ISOERIVANIN AND DEHYDROISOERIVANIN — MINOR SESQUITERPENE LACTONE COMPONENTS FROM *Balsamita major* DESF.*

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Two minor sesquiterpene lactone components, isoerivanin (*II*) and dehydroisoerivanin (*III*) were isolated from the species *Balsamita major* DESF. (*Compositae*) and their structure, including relative and absolute configuration, was derived.

Recently we described the relative and the absolute configuration of the sesquiterpenic lactone erivanin (*I*) which we isolated from the species *Balsamita major* DESF. (synonymum *Tanacetum balsamita* L.) of the *Compositae* family, tribe *Anthemideae*, subtribe *Chrysanthemineae*[1]. From the same plant material we now isolated two additional sesquiterpenic lactones to which we gave the names isoerivanin (*II*) and dehydroisoerivanin (*III*) after having determined their structures. The first had m.p. 172–174°C and the composition $C_{15}H_{22}O_4$ (M 266) and its IR spectrum indicated the presence of a γ-lactone group (1772, 1042 cm^{-1}) and a hydroxyl group (3480 cm^{-1}). A detailed analysis of the ^1H-NMR spectrum of isoerivanin (*II*) and its diacyl derivative *IV*, prepared by *in situ* acylation with trichloroacetyl isocyanate (TAI method; ref.[2,3]) showed that the structure of isoerivanin (*II*) differs from that of erivanin merely by the position of the double bond, as shown in formula *II*. According to this structure isoerivanin is structurally very close to α-santonin and its derivatives and this relationship was clearly confirmed by direct comparison of the fragmentation of isoerivanin (*II*) in the mass spectrum with the known fragmentations of α-santonin and related substances[4].

Similarly to erivanin isoerivanin also contained in the CD spectrum a positive band at 227 nm with $\Delta\varepsilon$ +0·35, indicating *S*-configuration of the centre $C_{(11)}$(ref.[1,5]). It also followed from the observed half-widths of the multiplets of protons $H_{(1)}$ and $H_{(3)}$ (7–8 Hz) that similarly as in erivanin the protons $H_{(1)}$ and $H_{(3)}$ in isoerivanin are also

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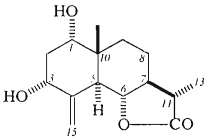
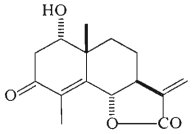
quasi-equatorial, under the assumption of the chair conformation of the unsaturated ring in the molecule of erivanin and the half-chair conformation of the unsaturated ring in the molecule of isoerivanin; in both molecules they indicate the probability of the same α-configuration of both hydroxy groups. The absolute configuration at $C_{(1)}$ in erivanin was confirmed recently by means of the benzoate rule[5].

The second lactone – dehydroisoerivanin – had m.p. 189–191°C and the composition $C_{15}H_{20}O_4$ (M 264), and its IR spectrum showed the presence of a γ-lactone group (1778, 1139 cm^{-1}), a conjugated oxo group in the six-membered ring (1670 cm^{-1}), a double bond (1619 cm^{-1}), and a hydroxyl group (3470, 3620 cm^{-1}). As in isoerivanin (*II*) the structure of dehydroisoerivanin was derived from a detailed analysis of its ^{1}H-NMR spectrum, as well as the ^{1}H-NMR spectrum of its acyl derivative *V*, prepared by *in situ* acylation using the TAI method[2,3]. In this case too the close relationship with α-santonin was confirmed by mass spectral fragmentation[4] (see Experimental). According to its structure dehydroisoerivanin (*III*) is in fact the so far undescribed 11,13-dihydroludovicin C and this relationship was also confirmed by the comparison of characteristic ^{1}H-NMR parameters of dehydroisoerivanin *III* and ludovicin C (*VI*) (ref.[6]) [$H_{(1)}$: 3·57 ($J_1 = 3$, $J_2 = 4$); $H_{(6)}$: 4·67 ($J_{6,7} = 11·5$); $H_{(14)}$: 1·32; $H_{(15)}$: 2·00 ($J = 1·5$)]. In the CD spectrum of compound *III* the band of the lactonic chromophore is probably shifted in comparison with the CD spectrum of compound *II* in consequence of conformational changes, and it is probably identical with the band at 244 nm; however, it is again positive, which would again indicate the same *S*-configuration of the centre $C_{(11)}$, as in native substances *I* and *II*. The absolute configuration of the centre $C_{(1)}$ in dehydroisoerivanin was derived directly from the difference of its molar rotation and the molar rotation of acyl derivative *V*, measured directly after *in situ* acylation with trichloroacetyl isocyanate. As shown recently[5] the TAI method can also be extended successfully to the *in situ* measured specific rotations. Analogous increments of molar rotations as in benzoates are then obtained, so that information on absolute configuration can be obtained from the observed acylation increments $\Delta[\phi]$ (TAC) as in the benzoate rule. In our case, the solution of compound *III* in dioxane had $[\alpha]_D = +36·2°$. From the observed ratio $\alpha_D(OTAC)/\alpha_D(OH) \cong \Phi(OTAC)/\Phi(OH) = +1·425$ the value $\Delta[\phi]_D$ (TAC) = $= \Phi(OTAC) - \Phi(OH) = +40·6°$ followed and – hence – the *S*-configuration on $C_{(1)}$.

