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SPATIAL STRUCTURES OF THE SESQUITERPENE GERMACRANE LACTONES TANACHIN AND TAMIRIN

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An x-ray investigation has been made of the sesquiterpene lactones tanachin and tamarin: diffractometer, CuKα-radiation, 845 and 981 reflections, respectively, direct method, R factors 0.064 and 0.065. The conformations of both molecules are boat-boat with configurations of the $^{1}D_{14}$ and $^{15}D_{5}$ types.

The structures of the sesquiterpine germacrane lactone tanachin and tamirin were established on the basis of spectral characteristics and chemical transformations [1-6]. However, stereochemical aspects of the structures of these compounds (the linkage of the rings and the conformation of ten-membered ring) on the basis of their PMR spectra caused difficulties because of the lability of the germacrane ring.

In order to establish reliably the spatial structures of tanachin and tamarin, we have carried out an x-ray structural investigation of them, results of which are shown in Fig. 1. It can be seen from Fig. 1 that the lactone ring in the 7,8 positions of these molecules is linked with the germacrane ring in the trans manner, as suggested previously [2]. The hydroxy groups in positions 1 and 6 in tanachin and in position 6 in tamirin are α-oriented. The conformation of the germacrane ring is characterized by the torsion angles given in Table 1. The values of −157.6° for the C9C10C1C2 torsion angle and 165.9° for the C3C4C5C6 torsion angle around the double bond in tanachin and corresponding values of −153.7° and 166.4° in tamirin permit these compounds to be assigned to the trans-trans germacranolides, i.e., to the germacrolides [7].

By projecting the molecule onto the plane perpendicular to the mean square plane of the germacrane ring it can be seen that the C1=C10 and C4=C5 double bonds are practically parallel while the methyl and methylene groups at C10 and C4 have the anti orientation similar to that found in mucrin [8]. Consequently, the germacrane rings in tanachin and tamirin have the boat-boat conformation with configurations of the $^{1}D_{14}$ and $^{15}D_{5}$ types.

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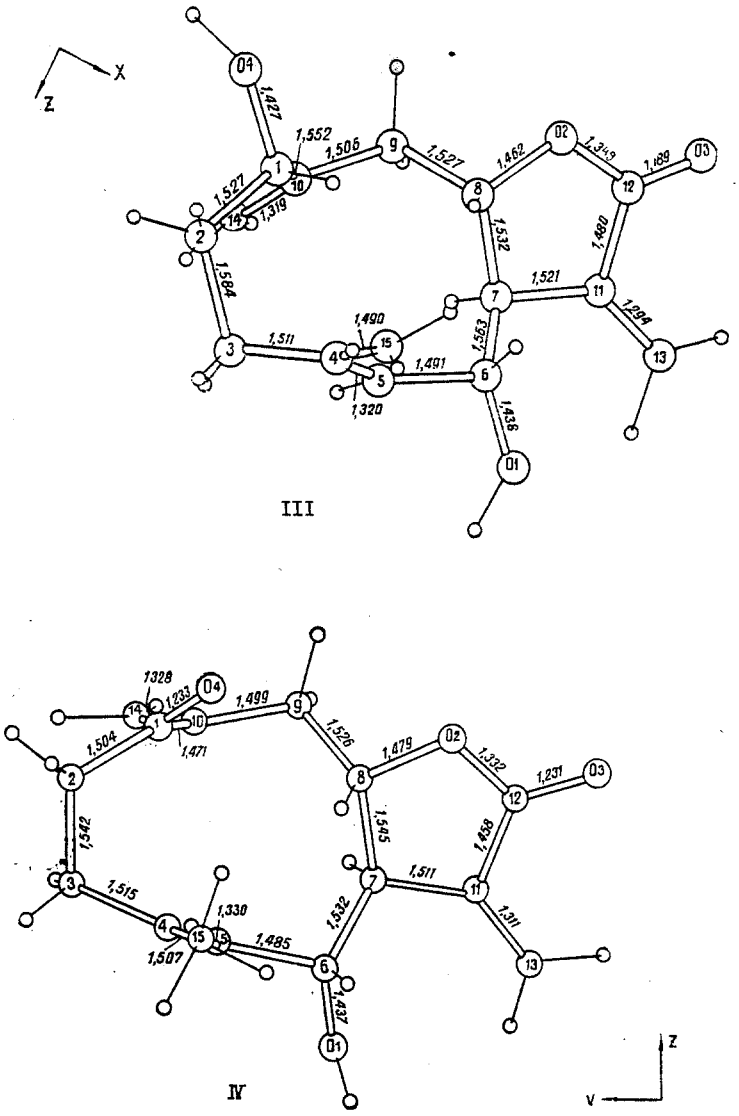
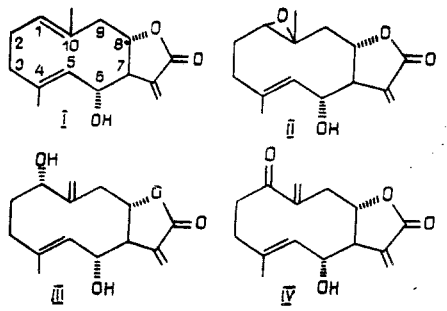


