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STRUCTURE OF SESQUITERPENIC LACTONES
FROM *Tanacetum vulgare* L.

Z.Samek[a], M.Holub[a], H.Grabarczyk[b], B.Drożdż[b] and V.Herout[a]

[a]*Institute of Organic Chemistry and Biochemistry,*
Czechoslovak Academy of Sciences, Prague 6 and

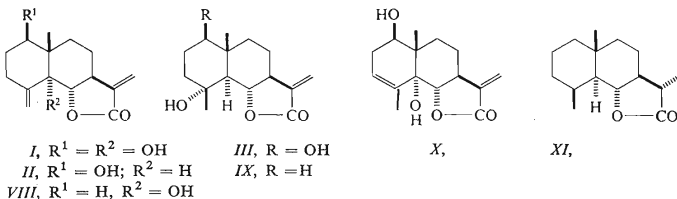[b]*Biological and Pharmaceutical Institute,*
Medical Academy, Poznań, Poland

The structure and the relative and absolute configuration of tanacetin (*I*) and 1β-hydroxyarbus-culin A (*III*), sesquiterpenic lactones isolated from *Tanacetum vulgare* L. (*Compositae*), have been determined mainly by PMR method. The presence of the sesquiterpenic lactone reynosin (*II*) has also been proved.

The sesquiterpenic lactone fraction obtained from *Tanacetum vulgare* L. (syno-nymum *Chrysanthemum vulgare* (L.) Bernh.) was studied by Suchý[1]. He described the isolation of the sesquiterpenic lactone *I* of the composition $C_{15}H_{20}O_4$ to which he gave the name tanacetin. The same plant material was investigated recently by two of us and from the sesquiterpenic lactone fraction four substances of the mentioned type[2] were isolated. One of them was identical with tanacetin[2] (*I*).

We investigated the structures of the three sesquiterpenic lactones *I*, *II* and *III*. The basic data on these substances are given in Table I. From the composition, IR spectra, and CD curves it followed that all three substances are sesquiterpenic hydroxy lactones with the usual α-methylene-γ-lactone ring *I*. From detailed analyses of the PMR spectra (Table II) of substances *I*—*III* and their trichloroacetylcarbamates *IV*—*VII* (TAC-derivatives; TAC = $CCl_3.CO.NH.CO$) prepared by *in situ* acylation of the free hydroxyl groups with trichloroacetyl isocyanate[3,4] the following structural aspects could be deduced: *a*) All three compounds contain a γ-lactone ring of secon-dary type, $CH_2=C(CO.O^+)$—$CH(CH_2)$—CH—O^+, one tertirary angular methyl group and one secondary hydroxyl group bound in its vicinal position to the angular methyl in the fragment CH_2—$CH(OH)$—$C(C,C)$—CH_3. The protons of the lactone ring were assigned in the usual manner on the basis of decoupling experiments. From the observed magnitudes of allylic couplings $^4|J| = 3.0 - 3.3$ Hz and of vicinal

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couplings of bridge head protons $^3J = 10\cdot8 - 11\cdot3$ Hz it further followed that it is a *trans* anellated lactone ring[5–8]. In the case of tanacetin (*I*) the proton of the lactone methine group of the CH—O type formed a doublet indicating in a normal case a tetrasubstituted carbon atom in vicinal position to this methine group, while in the case of substances *II* and *III* this proton formed the usual triplet or doublet of doublets indicating in addition to the bridge head coupling another vicinal coupling of approximately the same value $\left(^3J = 10\cdot8 - 11\cdot3 \text{ Hz}\right)$ and hence, in a normal case, also the presence of a methine group of type CH(C,C,C) in the second vicinal position of the methine CH—O of the lactone group. The presence of a secondary hydroxyl and the angular methyl, as well as their relative position, followed from the chemical shifts of corresponding methine protons ($3\cdot4-4\cdot2$ p.p.m.) and methyl protons ($0\cdot8-0\cdot96$ p.p.m.), and from their simultaneous paramagnetic acylation shifts $\Delta\delta$ H(TAC) $= 1\cdot30-1\cdot40$ p.p.m. and $\Delta\delta$ CH$_3$(TAC) $= 0\cdot15-0\cdot25$ p.p.m. (Table II); definitions: $\Delta\delta$ H$_i$(R) $= \delta$ H$_i$C$_i$(C$_j$—OH) $- \delta$H$_i$C$_i$(C$_j$—OR); R = acyl)[a], which are consistent with the known α- and γ-acylation shifts[3,4,9–11]. The presence of the methylene group in vicinal position to the secondary hydroxyl group followed from the presence of two vicinal couplings $^3J_1 = 4\cdot5-5$ and $^3J_2 = 11-11\cdot5$ Hz of the methine proton. From the magnitude of these couplings the equatorial position of the hydroxyl group also followed simultaneously. The relative 1,2- or 1,3-positions of the methine protons of the fragment CH—OH and the bridge head protons of the lactone ring were excluded by decoupling experiments. *b*) All three compounds contain in addition to an angular methyl also a second one-carbon side chain, *i.e.*, in the case of compounds *I* and *II* an unconjugated exomethylene group, and in the case of compound *III* a tertiary C-methyl group. *c*) In the molecule of substances *I* and *III* a tertiary hydroxyl is present in addition to the secondary hydroxyl group. From the comparison of the monocarbamate *IV* and dicarbamate *V* (acylation took place gradually) significant acylation shifts followed due to the acylation of the tertiary hydroxyl, as well as paramagnetic shifts for the protons of the unconjugated exomethylene group ($0\cdot27$ p.p.m.) and for the lactonic CH—O proton ($0\cdot19$ p.p.m.), and a dia-

