gum, IR $\nu_{max}^{CCl_4}$, cm^{-1}; 3520 (OH), 1670 (C=CCO), 3070, 900 (C=CH$_2$); MS *m*/*z* (rel. int.): 234.161 [M]$^+$ (2) (C$_{15}$H$_{22}$O$_2$), 219 [M − Me]$^+$ (4), 216 [M − H$_2$O]$^+$ (4), 147 [C$_{10}$H$_{11}$O]$^+$ (61), 93 [147 − CO, C$_2$H$_2$]$^+$ (100), 69 [C$_5$H$_9$]$^+$ (53).

$$[\alpha]^{\lambda}_{24°} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-272 \quad -285 \quad -328 \quad -580} \quad (c = 0.9,\ \text{CHCl}_3).$$

14-*Hydroxy*-5,6-cis-*caryophyllen-7-one* (**5**). Colourless gum, IR $\nu_{max}^{CCl_4}$, cm^{-1}: 3620 (OH), 1660 (C=CC=O), 3070, 905 (C=CH$_2$); MS *m*/*z* (rel. int.): 234.162 [M]$^+$ (2) (C$_{15}$H$_{22}$O$_2$), 216 [M − H$_2$O]$^+$ (7), 165 [M − C$_5$H$_9$]$^+$ (38), 147 [C$_{10}$H$_{11}$O]$^+$ (61), 93 [C$_7$H$_9$]$^+$ (100), 69 [C$_5$H$_9$]$^+$ (70).

$$[\alpha]^{\lambda}_{24°} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-196 \quad -206 \quad -234 \quad -381} \quad (c = 0.5,\ \text{CHCl}_3).$$

14-*Acetoxy*-5,6-cis-*caryophyllen-7-one* (**6**). Colourless gum, IR $\nu_{max}^{CCl_4}$, cm^{-1}: 1740 (OAc), 1680 (C=CC=O); MS *m*/*z* (rel. int.): 216.151 [M − HOAc]$^+$ (12) (C$_{15}$H$_{20}$O]$^+$ 147 [C$_{10}$H$_{11}$O]$^+$ (60), 93 [C$_7$H$_9$]$^+$ (90), 69 [C$_5$H$_9$]$^+$ (100).

Puliscabrin (**7**). Colourless gum, IR $\nu_{max}^{CCl_4}$, cm^{-1}: 1690, 1640 (C=CC=O), 3080, 900 (C=CH$_2$); MS *m*/*z* (rel. int.): 450.313 [M]$^+$ (6) (C$_{30}$H$_{42}$O$_3$), 432 [M − H$_2$O]$^+$ (0.5), 442 [M − CO]$^+$ (1.5), 233 [C$_{15}$H$_{21}$O$_2$]$^+$ (31), 217 [C$_{15}$H$_{21}$O]$^+$ (34), 147 [C$_{10}$H$_{11}$O]$^+$ (59), 93 [C$_7$H$_9$]$^+$ (62), 91 [C$_7$H$_7$]$^+$ (68), 69 [C$_5$H$_9$]$^+$ (100).

$$[\alpha]^{\lambda}_{24°} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-74 \quad -78 \quad -91 \quad -167} (c = 0.8,\ \text{CHCl}_3).$$

5,6-cis-*Puliscarbrin* (**8**). Colourless gum, IR $\nu_{max}^{CCl_4}$, cm^{-1}: 1680, 1635 (C=C–C=O), 3080, 900 (C=CH$_2$); MS *m*/*z* (rel.

Table 2. ^{1}H NMR spectral data of compounds **7–10** (400 MHz, $CDCl_3$, TMS as int. standard)

