9α-HYDROXYPARTHENOLIDE FROM *Zoegea baldschuanica* C. WINKL. AND ITS ABSOLUTE CONFIGURATION*

Miloš BUDĚŠÍNSKÝ[a], David ŠAMAN[a], Gerard NOWAK[b], Bohdan DROŻDŻ[b] and Miroslav HOLUB[a]

[a] *Institute of Organic Chemistry and Biochemistry,*
Czechoslovak Academy of Sciences, 166 10 Prague 6, Czechoslovakia and
[b] *Department of Medicinal Plants,*
Academy of Medicine, 60—623 Poznań, Poland

Received May 17th, 1983

From the aerial parts of *Zoegea baldschuanica* C. WINKL. was isolated 9α-hydroxyparthenolide (*I*), whose absolute configuration was established on the basis of CD spectra. ^{1}H NMR data for *I*, parthenolide (*VI*) and the derivatives *III* and *IV* are discussed.

Within the framework of investigations on sesquiterpenic lactones in species of the *Compositae* family we studied the *Zoegea baldschuanica* C. WINKL. species (*Compositae* family, *Cynarae* tribe). Using the described procedure[1], we prepared from the aerial parts of the plant the so-called lactone portion from which we obtained 9-hydroxyparthenolide (*I*), m.p. 140–142°C, $[\alpha]_D^{20}$ $-57{\cdot}0$. Its IR and mass spectra agreed with the assumed structure and the CD spectrum exhibited a maximum at 220 nm ($\Delta\varepsilon$ $-4{\cdot}6$). The compound was already obtained from the *Avillea garcini* DC species and its constitution and relative configuration were determined[2]. The 200 MHz ^{1}H NMR data, obtained by us for *I* (Table I; Fig. 1) agree well with those described[2], more important differences being found only for the protons at $C_{(2)}$ for which a reverse assignment had been given[2]. Our assignment changes also the pertinent coupling constants of the $H_{(2\alpha)}$ and $H_{(2\beta)}$ protons ($H_{(2\alpha)}$: δ 2·48 qd, $J_{2\alpha,2\beta} = 13$, $J_{2\alpha,3\alpha} = 13$, $J_{2\alpha,3\beta} = 5{\cdot}4$, $J_{2\alpha,1} = 13$ Hz; and $H_{(2\beta)}$: δ 2·25 bd, $J_{2\beta,2\alpha} = 13$, $J_{2\beta,3\alpha} = 5{\cdot}0$, $J_{2\beta,3\beta} = 1{\cdot}8$, $J_{2\beta,1} = 1{\cdot}8$ Hz). In the original assignment[2] the values of coupling constants (13 Hz) between the *cis*-oriented protons $H_{(1)}$, $H_{(2\alpha)}$ and $H_{(3\alpha)}$ are too high and might be tolerated perhaps only as extreme values for torsion angles of about 0°. However, such an arrangement would require also a similarly high value of $J_{2\beta,3\beta}$ for which the cited authors[2] found only 1·8 Hz. We are therefore of the opinion that the assignment of the $H_{(2\alpha)}$ and $H_{(2\beta)}$ hydrogens in the mentioned paper[2] is erroneous. Our proposed assignment (Table I), based on high ^3J values for the *trans*-oriented protons, agrees fully with the structure *I* in the form *II* which

---

* Part CCLXXVIII in the series On Terpenes; Part CCLXXVII: Biochem. Syst. Ecol., in press.

represents a usual conformation of *trans-trans*-germacranolides and which has been proved by NOE or shift reagents *e.g.* for tamaulipin A[3] or costunolide and its 11,13-dihydro derivative[4]. *in situ* Acylation of the hydroxy compound *I* with trichloroacetyl isocyanate[5,6] (TAI) afforded the mono-TAC derivative *III* whose ^1H NMR data (Table I) agreed well with the assumed structure. Besides the marked acylation shift of the $H_{(9)}$ proton signal ($\Delta\delta = 0{\cdot}96$ ppm), more pronounced downfield shifts were observed only for the $H_{(8\alpha)}$ and $H_{(8\beta)}$ protons ($\Delta\delta = 0{\cdot}14$ and $0{\cdot}12$ ppm, respectively). For the assignment of the 9α-OH configuration, the upfield shift of the $H_{(7)}$ signal ($\Delta\delta = -0{\cdot}10$ ppm) is important, indicating a *syn*-orientation of $H_{(7)}$ with respect to the hydroxy group. Very similar chemical shifts and coupling constants have been described[7] for 9α-acetoxyparthenolide (*IV*). In this context, some discrepancies in the literature are worth notice. Bohlmann and Zdero[7] described the isolation of 9α-acetoxyparthenolide (*IV*) but evidently erroneously