I, R^1 = R^2 = OH   *III*, R = OH   *X*,   *XI*,
II, R^1 = OH; R^2 = H   *IX*, R = H
VIII, R^1 = H, R^2 = OH

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[a] *i, j* indicate the position in the chosen numbering.

TABLE I
The Properties of Tanacetin (*I*), Reynosin (*II*) and 1β-Hydroxyarbusculin A (*III*)

Compound M.p., °C	Composition (act. H)	Mass spectrum[a] m/e	IR spectrum[b] cm^{-1}	CD[c], nm ([θ])
I 205	$C_{15}H_{20}O_4$ (2)	264 (M) 236 (M — 18) 218 (M — 18 — 18)	3 615, 3 570, 1 765 1 649, 1 410, 1 130	252 (−2 770°)
II 137—140	$C_{15}H_{20}O_3$ (1)	248 (M) 230 (M — 18)	3 620, 3 500, 1 764, 1 672, 1 651, 1 413, 1 134	254 (−2 570°)
III 194—196	$C_{15}H_{22}O_4$ (2)	248 (M — 18) 230 (M — 18 — 18)	3 620, 3 570, 1 768, 1 672, 1 411, 1 132	254 (−2 410°)

[a] Measured on an AEI MS 902 spectrograph; [b] measured with a Zeiss UR-10 (Jena) spectrograph, in chloroform; [c] taken on a Roussel-Jouan Dichrographe CD-185 in methanol.

magnetic shift for the allylic bridge head proton (0·10 p.p.m.). These shifts are consistent with the presence of a tertiary hydroxyl in the fragment CH$_2$=C—C(OH,C)——CH(O$^+$)—CH—C(CO.O$^+$)=CH$_2$ Simultaneously, from the axial position of the allylic bridge head proton, deduced from the magnitude of the vicinal bridge head coupling, and from the mentioned diamagnetic shift of the acylation signal of this proton it follows that the tertiary hydroxyl is in an axial position (1,3 van der Waals effect[10]). In the case of substance *III in situ* acylation with trichloroacetyl isocyanate took place on both hydroxyl groups simultaneously and induced simultaneous significant paramagnetic shifts in the case of both tertiary methyl groups signals (0·22—0·26 p.p.m.; ref.[9,12−14]) and the signal of the methine proton of type CH——C(C,C,C) bound to the carbon atom in the neighbourhood of the lactone methine CH—O (1·12 p.p.m.). These shifts indicated the presence of a tertiary hydroxyl in the fragment CH$_3$—C(C,OH)—CH(C)—CH(O$^+$)—CH—C(CO.O$^+$)=CH$_2$. A pronounced paramagnetic shift of the methine proton CH—C(C,C,C) caused by acylation (1·12 p.p.m.) is consistent with the known β-shift in the relative axial-equatorial arrangement of the HO—C—C—H fragment[11], and it indicates a relative *cis* configuration of the methine proton and the tertiary hydroxyl.

From all these facts it followed that all three compounds *I* to *III* are selin-11(13)-en-6,12-olides.* Tanacetin has the structure represented by formula *I* and is, therefore,

*   In the literature on the chemistry of substances with the basic skeleton of 4,10-dimethyl-7-isopropylbicyclo[4,4,0]decane nomenclature is not yet unified, as for the mentioned basic skeleton both the name "selinane" and "eudesmane" is used. We prefer the name "selinane" which we proposed earlier[15−17].

