

ABSOLUTE CONFIGURATION OF XERANTHOLIDE,
A SESQUITERPENIC LACTONE FROM *Anthemis austriaca* JACQ.*

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The isolation of the sesquiterpenic lactone xerantholide (*I*) from *Anthemis austriaca* JACQ. of Polish and Turkish origin is described and its structure confirmed. Absolute configuration is also derived.

Recently we published a communication on the isolation, structure and partial configuration of xerantholide, a sesquiterpenic lactone from the aerial parts of *Xeranthemum cylindraceum* SIBTH. et SMITH.¹ On the basis of physical methods, mainly ¹H NMR spectroscopy we proposed for xerantholide a structure with undetermined spacial orientation of the substituents on C₍₁₎ and C₍₁₀₎. From an X-ray study it followed² that the proposed partial structure of xerantholide is correct and that the relative configuration of the remaining chiral centres C₍₁₎ and C₍₁₀₎ corresponds to formula *I*.

X-Ray analysis further indicated that the molecule of xerantholide assumes in the crystal a conformation with the seven-membered ring in pseudo-chair form, with the five-membered homocycle almost planar and with the lactone ring clearly non-planar².

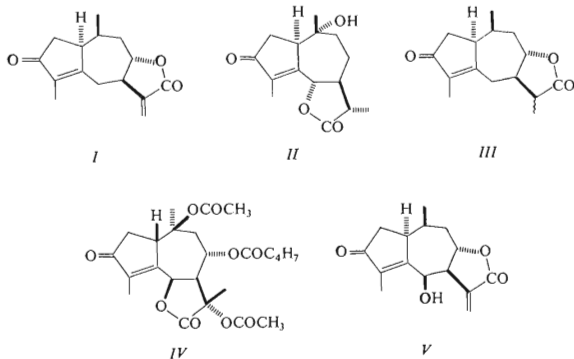
In connection with the study of sesquiterpenic lactones from *Compositae* we also investigated the species *Anthemis austriaca* JACQ. (tribe *Anthemideae*) of Polish origin. We obtained from its aerial parts the so-called lactonic fraction in the described way^{3,4}, and on chromatographing it on a silica gel column we isolated xerantholide (*I*) with m.p. 190–192°C and $[\alpha]_D^{20} + 223.3^\circ$. Its IR spectrum, ¹H NMR spectrum and mixture melting point showed that it was identical with a standard

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sample of xerantholide obtained from *X. cylindraceum*¹. From the aerial parts of *A. austriaca* of Turkish origin we obtained xerantholide with m.p. 189°C, $[\alpha]_D^{20} +214.6^\circ$, the IR spectrum, ¹H NMR spectrum and mixture melting point of which confirmed its identity with xerantholide from *X. cylindraceum* and from *A. austriaca* of Polish origin.

The absolute configuration of xerantholide was derived from its CD spectrum. The part of the CD spectrum of xerantholide about 250 nm, which in other instances and in the case of a known structure and relative configuration of the exomethylene- γ -lactone ring indicates the absolute configuration of this grouping⁵, could not be exploited for our purpose owing to its poor distinctness. Therefore, we turned our attention to those maxima in the CD spectrum of xerantholide which depend on the chirality of the α,β -cyclopentenone grouping. On the basis of a comparison of the CD spectra (Table I) of xerantholide (*I*) on the one hand and substances of known absolute configuration on the other, which also have a similar chromophore as for example isophotosantonin lactone (*II*) or 6-deoxy-11,13-dihydromikanocryptin⁶ (*III*) which show a similar course of the CD curve in the region about 320 nm or about 235 nm as xerantholide, and triester keto lactone *IV* (ref.⁷) the CD curve of which takes an opposite direction in the mentioned regions, it follows that the absolute configuration of the chirality centre $C_{(1)}$ is the same as in compounds *II* and *III* – *S* – and opposite from that in compound *IV*. Hence, formula *I* also represents the absolute configuration of xerantholide.



In order to compare the conformation of xerantholide in crystalline state and in solution, we carried out ¹H NMR measurements at 200 MHz frequency. A detailed analysis of the spectra gave a complete set of chemical shifts and coupling constants

of all hydrogens. The data are presented in Table II. Conformational information is included in vicinal coupling constants of protons $^3J_{H,H}$. Experimental values of $^3J_{H,H}$ (Table III) in solution correspond very well with the angles observed in crystals. The high values of allylic interactions $^4J_{7,13}$ and $^4J_{7,13'}$ (3.0 or 3.4 Hz, respectively) are in agreement with geometrical conditions found in crystals (the angle $H_7-C_7-C_{11}-C_{13} = 93.4^\circ$, maximal π -contribution to $^4J_{H,H}$ is at 90°). Identical values of both *cis*-homoallylic couplings $^5J_{6,15}$ (1.6 Hz) also correspond to equal dihedral angles $H_6-C_6-C_5-C_4$ (about 59°) of both hydrogens in the position 6.