	7	**8**	**9**	**10***
H-1	2.41 *ddd br*	2.46 *ddd br*	2.44 *ddd br*	2.91 *ddd br*
H-5	6.45 *dd br*	5.67 *dd br*	5.71 *dd br*	6.30 *s*
H-8	2.93 *dd*	2.75 *dd*	2.75 *dd*	
H-8′	2.33 *dd*	2.60 *dd*	2.55 *dd*	
H-9	1.75 *dd br*	1.90 *m*	2.0–1.7 *m*	1.93 *m*
H-10	1.83 *dd*	1.90 *m*		2.0 *m*
H-10′	1.59 *dd*	1.69 *dd*		1.71 *dd*
H-12	1.02 *s*	1.05 *s*	1.04 *s*	1.07 *s*
H-13	1.01 *s*	1.01 *s*	1.01 *s*	
H-14	4.03 *d*	4.06 *d br*	4.26 *d br*	—
H-14′	3.99 *d*	3.97 *d br*	3.69 *d*	—
H-15	5.01 *s br*	4.95 *s br*	4.94 *s br*	1.36 *d*
H-15′	4.96 *s br*	4.86 *s br*		
H-5′	4.46 *dd br*	4.50 *d br*	4.35 *dd br*	5.89 *dd br*
H-8_1′	2.74 *dd*	2.67 *dd*	3.06 *dd*	3.03 *dd*
H-8_2′	2.50 *dd*	2.50 *dd*	2.30 *dd*	2.46 *dd*
H-12	1.08 *s*	1.07 *s*	1.06 *s*	1.09 *s*
H-13	1.06 *s*	1.06 *s*	1.05 *s*	
H-14_2	5.96 *d*	5.95 *d*	5.82 *s br*	6.01 *d*
H-12′	5.68 *s br*	5.62 *s br*	5.71 *s br*	5.58 *s br*
H-15_1·	4.76 *s br*	4.76 *s br*	4.76 *s br*	4.81 *s br*
H-15_2′	4.62 *s br*	4.64 *s br*	4.68 *s br*	4.65 *s br*

*H-2 δ 1.93 *m*.

J(Hz): Compound **7**: 1, 9 = 9; 1, 10 = 8; 1, 10′ = 11; 4, 5 = 12; 4′, 5 = 4; 8, 8′ = 15; 8, 9 = 11.5; 8′, 9 = 1.5; 10, 10′ = 11; 14, 14′ = 12; 4_1′, 5′ = 9; 4_2′, 5 = 3.5; 5_1′, 14′ = 1.5; 8_1′, 8_2′ = 12; 8_1′, 9 = 11; 8_2′, 9 = 3.5; compound **8**: 1, 9 = 1, 10 = 1, 10′ ~ 9; 4, 5 = 11.5; 4′, 5 = 4.5; 8′, 14′ = 1.5; 8, 8′ = 17; 8, 9 = 10; 8′, 9 = 2; 10, 10′ = 11; 4_1′, 5′ = 10; 8_1′, 8_2′ = 12; 8_1′, 9 = 12; 8_2′, 9 = 3.5; compound **9**: 1, 9 = 1, 10 = 1, 10′ ~ 9; 4, 5 = 11.5; 4′, 5 = 4; 8, 8· = 18; 8, 9 = 11; 8, 9′ = 1.5; 14, 14· = 11.5; 4_1′, 5′ = 7; 4_2′, 5′ = 4; 8_1·, 8_2′ = 8_1′, 9· = 11; 8_2′, 9 = 4; compound **10**: 1, 9 = 1, 10 ~ 9; 2, 15 = 7; 4_1·, 5′ = 11.5; 4_2·, 5′ = 4; 8′, 14′ = 1; 8_1′, 8_2· = 8_1′, 9′ = 11.5; 8_2′, 9′ = 3.

int.): 450.313 $[M]^+$ (6) ($C_{30}H_{42}O_3$), 422 (2), 233 (28), 217 (28), 147 (62), 93 (67), 91 (65), 69 (100).

5,6-cis-5′-*epi-Puliscabrin* (**9**). Colourless gum, IR$\nu_{max}^{CCl_4}$, cm^{-1}: 1680 (C=C–C=O), 3080, 900 (C=CH_2); MS *m/z* (rel. int.): 450.313 $[M]^+$ (7) ($C_{30}H_{42}O_3$), 233 (32), 217 (30), 147 (65), 93 (57), 91 (55), 69 (100).

4, 14-*Di*-2, 15-*dihydro puliscabrin* (**10**). Colourless gum, IR$\nu_{max}^{CCl_4}$, cm^{-1}: 1680 (C=C–C=O), 910 (C=CH_2); MS *m/z* (rel. int.): 466.308 $[M]^+$ (3) ($C_{30}H_{42}O_4$), 410 $[M - C_4H_8]^+$ (35), 233 (28), 232 (38), 231 (36), 176 (100), 69 (47).

Acknowledgements—We thank Dr B. de Winter and Miss M. Welman, Botanic Research Institute, Pretoria, for their help during plant collection and identification of plant material and the Deutsche Forschungsgemeinschaft for financial support.

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