TABLE II

Characteristic Parameters of PMR Spectra of Tanacetin (*I*), Reynosin (*II*), 1β-Hydroxyarbusculin A (*III*) and of Their Trichloroacetyl carbamates *IV*— *VII*

Compound[a]	H$_{(1)}$	H$_{(6)}$	H$_{(7)}$	H$_{(13)}$	H$_{(14)}$	H$_{(15)}$
I[b]	4·16 (5·0; 11·3)	4·25 (11·3)	3·33	6·08 (3·30) 5·40 (3·30)	0·84	5·02 (2 *H*)
IV[c,d]	5·47 (5·0; 11·5)	4·25 (11·0)	3·36	6·09 (3·30) 5·42 (3·30)	1·09	5·09 (2 *H*)
V[c,e,f]	5·38[g]	4·44 (11·5)	3·17	6·14 (3·40) 5·49 (3·10)	1·15	5·36 (2 *H*)
II	3·52 (4·5; 11)	4·02 $J_{5,6}$ = 10·8 $J_{6,7}$ = 10·8	2·51	6·07 (3·20) 5·39 (3·20) $^2J \neq 0 \ll 0.5$	0·80	4·98 (1 *H*) 4·86 (1 *H*)
VI[c,h]	4·87 (4·5, 11)	4·02 $J_{5,6}$ = 10·8 $J_{6,7}$ = 10·8	2·50	6·09 (3·20) 5·43 (3·10)	0·97	5·05 (1 *H*) 4·92 (1 *H*)
III[i]	3·44	4·11 $J_{5,6}$ = 11·3 $J_{6,7}$ = 10·8	2·59	6·11 (3·20) 5·45 (3·15) $^2J \neq 0 \ll 0.5$	0·96[j]	1·35
VII[c,k,l]	4·84 (4·5; 11·5)	4·16 $J_{5,6}$ = 11·3 $J_{6,7}$ = 11·3	2·66	6·17 (3·30) 5·84 (3·00)	1·18[m]	1·61

[a] Measured on Varian HA-100 instrument, solvent deuteriochloroform, internal standard tetramethylsilane; all data from first-order analysis, chemical shifts are given in δ-scale; splittings are given in parentheses if not stated otherwise. [b] H$_{3a}$: 2·66 td (J_1 = 6, $J_2 = J_3$ = 13·5); H$_{3e}$: 2·14 ddd (J_1 = 2, J_2 = 5, J_3 = 13·5); $^4J_{3a,15} > {}^4J_{3e,15}$, [c] Prepared in situ with trichloroacetyl isocyanate[3,4]. [d] H$_{3a}$: 2·76 td (J_1 = 6, $J_2 = J_3$ = 14); H$_{3e}$: 2·24 ddd (J_1 = 2, J_2 = 5·5, J_3 = = 14); $^4J_{3a,15} > {}^4J_{3e,15}$; NH: 8·26. [e] Acetylation product *IV* was formed immediately; the spectrum of *V* was measured after five days standing of the deuteriochloroform solution of *IV* containing a small excess of trichloroacetyl isocyanate. [f] H$_{3a}$, H$_{3e}$: > 2·50 p.p.m.; NH: 8·46 and 8·47. [g] overlap with signals of H$_{15}$. [h] NH: 8·36. [i] H$_5$: 1·82 d, $J_{5,6}$ = 11·5. [j] Methyl signal appeared as a doublet with a splitting of 0·6 Hz, corresponding probably to the long-range coupling with H$_{9a}$. [k] Acetylation was carried out after addition of deuteriotrifluoroacetic acid; therefore the signals of NH were not observed. [l] H$_5$: 2·93 d, $J_{5,6}$ = 11·5. [m] Broadened singlets.

1β,5α-dihydroxy-6β,7αH-selina-4(15),11(13)-dien-6,12-olide. Substance *II* is identical with reynosin (*II*) (1β-hydroxy-5α,6β,7αH-selina-4(15),11(13)-dien-6,12-olide) which was isolated from *Ambrosia confertiflora*[18]. Structure *II* was also assigned to one of the selinanolides isolated from *Chrysanthemum parthenium*[19] which is, according to its m.p. and PMR spectrum, very probably identical with reynosin[18] (*II*). We also corroborated the identity of our isolated substance *II* with reynosin by comparison of IR and PMR spectra of authentic samples. For the native compound *III*, for which we propose the name 1β-hydroxyarbusculin A, it followed that it had the structure represented by formula *III* (1β,4α-dihydroxy-5α,6βH-selin-11(13)-en-6,12-olide). The structure of substances *I* and *III* was proved by direct correlation of PMR data (Table II) with the published data on the structurally very close selinanolides arbusculin C[20] (*VIII*) and arbusculin A[21] (*IX*). In agreement with the equatorial position of the secondary hydroxyl on $C_{(1)}$, and in view of the long-range shielding and sterical effects of the little exposed hydroxyl group, all characteristic protons (except for $H_{(1)}$) of substances *I* and *VIII*, and substances *III* and *IX*, display practically identical distribution of the chemical shifts, as well as an identical continuity of the vicinal and long-range couplings.