TABLE I

CD Spectra of xerantholide (*I*), 6-deoxy-11,13-dihydromikanocryptin (*III*), isofotosantonin-lactone (*II*) and triester ketolactone (*IV*)

Substance	nm		nm	
<i>I</i>	317	-0.68	238	+9.70
<i>III</i>	306	-0.67	240	+7.03
<i>II</i>	320	-1.41	238	+8.22
<i>IV</i>	330	+1.38	234	-9.87

TABLE II

1H NMR parameters of xerantholide in deuteriochloroform

Proton	Chemical shifts and coupling constants				
H_1	3.20	$J_{1,2\alpha} = 6.8, J_{1,2\beta} = 1.6, J_{1,10} = 2.2, J_{1,15} = 1.5$			
$H_{2\alpha}$	2.66	$J_{2\alpha,2\beta} = 18.8, J_{2\alpha,1} = 6.8$			
$H_{2\beta}$	2.12	$J_{2\beta,2\alpha} = 18.8, J_{2\beta,1} = 1.6, J_{2\beta,10} = 1.2$			
$H_{6\alpha}$	3.16	$J_{6\alpha,6\beta} = 19.4, J_{6\alpha,7} = 3.0, J_{6\alpha,15} = 1.6$			
$H_{6\beta}$	2.48	$J_{6\beta,6\alpha} = 19.4, J_{6\beta,7} = 11.6, J_{6\beta,15} = 1.6$			
H_7	3.05	$J_{7,6\alpha} = 3.0, J_{7,6\beta} = 11.6, J_{7,8} = 9.4, J_{7,13} = 3.0, J_{7,13'} = 3.4$			
H_8	4.14	$J_{8,7} = 9.4, J_{8,9\alpha} = 12.0, J_{8,9\beta} = 3.2$			
$H_{9\alpha}$	1.94	$J_{9\alpha,9\beta} = 13.0, J_{9\alpha,8} = 12.0, J_{9\alpha,10} = 4.0$			
$H_{9\beta}$	2.43	$J_{9\beta,9\alpha} = 13.0, J_{9\beta,8} = 3.2, J_{9\beta,10} = 3.8$			
H_{10}	2.34	$J_{10,9\alpha} = 4.0, J_{10,9\beta} = 3.8, J_{10,1} = 2.2, J_{10,14} = 7.2, J_{10,2\beta} = 1.2$			
H_{13}	5.61	$J_{13,7} = 3.0, J_{13,13'} = 0$			
$H_{13'}$	6.30	$J_{13',7} = 3.4, J_{13',13} = 0$			
H_{14}	0.75	$J_{14,10} = 7.2$			
H_{15}	1.74	$J_{15,1} = 1.5, J_{15,6\alpha} = 1.6, J_{15,6\beta} = 1.6$			

The *trans*-homoallylic coupling ${}^5J_{1,15}$ has the value 1.5 Hz, in agreement with the angle $C_4-C_5-C_1-H_1 = 122^\circ$ in crystals. Therefore it may be summarized that the conformations of xerantholide in crystals and in solution are very similar.

Xerantholide (*I*) is structurally closely related to mikanocryptin⁶ (*V*) which was isolated from *Mikania micrantha* H. B. K. (ref.⁶) and *Melampodium divaricatum* (RICH. in. PERS) DC (ref.⁸), the structure of which was also confirmed by X-ray analysis⁹. From the comparison of the data obtained by X-ray analysis of xerantholide² (*I*) and mikanocryptin⁹ (*V*), such as interatomic distances, valence angles and torsion angles, it followed that the conformation of the molecules of both mentioned substances is very similar in crystalline form. Both *I* and *V* also belong to the same enantiomeric series.

The occurrence of guaianolides in *Compositae* is rather general¹⁰ from the point of view of tribal classification of parent species. This also follows from the tribal classification of the parent species in which xerantholide (*I*) or the structurally very closely related mikanocryptin (*V*) were detected. Xerantholide (*I*) was obtained from *X. cylindraceum* which belongs to the tribe *Cynareae*¹ and from *A. austriaca* which is classified among the species of *Anthemideae* tribe. Mikanocryptin (*V*) was isolated from *Mikania micrantha*⁶, belonging to the tribe *Eupatorieae*, and from *Melampodium divaricatum* from the tribe *Heliantheae*⁸. Hence, it is unlikely that the native substances of the xerantholide type could be utilized for internal chemosystematics of *Compositae*.

