

## ARCTOLIDE — A NEW SESQUITERPENIC LACTONE FROM

*Arctotis grandis* THUNB.\*Z.SAMEK<sup>a</sup>, M.HOLUB<sup>a</sup>, B.DROŽDŽ<sup>b</sup> and H.GRABARCZYK<sup>b</sup><sup>a</sup> Institute of Organic Chemistry and Biochemistry,  
Czechoslovak Academy of Sciences, 166 10 Prague and<sup>b</sup> Institute of Biology and Pharmacy,  
Medical Academy, Poznań, Poland

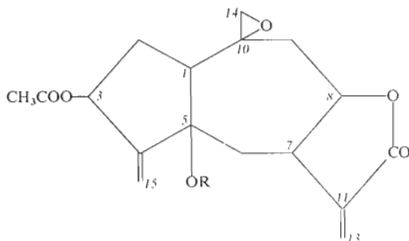
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From the above-ground part of the species *Arctotis grandis* THUNB. a new sesquiterpenic lactone was isolated, named arctolide. On the basis of physical methods, mainly <sup>1</sup>H-NMR spectroscopy, it was assigned the structure *III* with a relative configuration.

During a systematic study of sesquiterpenic lactones of the species of *Compositae* family we also investigated species classified as the *Arctoteae* tribe, as for example the species *Venidium hirsutum* and other. We now investigated the species *Arctotis grandis* THUNB. From its above-ground part we isolated substance *I* in the described manner<sup>1</sup>, which we named arctolide and which had m.p. 144–145°C and the composition C<sub>17</sub>H<sub>20</sub>O<sub>6</sub>. The IR spectrum of arctolide (*I*) contained bands at 3580 and 3530 cm<sup>-1</sup> (hydroxyl), at 1772 and 1162 cm<sup>-1</sup> (exomethylene-γ-lactone) and at 1740 and 1244 cm<sup>-1</sup> (acetate). The mass spectrum of arctolide did not display a molecular peak but signals of fragments of *m/e* 260 (*M* - 60), 242 (*M* - 60 - 18) and 60 (CH<sub>3</sub>COOH).

The structure of arctolide was derived directly from the analysis of its 100 MHz <sup>1</sup>H-NMR spectrum, using decoupling experiments. This spectrum was fully informative and its assignment is shown in Table I. From the multiplicity of the signals observed and from the topological continuity of vicinal long-range couplings of individual protons the structure expressed by formula *I* follows for arctolide. The structural assignment of the <sup>1</sup>H-NMR spectrum of arctolide was further confirmed by <sup>1</sup>H-NMR spectrum of its trichloroacetylcarbamoyl derivative *II* (TAC-derivative), obtained by acylation of arctolide *in situ* with trichloroacetyl isocyanate (TAI-method<sup>2,3</sup>). The characteristic parameters of the signals of protons of compound *II*, as well as the acylation shifts measured ( $\Delta^5\delta H_i$  (OH, OTAC) =  $\delta H_i$  (5-OH) -  $\delta H_i$  (5-CONHCOCCl<sub>3</sub>); ppm, *i* = 1–15) are also listed in Table I. As known from the study of model systems OH-acetyl<sup>4</sup>, the induced paramagnetic

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- I, R = H  
 II, R = CONHCOCl<sub>3</sub>