TABLE I

^1H NMR Parameters of some parthenolide derivatives in deuteriochloroform

Parameter	*I*	*III*	*IV*[a]	*VI*
H-1	5·63	5·69	5·43	5·21
H-2 (β)	2·50	2·48	[a]	2·46
H-2′ (α)	2·30	2·31	2·30	2·09—2·24
H-3 (β)	2·18	2·17	[a]	
H-3′ (α)	1·30	1·35	1·30	1·25
H-5	2·75	2·78	2·72	2·79
H-6	3·85	3·91	3·88	3·86
H-7	3·41	3·31	3·22	2·78
H-8 (α)	2·37	2·51	2·45	2·09—2·24
H-8′ (β)	1·93	2·05	1·90	1·73
H-9	4·34	5·30	5·19	2·38[c]
H-13	6·32	6·29	6·29	6·34
H-13′	5·64	5·64	5·55	5·62
H-14	1·71	1·80	1·77[b]	1·72
H-15	1·30	1·30	1·29[b]	1·31
^2J: $J_{2\alpha,2\beta}$	13·5	13·5	[a]	13·8
$J_{3\alpha,3\beta}$	13·2	13·0	[a]	13·0
$J_{8\alpha,8\beta}$	15·2	15·6	15	13·0
^3J: $J_{1,2\alpha}$	4·2	4·0	4	4·0
$J_{1,2\beta}$	12·0	11·8	10	12·2
$J_{2\alpha,3\alpha}$	6·2	6·2	[a]	6·0
$J_{2\alpha,3\beta}$	2·2	2·0	[a]	[d]
$J_{2\beta,3\alpha}$	12·5	12·5	[a]	12·5
$J_{2\beta,3\beta}$	5·2	5·3	[a]	5·3
$J_{5,6}$	9·0	9·1	8·7	8·9
$J_{6,7}$	8·1	8·3	8	8·3
$J_{7,8\alpha}$	1·5	1·3	1·5	1·4
$J_{7,8\beta}$	8·4	8·3	8	[d]
$J_{8\alpha,9}$	6·2	6·2	5·5	6
$J_{8\beta,9}$	1·3	1·2	1	1·4
^4J: $J_{7,13}$	3·8	3·7	3·5	3·6
$J_{7,13'}$	3·3	3·4	3·1	3·3
$J_{1,9}$	1·4	1·4	[a]	[d]
$J_{1,14}$	1·3	1·3	1·5	1·2
$J_{3\alpha,15}$	0·6	0·6	[a]	0·7
^5J: $J_{2\alpha,9}$	1·5	1·5	[a]	[d]
$J_{2\alpha,14}$	1·3	1·3	[a]	1·3

[a] Data taken from ref.[7]; some parameters are not given; [b] in ref.[7] the H-14 and H-15 are interchanged; [c] H-9 (α) is overlapped in the four proton multiplet at δ 2·09—2·24; [d] undetermined values.

depicted its formula as 9β-acetoxyparthenolide (*V*). In a subsequent paper, the same authors[8] described the isolation of the compound *V*, referring to the structural identification in the preceding paper[7]. From here, the report about isolation of both acetates was taken into the review of Fischer and coworkers[9], although the 9β-acetoxy derivative obviously had never been isolated. For comparison, Table I contains also our 200 MHz ^{1}H NMR data of the parent parthenolide (*VI*) which so far have been rather incomplete[10].