Absolute configurations of all three substances, *I–III*, followed from CD measurements. The lactonic chromophore gives in all cases a negative CE with an elipt018icity of the range about $-2500°$ (Table I); according to empirical rules[22,23] it indicates in the case of selin-11(13)-en-6,12-olides a *trans* anellation of the lactone ring. However, this rule was deduced from a group of substances in which the same absolute β-configuration of the $C_{(7)}—C_{(11)}$ bond ((7S)-selinan-6,12 olides) is supposed. If this supposition is correct, then — in view of the fact that in enantiomeric compounds the sign of CE of the lactone chromophore should be opposite, *i.e.* positive for *trans* and negative for *cis* lactones — the sign of the CE of the lactone chromophore could be significant either for the annelation if the absolute configuration of the center at $C_{(7)}$ is known, or for absolute configuration of the centra $C_{(6)}$ and $C_{(7)}$ if their relative configuration is known, *i.e.* for the absolute configuration of the center $C_{(6)}$. Hence, in our case the *trans* annelation of the lactone found on the basis of PMR spectra, and the negative sign of CE, determine according to the above mentioned empirical correlations absolute configuration α for the $C_{(6)}—O$ bond, and configuration β for the $C_{(7)}—C_{(11)}$ bond, and therefore also the fact that all three substances *I–III* belong to common (7S)-selinan-6,12-olides. In the case of reynosin (*II*) its belonging to the mentioned group was also confirmed by correlation, *via* santamarin (*X*)[18,24] with 4α,5α,6β,7αH-selina-6,12-olide (*XI*) (santanolide C)[24–26].

From the chemotaxonomic point of view the occurrence of sesquiterpenic lactones of the selinane type is in agreement with the view that the occurrence of the substances of this type[27] in *Compositae, Anthemidae* tribe, where *Tanacetum vulgare* L. belongs, is quite typical.

REFERENCES

1. Suchý M.: This Journal *27*, 1058 (1962).
2. Grabarczyk H., Drożdż B., Możdżanowska A.: Dissert. Pharm. Pharmacol., in press.
3. Goodlet V. W.: Anal. Chem. *37*, 431 (1965).
4. Trehan I. R., Monder C., Bcse A. K.: Tetrahedron Letters *1968*, 67.
5. Pinhey J. T., Sternhell S.: Australian J. Chem. *18*, 543 (1965).
6. Herz W., Aota K., Holub M., Samek Z.: J. Org. Chem. *35*, 2611 (1970).
7. Samek Z.: Tetrahedrom Letters *1970*, 671.
8. Samek Z., Holub M., Vokáč K., Drożdż G., Jommi G., Gariboldi P., Corbella A.: This Journal *37*, 2611 (1972).
9. Jackman L. M.: *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry.* Pergamon Press, London 1959.
10. Bhacca N. S., Williams D. H.: *Application of the NMR Spectroscopy in Organic Chemistry.* Holden-Day, San Francisco 1964.
11. Narayan C. R., Sarma M. R.: Tetrahedron Letters *1968*, 1553.
12. Holub M., Motl O., Samek Z., Herout V.: This Journal *37*, 1186 (1972).
13. Holub M., Samek Z., De Groote R., Herout V., Šorm F.: This Journal *38*, 1551 (1973).
14. Holub M., Samek Z.: This Journal *38*, 1428 (1973).
15. Motl O., Herout V., Šorm F.: This Journal *23*, 1293 (1958).
16. Šorm F., Herout V., Plíva J.: Uspechi Chim. *22*, 564 (1953).
17. Kovács Ö., Herout V., Horák M., Šorm F.: This Journal *21*, 225 (1956).
18. Yoshioka H., Renold W., Fischer N. H., Higo A., Mabry T. J.: Phytochemistry *9*, 823 (1970).
19. Romo J., Romo de Vivar A., Treviño R., Joseph-Nathan P., Diaz E.: Phytochemistry *9*, 1615 (1970).
20. Irwin M. A., Geissman T. A.: Phytochemistry *10*, 637 (1971).
21. Irwin M. A., Geissman T. A.: Phytochemistry *8*, 2411 (1969).
22. Waddel T. G., Stöcklin W., Geissman T. A.: Tetrahedron Letters *1969*, 1313.
23. Stöcklin W., Waddel T. G., Geissman T. A.: Tetrahedron *26*, 2397 (1970).
24. Romo de Vivar A., Jimenez H.: Tetrahedron *21*, 1741 (1965).
25. Cocker W., McMurray T. B. H.: J. Chem. Soc. *1956*, 4549.
26. Kulkarni G. H., Kelkar G. R., Bhattacharryya S. C.: Tetrahedron *29*, 2639 (1964).
27. Herout V. in the book: *Pharmacognosy and Phytochemistry* (H. Wagner, L. Hörhammer, Eds). Springer, Berlin 1971.

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