(downfield) acylation shifts are caused mainly by anisotropic shielding effects of the acyl carbonyl. The same is true of the system OH—TAC (ref.<sup>5-12</sup>). The observed long-range effects are maximum with protons in the  $\alpha$  and  $\beta$  positions and they may have rough values up to 1.5 ppm<sup>4-12</sup>. For the interpretation of these long-range effects the "spacial proximity" criterion may be applied. In the case of vicinal effect this criterion can be concretized to the spacial sector approximately limited by the *syn*-periplanar and *syn*-clinal configuration of the C—OH ( $\alpha$ ) bonds and C—H ( $\beta$ ) bonds. In a positive case, *i.e.* when a significant paramagnetic acylation shift is observed, both structural and conformational information may be obtained simultaneously from the observed shifts. In the case of arctolide (I) such shifts come into consideration for protons  $H_{(1)}$  and  $H_{(6)}$ . An adequate steric situation in fragments  $C_{(5)}-C_{(1)}$  and  $C_{(5)}-C_{(6)}$  is represented schematically by the Newman projections of one of the possible conformations, *i.e.* twist- $C_{(5)}$ -chair-like conformation, shown in Fig. 1. The different steric dispositions of protons on  $C_{(6)}$  are also confirmed by the vicinal interactions with  $H_{(7)}$ . The  $\gamma$ -shifts of the signals of protons on  $C_{(15)}$  are also significant; they are consistent with the  $\gamma$ -shifts in similar systems, as for example in tanacetin<sup>8</sup> and erivanin<sup>11</sup>. The differing values of the acylation shifts of  $H_{(15)}$  and  $H_{(15')}$  simultaneously indicate the distinctly differing steric dispositions for long-range effects, similarly as in the case of vicinal effects. When choosing the assignment of protons on  $C_{(15)}$  relatively to  $C_{(3)}$ , then the proton  $H_{(15)}$  may be indicated as *cisoid* on the basis of its acylation shift, and  $H_{(15')}$  as *transoid*, on the same basis. In Table I that geminal proton, the signal of which lies at a higher field is indicated with a dash. This assignment is in agreement with the sequence of long-range interactions  ${}^4J_{3,15}$   ${}^4J_{3,15'}$ , which is consistent with the usual relation for allylic interaction  ${}^4J$  (*cisoid*)  $>$   ${}^4J$  (*transoid*)<sup>13,14</sup> (the systems with a double bond conjugated with a carbonyl are an exception, as for example exomethylene  $\gamma$ -lactones, where the inversed relation applies; see for example  $H_{(13)}$  and  $H_{(13')}$ <sup>15,16</sup>). Further

more important shifts were also observed for signals of protons  $H_{(8)}$ ,  $H_{(9)}$  and  $H_{(9')}$ , where  $\Delta^5\delta H_{(8)}$  and  $\Delta^5\delta H_{(9)}$  are positive and  $\Delta^5\delta H_{(9')}$  is negative. Such shifts cannot be assigned to acylation long-range effects from the position  $C_{(5)}$  to the fragment  $C_{(9)}H_2-C_{(8)}H$  in a rigid conformation of the molecule. Evidently effects which are caused primarily by the pseudorotation of the positions of protons  $H_{(8)}$ ,  $H_{(9)}$  and  $H_{(9')}$  with respect to anisotropic shielding fields are in play, which may be induced potentially, for example, in the epoxide group on  $C_{(10)}$  or in the exomethylene double bond on  $C_{(4)}$ , or also in the acetyl group on  $C_{(3)}$ . Such pseudorotation, induced by acylation of  $C_{(5)}-OH$  is possible in the given case, because (as follows from the above discussed acylation shifts of protons on  $C_{(1)}$  and  $C_{(6)}$ ) the relative *cis* position of  $H_{(1)}$  and  $C_{(5)}-OH$  is involved, and hence also the *cis* annelation of the five-membered and the seven-membered homocyclic ring. In such a case the annelation could easily be the cause of the pseudorotation on the fragment  $C_{(5)}-C_{(1)}$ , for example from the fragment of type *a* to *b* or *vice versa*, as schematically illustrated in Fig. 1. From the analysis of the conformational possibilities of the molecule *I*, carried out with Dreiding models, it follows that such a pseudorotation need not in the majority of cases result in a significant variation of the dihedral angles (and hence also of the corresponding vicinal coupling constants), which are observable in this case as has been found (Table I). One of the possible structures permitting a consistent interpretation of the acylation shifts of  $\Delta^5\delta H_i$  (OH, OTAC) and vicinal and long-range coupling constants would be represented by formula *III*, with conformation containing vicinal fragments (*a-f*) with relative configurations illustrated

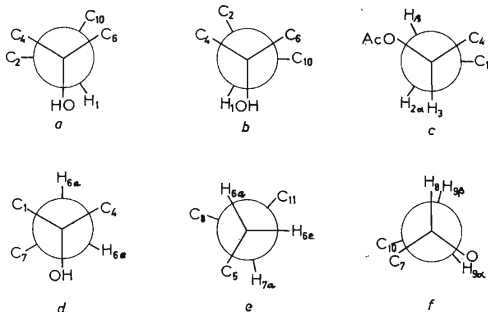


FIG. 1

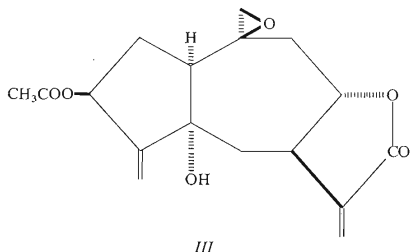
Schematic Representation of Probable Configurational Types of Some Fragments of the Molecule of Arctolide in Newman Projections

TABLE I

Comparison of the Parameters of the  $^1\text{H-NMR}$  Spectra of Arctolide (*I*) and Its Trichloroacetylcarbamoyl Derivative *II*