The absolute configuration of 9α-hydroxyparthenolide (*I*) was established by comparison of its CD spectrum with that of parthenolide (*VI*) (220 nm, $\Delta\delta$ $-0{\cdot}42$) whose absolute configuration is known[11]. From the shape of the CD spectra of compounds *I* and *VI* and their known relative configuration and conformation we can deduce that the absolute configuration of 9α-hydroxyparthenolide can be expressed by formula *I*.

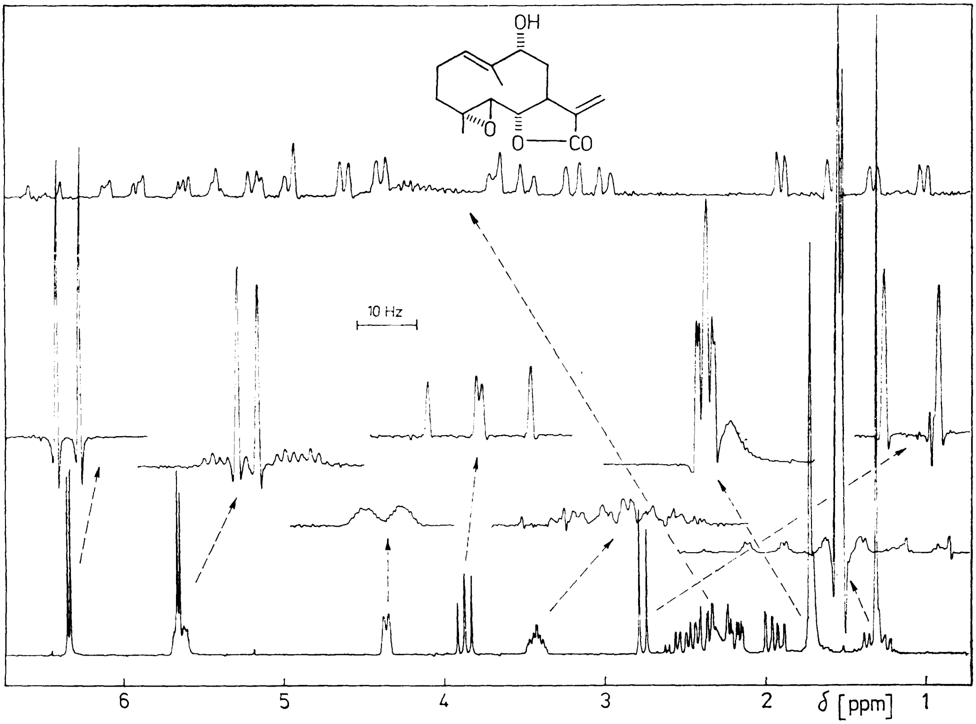
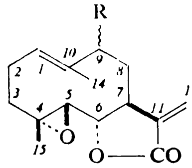
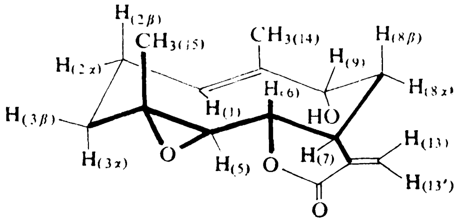


FIG. 1
^{1}H NMR spectrum (200 MHz; deuteriochloroform) of 9α-hydroxyparthenolide (*I*)



I, R = α-OH
III, R = α-OCONHCOCCl$_3$
IV, R = α-OCOCH$_3$
V, R = β-OCOCH$_3$
VI, R = H



II

The germacranolide structure of 9α-hydroxyparthenolide (*I*) is in accord with the classification of the parent plant *Z. baldschuanica* C. Winkl. in the *Cynarae* tribe, for which sesquiterpenic lactones of guaianolide and germacranolide type are characteristic components[12]. The presence of 9α-hydroxyparthenolide (*I*) in the *Anvillea garcini* DC species (*Compositae* family, *Inulae* tribe) shows that an introduction of a free or esterified hydroxyl at $C_{(9)}$ in the germacranolide skeleton is not a chemosystematic character in the *Compositae* family. This assumption agrees also with the fact that 9α-hydroxyparthenolide acetate (*IV*) was obtained from the species of the *Anthemidae* tribe (*Anthemis cretica*[8] and *Matricaria suffruticosa*[7]).