TABLE III

Dihedral angles in crystal and experimental proton coupling constants of xerantholide

Fragment	Dihedral angle	Experimental ${}^3J_{H,H}$
$H_1-C_1-C_2-H_{2\alpha}$	1.3°	6.8
$H_1-C_1-C_2-H_{2\beta}$	120.1°	1.6
$H_{6\alpha}-C_6-C_7-H_7$	68.2°	3.0
$H_{6\beta}-C_6-C_7-H_7$	179.5°	11.6
$H_7-C_7-C_8-H_8$	158.3°	9.4
$H_8-C_8-C_9-H_{9\alpha}$	174.4°	12.0
$H_8-C_8-C_9-H_{9\beta}$	67.6°	3.2
$H_{9\alpha}-C_9-C_{10}-H_{10}$	67.5°	4.0
$H_{9\beta}-C_9-C_{10}-H_{10}$	49.6°	3.8
$H_{10}-C_{10}-C_1-H_1$	70.1°	2.2

EXPERIMENTAL

The melting points were determined on a Kofler block and they were not corrected. The ^1H NMR spectra were measured on a Varian XL-200 instrument. Optical rotation was measured on an objective Perkin-Elmer 141 polarimeter in methanol. The CD spectra were measured on a Roussel-Jouan Dichrographe CD 185 in methanol.

Isolation of Xerantholide (*I*) from *A. austriaca*

A) *Of Polish origin*: The plant material was cultivated in the botanical gardens of the Department of Medicinal Plants in Poznań from seeds donated in 1975 by the Botanical Gardens of the University of Göttingen (GFR). Its voucher is deposited in the herbarium of the Department of Medicinal Plants, Institute of Drugs, Academy of Medicine, Poznań, Poland, under the number RL 518/76. The fresh aerial parts were worked up in the described manner^{3,4} and 1.5 g of the so-called lactic fraction were obtained. This fraction (1.0 g) was chromatographed on a silica gel column (50 g) using elution with benzene with increasing amounts of acetone (for 10 to 30% of acetone). From the medium fractions of this chromatography a mixture of substances (120 mg) was obtained which on repeated chromatography on silica gel (15 g) with ethyl acetate afforded xerantholide (*I*; 45 mg) of m.p. 190–192°C (methanol, ethyl acetate) and $[\alpha]_{\text{D}}^{20} + 223.3^\circ$ (*c* 0.38). The mixture melting point with a sample of xerantholide from *X. cylindraceum*¹ and *A. austriaca* of Turkish origin was undepressed. IR spectrum (cm^{-1} ; spectrophotometer Zeiss UR 20 (Jena); measured in chloroform): 1 769, 1 156, 1 407 (exomethylene- γ -lactone), 1 694, 1 639 (conjugated ketone in a five-membered ring). UV spectrum (λ_{max} in nm, log ϵ): 240, 4.3; 212, 4.1. Mass spectrum (AEI MS 902 spectrometer), *m/e*: 246 (M), 218, 175, 161. CD spectrum (nm, $\Delta\epsilon$): 317, -0.68; 284, ± 0 ; 238, +9.70; 209, ± 0 . For $\text{C}_{15}\text{H}_{18}\text{O}_3$ (246.3) calculated: 74.14% C, 7.37% H; found: 73.10% C, 7.11% H.

B) *Of Turkish origin*: Dry, ground aerial parts (2 kg) of the plant, collected in the surroundings of Kırklareli-Demirköy (European part of Turkey) in 1977 were extracted with ethanol. Its voucher is deposited in the herbarium of the Faculty of Pharmacy, University of Istanbul, Turkey, under the number ISTE 38059. The extract was concentrated under reduced pressure to a syrup (165 g) which was extracted with low-boiling light petroleum and then benzene. The benzene fraction was evaporated in a vacuum and the residue (8 g) was chromatographed on a column of neutral alumina (800 g, act. III) with benzene with addition of chloroform. Elution with benzene containing 10% of chloroform gave xerantholide (*I*) with m.p. 189°C (benzene, methanol) and $[\alpha]_{\text{D}}^{20} + 214.6$ (*c* 0.26). The mixture melting point with a sample of xerantholide from *X. cylindraceum*¹ and *A. austriaca* of Polish origin was undepressed. IR spectrum (in cm^{-1} ; spectrophotometer Perkin-Elmer 297; KBr): 1 760, 1 135 (exomethylene- γ -lactone), 1 685, 1 630 (conjugated ketone in a five-membered ring). Mass spectrum (JEOL D 100) *m/e*: 246 (M), 232, 218, 188, 175, 161, 158, 155, 146. CD spectrum (nm, $\Delta\epsilon$): 315, -0.49; 283, ± 0 ; 236, +9.25; 208, ± 0 . For $\text{C}_{15}\text{H}_{18}\text{O}_3$ (246.3) calculated: 73.14% C, 7.37% H; found: 72.96% C, 7.18% H.

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