	$I^{a,b}$	$I^a$	$J^c$
H <sub>1</sub>	3.09 t ( $J_{1,2} \cong J_{1,2'} \cong 9$ )	1.95 (DR)	-1.14
H <sub>2</sub>	2.56 (DR; $J_{2,3} = 8.5$ )	2.52 ddd ( $J_{2,2'} = 13; J_{2,1} = 7; J_{2,3} = 8.5$ )	-0.04
H <sub>2'</sub>	1.52 ddd ( $J_{2,2'} = 14; J_{2,1} = 9.5; J_{2,3} = 6.5$ )	1.50 ddd ( $J_{2,2'} = 13; J_{2,1} = 11.5; J_{2,3} = 6.5$ )	-0.02
H <sub>3</sub>	5.69	5.66 ddt ( $J_{3,2} = 8.5; J_{3,2'} = 6.5; J_{3,1} \cong J_{3,1'} = 1.9$ )	-0.03
H <sub>6</sub>	2.95 dd ( $J_{6,6'} = 16; J_{6,7} = 1$ )	2.29 dd ( $J_{6,6'} = 15.5; J_{6,7} < 2$ )	-0.66
H <sub>6'</sub>	1.91 dd ( $J_{6,6'} = 16; J_{6,7} = 10.5$ )	1.86 dd ( $J_{6,6'} = 15.5; J_{6,7} = 10.5$ )	-0.05
H <sub>7</sub>	3.37 tm ( $J_{7,8} \cong J_{7,6'} \cong 10$ )	3.39 tm ( $J_{7,8} \cong J_{7,6} \cong 10$ )	+0.02
H <sub>8</sub>	4.16 dt ( $J_{8,9} = 6.5; J_{8,7} \cong J_{8,9'} \cong 9.5$ )	4.26 dt ( $J_{8,9} = 7.5; J_{8,7} = J_{8,9'} \cong 9.5$ )	+0.10
H <sub>9</sub>	2.58 dd ( $J_{9,8} = 6.5; J_{9,9'} = 14$ )	2.74 dd ( $J_{9,9'} = 14.5; J_{9,8} = 7.5$ )	+0.16
H <sub>9'</sub>	2.05 dd ( $J_{9,8} = 9.5; J_{9,9'} = 14$ )	1.89 dd ( $J_{9,9'} = 14.5; J_{9,8} = 9.5$ )	-0.16
H <sub>13</sub>	6.28 d ( $3.5 = J_{13,7}$ )	6.27 d ( $J_{13,7} = 3.4$ )	-0.01
H <sub>13'</sub>	5.64 d ( $J_{13,7} = 3.2$ )	5.61 d ( $J_{13,7} = 3.2$ )	-0.03
H <sub>14</sub>	2.70 d ( $J_{14,14'} = 4$ )	2.64 s	-0.06
H <sub>14'</sub>	2.61 d ( $J_{14,14'} = 4$ )	2.64 s	+0.03
H <sub>15</sub>	5.46	5.39 d ( $J_{15,3} \cong 2.1$ )	-0.07
H <sub>15'</sub>	5.46	5.25 d ( $J_{15,3'} \cong 1.8$ )	-0.21
CH <sub>3</sub> CO	2.10 s	2.11 s	+0.01

<sup>a</sup> Measured on a Varian HA-100 instrument in deuteriochloroform, using tetramethylsilane as internal reference; all the data are obtained from a first-order analysis; chemical shifts are in ppm,  $\delta$ -scale, splittings are in Hz; <sup>b</sup> measured after addition of a few drops of trichloroacetyl-isocyanate to a solution in deuteriochloroform after the exchange experiment with deuterioacetic acid has been carried out; <sup>c</sup>  $\Delta \delta \text{H}_i(\text{OH}, \text{OTAC}) = \delta \text{H}_i(\text{C}_5\text{-OH}) - \delta \text{H}_i(\text{C}_5\text{-OTAC})$ ; i = 1-15; TAC = CONHCOCCl<sub>3</sub>.



in Fig. 1. Among a series of conformational possibilities following for the structure *III* when the fragments of type *a–f* are used, two conformations  $K_1$  and  $K_2$  can be selected, in principle, which differ substantially in their fragments of type *a* and *b* and which have the remaining fragments (*a–f*) similar. In the first case the  $C_{(5)}$ -boat-like conformation of the seven-membered ring and the  $C_{(4)}$ -half-chair conformation of the five-membered homocyclic ring is associated with the fragment of the type *a*, and in the second case the  $C_{(5)}$ -chairlike conformation of the seven-membered ring and the  $C_{(2)}$ -half-chair conformation of the five-membered ring is associated with the fragments of the type *b*. The observed upfield shifts of protons  $H_{(8)}$  and  $H_{(9)}$  would not be caused by the van der Waals effect, but by the fact that these protons get into the diamagnetic sector of the shielding field of the exomethylene double bond on  $C_{(4)}$  during pseudorotation  $K_2 \rightarrow K_1$  if the conformation  $K_1$  is assigned to the trichloroacetylcarbamoyl derivative and the conformation  $K_2$  to the native arctolide.