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Mass spectrum was taken on an AEI 902 spectrometer, IR spectrum on a Perkin-Elmer spectrophotometer (in chloroform). CD spectra were obtained with a Rousell–Jouan CD 185 dichrographe and optical rotation was measured on an objective Perkin–Elmer polarimeter in methanol. ^{1}H NMR spectra were measured in the FT mode on a Varian XL-200 (200 MHz) instrument in deuteriochloroform with tetramethylsilane as internal standard. For better resolution, exponential multiplication with Gaussian apodization of FID was used. The NMR parameters were obtained from the expanded spectra (1—2 Hz/cm) by the first order analysis.

Isolation of 9α-Hydroxyparthenolide (*I*)

The *Z. baldschuanica* C. Winkl species was cultivated in the botanical garden of the Department of Medicinal Plants, Academy of Medicine, Poznań, Poland, and its voucher (RL 551/81) is deposited in the herbarium of the said Institute. Dried aerial parts (60 g) were worked up in the usual manner[1], affording 350 mg of a lactone portion which on dilution with chloroform and addition of ether deposited crystalline 9α-hydroxyparthenolide (*I*) (75 mg). Further portion of *I* (22 mg) was obtained from the mother liquors by chromatography on silica gel (20 g) in chloroform–acetone (4 : 1). The product melted at 140—142°C, $[\alpha]_D^{20}$ −57·0; composition $C_{15}H_{20}O_4$. IR spectrum, cm^{-1}: 1 767 (γ-lactone), 1 625, 1 661 (double bond), 3 605, 3 485 (hydroxyl). Mass spectrum (*m*/*z*): 264 (M), 246 (M—18), 188. CD spectrum, nm (Δε): 220, (−4·6) (last reading). For $C_{15}H_{20}O_4$ (264·3) calculated: 68·16% C, 7·63% H, 0·39% H act.; found: 67·95% C, 7·81% H, 0·48% H act.

Two of us (G. N., B. D.) are indebted to the Polish Academy of Sciences, represented by its Institute of Organic Chemistry, for the coordination and financial support of a part of this work (problem number MR I 12 152/3).

Elemental analysis was performed by Mrs A. Froňková in the Analytical Laboratory (Dr J. Horáček, Head) of the Institute. IR *and* CD *spectra were taken and interpreted by Dr S. Vašíčková, mass spectra were measured and interpreted by Dr L. Dolejš. Optical rotation measurements were carried out by Mrs Z. Ledvinová. Our thanks are due to all of them.*

REFERENCES

1. Drożdż B., Piotrkowski J.: J. Pharm. Pharmacol. *25*, 91 (1973).
2. Tyson R. L., Chang C.-j., Mc Laughlin J. L., Aynehchi Y., Cassady J. M.: Experientia *37*, 441 (1981).
3. Bhacca N. S., Fischer N. H.: Chem. Commun. *1969*, 68.
4. Tori K., Horibe I., Tamura Y., Tada H.: Chem. Commun. *1973*, 620.
5. Goodlett V. W.: Anal. Chem. *37*, 431 (1965).
6. Samek Z., Buděšínský M.: This Journal *44*, 558 (1979).
7. Bohlmann F., Zdero C.: Chem. Ber. *108*, 437 (1975).
8. Bohlmann F., Zdero C.: Chem. Ber. *108*, 1902 (1975).
9. Fischer N. H., Olivier E. J., Fischer H. D.: Fortschr. Chem. Org. Naturst. *38*, 63 (1979).
10. Govindachari T. R., Joshi B. S., Kamat V. N.: Tetrahedron *31*, 1509 (1968).
11. Bowdekar A. S., Kelkar G. R., Bhattacharyya S. C.: Tetrahedron Lett. 1966, 1225.
12. Herout V. in the book: *Pharmacognosy and Phytochemistry* (H. Wagner, L. Hörhammer, Eds), p. 93. Springer, Berlin 1971.

Translated by M. Tichý.