In the *Anthemideae* tribe, where the species *Balsamita major* DESF. is classified without restriction, a series of sesquiterpenic lactones was found which according to their skeletal type belong predominantly among germacranolides, guaianolides and santanolides[7]. The last mentioned type is said to have been isolated within the *Anthemideae* tribe only in the species of the *Artemisia*[7] genus. On the basis of this work and in view of the papers of further authors this finding should be widened to the extent that santanolides are present within the frame of the *Anthemideae* tribe also in the species of the genera *Tanacetum* and *Balsamita* in addition to the genus *Artemisia*.



I



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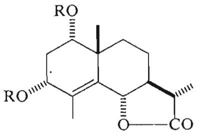
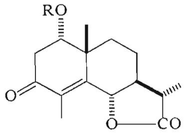
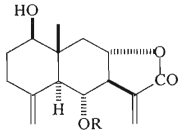


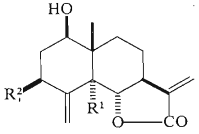
II; R = H
IV; R = CONHCOCCl$_3$



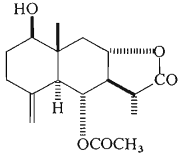
III; R = H
V; R = CONHCOCCl$_3$



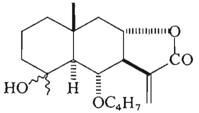
VII; R = COCH$_3$
IX; R = COC(CH$_3$)=CHCH$_3$



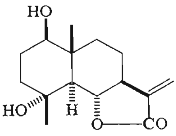
XII; R^1, R^2 = H
XIII; R^1 = OH, R^2 = H
XVIII; R^1 = H, R^2 = OH



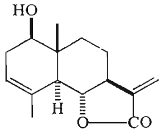
VIII



X

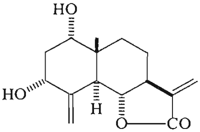


XI

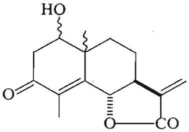


XIV

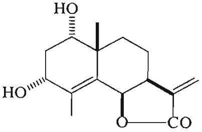
The species *Balsamita major* DESF. contains three santanolides, erivanin (*I*), isoerivanin (*II*) and dehydroisoerivanin (*III*). In the *Tanacetum cinerariaefolium* SCH. BIP. species (synonymum *Chrysanthemum cinerariaefolium* VISSIANI) β-cyclopyrethrosin (*VII*) (ref.[8]), dihydro-β-cyclopyrethrosin (*VIII*) (ref.[8]) and chrysanin (*IX*) (ref.[8]) were found, while in the species *Tanacetum pseudoachillea* C. WINKL. tanapsin (*X*) (ref.[10]) was found in addition to chrysanin (*IX*) (ref.[10]) (by the other authors called tachilin[9]), and in *Tanacetum vulgare* L. 1β-hydroxyarbusculin A (*XI*) (ref.[11]), reynosin (*XII*) (ref.[11]) and tanacetin (*XIII*) (ref.[11]) were found, and in *Tanacetum parthenium* SCH. BIP. santamarin (*XIV*) (ref.[12]) was found.



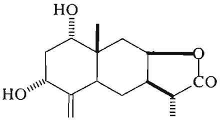
XV



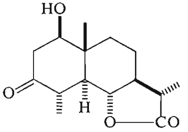
XVI



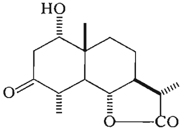
XVII



XIX



XX



XXI

Among native sesquiterpenic lactones and with respect to their structure ludovicin B (*XV*) (ref.[6]), ludovicin C (*VI*) (ref.[6]), armexifolin (*XVI*) (ref.[13]) – which is either identical or stereoisomeric with ludovicin C – armexin (*XVII*) (ref.[14]) and ridentin B (*XVIII*) (ref.[15]) are closest to erivanin (*I*), isoerivanin (*II*) and dehydroisoerivanin (*III*). In contrast to the substances *I–III* described by us all the mentioned native substances have the exomethylene double bond conjugated with the lactone carbonyl.