The relative stereostructure *III* of the native substance *I* proposed by us is indeed one of the several possible stereostructures of this compound, and the information obtained so far cannot confirm it unambiguously, but the majority of the structural elements of the proposed formula *III* may be considered as very probable. In the first place there is the *cis* annelation of the five and seven-membered homocyclic rings, further the *trans* annelation of the  $\gamma$ -lactone ring (in addition to the vicinal coupling constant  $J_{7,8}$  the *trans* annelation is also indicated by the values of the allylic constants  $J_{7,13}$  and  $J_{7,13'}$ , in agreement with the "lactone rule":  $J_{7,13}$  (*trans* lactone)  $\geq 3$  Hz<sup>16</sup>; as already mentioned elsewhere the conditions for the validity of this rule are very well fulfilled in the guaianolide series<sup>17,18</sup>; the CD measurement did not afford any significant CE for the lactone chromophore), and also the relative conformations of the fragments  $C_{(5)}-C_{(1)}$  and  $C_{(7)}-C_{(8)}$ . The formulation of the configuration of the  $C_{(10)}$  centre is supported by the observed absence of the long-range coupling constants of protons  $H_{(14)}$  and  $H_{(14')}$ , which – according to our present knowledge – seems to be characteristic of  $1\alpha$ H-guaianolides with

an epoxide at  $C_{(10)}$  and an  $\alpha$ -configuration at  $C_{(14)}$  (for example see epoxides of artabsin and isophotosantonin series<sup>19</sup>; this problem will be the subject of a special study).

## EXPERIMENTAL

The melting point was determined on a Kofler block and it was not corrected. For TLC silica gel G Merck was used. The IR spectrum was measured in chloroform on a Zeiss UR-10 (Jena) and a Specord 71 spectrophotometer. The <sup>1</sup>H-NMR spectrum was measured on a Varian HA-100 apparatus. The mass spectrum was measured on an AEI MS 902 apparatus. Optical rotation was determined with an objective polarimeter in methanol. Circular dichroism was measured on a Roussel-Jouan Dichrographe CD 185 in methanol.

### Isolation of Arctolide

The ground above-ground part of *A. grandis* (*Compositae*, *Arctotae*) (13 kg) was worked up in the described manner<sup>1</sup> and 5 g of lactone fraction were obtained. This was chromatographed on silica gel (250 g). Elution was carried out first with benzene and then with mixtures of benzene with increasing amounts of acetone 1%, 2%, etc., up to 5%, and then 10% under control by TLC. From the last fractions a material was obtained which was rechromatographed on silica gel, elution with ethyl acetate, affording arctolide (415 mg), m.p. 144–145°C (methanol, ether),  $[\alpha]_D +64.1$  ( $c = 0.42$ ). IR spectrum: 3580 and 3530  $\text{cm}^{-1}$  (hydroxyl), 1772 and 1162  $\text{cm}^{-1}$  (exomethylene- $\gamma$ -lactone), 1740 and 1244  $\text{cm}^{-1}$  (acetate). Mass spectrum ( $m/e$ ): 260 ( $M - 60$ ), 242 ( $M - 60 - 18$ ), 60 ( $\text{CH}_3\text{COOH}$ ). CD spectrum (in methanol;  $\lambda$  nm,  $\Delta\epsilon$ ): 196, 0; 206, +6.58; 238, 0; 243, -0.03; 251, 0; 270, +0.1; 320, 0. For  $\text{C}_{17}\text{H}_{20}\text{O}_6$  (320.3) calculated: 63.74% C, 6.29% H, 0.31% H act.; found: 64.03% C, 6.47% H, 0.37% H act.

*The elemental analysis was carried out in the analytical department of our Institute (head Dr J. Horáček by Mrs E. Sýkorová and Dr V. Pechanec. The IR spectrum was measured by Mrs S. Holubová and Mrs K. Matoušková and interpreted by Dr S. Vašíčková of our Institute. Dr S. Vašíčková also measured and interpreted the CD curves.*

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