TABLE I

Characteristic Parameters of the ^{1}H-NMR-Spectra of Isoerivanin (*II*) and Dehydroisoerivanin (*III*)

Compound[a]	$H_{(1)}$	$H_{(2)}$	$H_{(2')}$	$H_{(3)}$	$H_{(6)}$	$H_{(13)}$	$H_{(14)}$	$H_{(15)}$
II	3·56[b]	—	—	3·96[b]	4·55 $J_{6,7} = 11$ $J_{6,15} = 1{\cdot}6$	1·24 d (6·8)	1·08	2·05 d $J_{15,6} = 1{\cdot}6$
IV[c]	4·99[b]	2·37[d]	2·37[d]	5·40	4·60 $J_{6,7} = 11$ $J_{6,15} \neq 0$	1·26 d (6·5)	1·25	2·00 $J_{15,6} \neq 0$
$\Delta^{(1,3)}\delta H(II)$[e]	1·43	—	—	1·44	0·05	0·02	0·17	−0·05
III	3·81 dd $J_{1,2} = 2{\cdot}5$ $J_{1,2'} = 4$	2·91 dd $J_{2,1} = 2{\cdot}5$ $J_{2,2'} = 17$	2·63 dd $J_{2',1} = 4$ $J_{2',2} = 17$	—	4·69 $J_{6,7} = 11$ $J_{6,15} = 1{\cdot}7$	1·26 d (6·8)	1·35	2·03 d $J_{15,6} = 1{\cdot}7$
V[f]	5·12 t (3)	2·98 dd $J_{1,2} = 2$ $J_{2,2'} = 17$	2·78 dd $J_{2',1} = 4$ $J_{2',2} = 17$	—	4·71 $J_{6,7} = 10{\cdot}5$ $J_{6,15} = 1{\cdot}5$	1·28 (6·8)	1·45	2·06 d $J_{15,6} = 1{\cdot}5$
$\Delta^{(1)}\delta H(III)$[e]	1·31	0·07	0·15	—	0·02	0·02	0·10	0·03

[a] Measured on a Varian HA-100 instrument; solvent deuteriochloroform, internal standard tetramethylsilane (TMS); first-order analysis, chemical shifts in δ-TMS scale, splitting in Hz (in parentheses if not stated otherwise). [b] Multiplet, $W_{1/2} \approx 7-8$ Hz. [c] NH-Signals at δ 8·43 and 8·74. [d] Triplet, 2 H, center of an AB-system. [e] Acylation shifts: $\Delta^{(i,j)}\delta H_k = \delta H_k(C_{i,j}—OR) - \delta H_k(C_{i,j}—OH)$, i, j denotes positions of OH being acylated, k denotes affected proton in arbitrary numbering. [f] NH-Signal δ 8·36.

Among the sesquiterpenic lactones which have a methyl group on $C_{(11)}$ and which are structurally similar with the compounds *I*–*III* studied by us we may mention arshubin[16] (*XIX*), arsanin[17] (*XX*) and arsantin[17] (*XXI*). All the native sesquiterpenic lactones mentioned which are structurally related with the native compounds *I*–*III* were obtained from various species of the *Artemisia* genus.

These similarities regarding the parallel occurrence of sesquiterpenic lactones in the representatives of the *Artemisia* group and of the *Chrysanthemum* complex can contribute as further valuable indications for the solution of phylogenetic relationships within the *Anthemideae* tribe.

EXPERIMENTAL

The melting points were determined on a Kofler block and they were not corrected. The IR spectra were measured in chloroform by means of a Zeiss UR 10 spectrophotometer. The mass spectra were measured on an AEI MS 902 spectrometer. The ^{1}H-NMR spectra were recorded with a Varian HA-100 spectrometer. The CD spectra were measured on a Roussel–Jouan Dichrographe CD 185 in methanol.

Isolation of Isoerivanin (*II*) and Dehydroisoerivanin (*III*)

From the fraction from which erivanin (*I*) was isolated[1] isoerivanin, $C_{15}H_{22}O_4$, m.p. 172–174°C was obtained by repeated chromatography on silica gel. IR spectrum (in cm^{-1}): 1772, 1042 (γ-lactone), 3480 (hydroxyl). Mass (*m*/*e*): 266 (M), 251, 248, 233, 230, 222, 220, 215, 205, 193, 187, 185, 177, 175, 165, 163, 159, 149, 147, 145, 137, 135, 133, 132, 131, 125, 123, 121, 120, 119, 111, 109, 107, 105, 97, 95, 93, 91, 83, 81, 79, 77, 74, 71, 69, 67, 65, 57, 55, 53, 43, 41, 39, 32, 31, 29, 28, 27. CD: 227 nm, $\Delta\varepsilon$ + 0·35. For $C_{15}H_{22}O_4$ (266·3) calculated: 67·65% C, 8·33% H, 0·86% H act.; found: 67·37% C, 8·42% H, 0·95% H act. From subsequent fractions dehydroisoerivanin (*III*) was obtained, $C_{15}H_{20}O_4$, m.p. 189–191°C. IR spectrum (in cm^{-1}): 1778, 1139, (γ-lactone), 1670 (conjugated ketone in a six-membered ring), 1619 (double bond), 3470, 3620 (hydroxyl). Mass spectrum (*m*/*e*): 226, 249, 246, 236, 231, 221, 218, 207, 203, 195, 193, 192, 191, 185, 180, 177, 175, 173, 165, 163, 150, 149, 147, 145, 137, 136, 135, 133, 123, 121, 119, 117, 115, 109, 107, 105, 97, 95, 93, 91, 85, 83, 81, 79, 77, 71, 69, 67, 65, 60, 57, 55, 53, 51, 43, 41, 39, 32, 29, 28. CD: 324 nm, $\Delta\varepsilon$ −1·32; 276 nm, $\Delta\varepsilon$ ±0; 244 nm, $\Delta\varepsilon$ +7·4. For $C_{15}H_{20}O_4$ (264·3) calculated: 68·16% C, 7·63% H, 0·38% H act.; found: 67·92% C, 7·76% H, 0·42% H act.

The elemental analyses were carried out in the analytical department of our Institute (head Dr J. Horáček) by Mrs E. Sýkorová, Mr V. Štěrba and Dr V. Pechanec. The IR spectra were measured by Mrs S. Holubová, Mrs K. Matoušková and Mr P. Formánek and interpreted by Dr S. Vašíčková. Dr S. Vašíčková also measured and interpreted the CD curves. The mass spectra were measured and interpreted by Dr L. Dolejš. We express our sincere thanks to all those mentioned.

REFERENCES

1. Samek Z., Holub M., Błoszyk E., Drożdż B., Herout V.: This Journal *40*, 2676 (1975).
2. Goodlet V. W.: Anal. Chem. *37*, 431 (1965).
3. Samek Z., Buděšínský M.: This Journal *44*, 558 (1975).
4. Wasada N., Tsuchiya T., Yoshii E., Watanabe E.: Tetrahedron *23*, 4623 (1967).

5. Samek Z.: Symposium Papers of 11th IUPAC Symposium on Chemistry of Natural Products, Golden Sands, Bulgaria, Vol. 4, Part 1, p. 390 (1978).
6. Lee K. H., Geissman T. A.: Phytochemistry *9*, 403 (1970).
7. Greger H. in the book: *The Biology and Chemistry of the Compositae* (V. H. Heywood, J. B. Harborne, B. I. Turner, Eds), p. 899. Academic Press, New York 1977.
8. Doskotch R. W., El-Feraly F. S., Hufford C. D.: Can. J. Chem. *49*, 2103 (1971).
9. Yunusov A. I., Kasimov S. Z., Sidyakin G. P.: Khim. Prir. Soedin. *1973*, 276.
10. Yunusov A. I., Kasimov S. Z., Sidyakin G. P.: Khim. Prir. Soedin. *1976*, 261, 309.
11. Samek Z., Holub M., Grabarczyk H., Drożdż B., Herout V.: This Journal *38*, 1971 (1973).
12. Romo de Vivar A., Jiménez H.: Tetrahedron *21*, 1741 (1965).
13. Romo de Vivar A., Vásquez F., Zetina C.: Rev. Latinoamer. Quím. *8*, 127 (1977).
14. Romo J., Tello H.: Rev. Latinoamer. Quím. *3*, 122 (1973).
15. Irwin M. A., Geissman T. A.: Phytochemistry *12*, 871 (1973).
16. Zakirov S. Kh., Kasimov S. Z., Sidyakin G. P.: Khim. Prir. Soedin. *1976*, 548.
17. Moiseieva G. P., Akiev B., Kasimov S. Z., Sidyakin G. P.: Khim. Prir. Soedin. *1973*, 167.

Translated by Ž. Procházka.

Note added in proof: It is only quite recently that we became acquainted with the paper by Soviet authors Serkerov S. V., Aleskerova A. N.: Khim. Prir. Soedin. *1978*, 75, in which the isolation of a native substance from the species *Artemisia fragrans*, called alchanin, is described. The authors derived for it the structure with an incomplete relative configuration. It is probable that this substance is identical with dehydroisoerivanin (*III*) described by us.