Fig. 1. Geometry of the tanachin (III) and tamirin (IV) molecules.

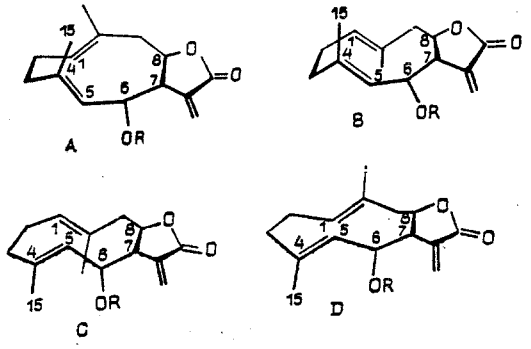
TABLE 1. Intracyclic Torsion Angles (deg) of the Mucrin (II), Tanachin (III), and Tamirin (IV) Molecules

Angle	II	III	IV	Angle	C_s theor	II	IV
1—2—3—4	40,1	—33,8	—36,4	12—11—7—8	46,1	8,6	11,4
2—3—4—5	34,3	103,1	106,5	02—12—11—7	—28,6	—5,1	—6,5
3—4—5—6	—170,5	—165,9	—166,4	8—02—12—11	0,0	—1,2	—1,8
4—5—6—7	114,9	119,2	110 4	7—8—02—12	28 6	6,6	9,2
5—6—7—8	—46,2	—67,3	—56,6	11—7—8—02	—46,1	—8 9	—12,3
6—7—8—9	110,6	110 8	107,5		C_2 theor	III	
7—8—9—10	—68,7	—73 0	—82,0				
8—9—10—1	—62,1	—66,3	—58,0				
9—10—1—2	149,5	157,6	153,7	8—02—12—11	15,1	2,9	
10—1—2—3	—114,7	—57,6	—57,1	7—8—02—12	—39,4	—7,3	
				11—7—8—02	48,1	8,4	
				12—11—7—8	—39,4	—6,8	
				02—12—11—7	15,1	2,8	

The natural sesquiterpine germacrane lactones mucrin (II), tanachin (III), and tamirin (IV) differ structurally from one another at the 1,10 positions, i.e., as if they were biogenetic derivatives at the 1,10 center of deacetyllaurenobiolide (I) [9]:



It is known that such germacrane 7,8-lactones are conformationally labile. For example, for laurenobiolide in solution at −15°C all four conformations, A-D, are observed in a ratio of 5:4:3:1 [10]:



An intercomparison of the spatial structures of the 7,8-lactones (II), (III), and (IV) under investigation with the aim of detecting conformational changes appeared of interest. The conformations shown schematically indicate that conformational states A and B are identical in the C3-C9 section and are predominating in laurenobiolide. A similar picture for the C3-C9 section is observed in compounds (II), (III), and (IV), where its conformation corresponds to A and B. Conformations C and D are hindered because of the steric repulsion of the syn-directed C15-methyl group and the α-OR substituent at C-6. Analysis of the literature confirms this hypothesis. In actual fact, in the 7,8- (or 7,6-) -trans-germacrolides with the α-orientation of the OR substituent in position 6 conformation A or B predominates [11, 12]. Consequently, in the case of the β-orientation of a OR substituent at C6 the C and D conformations are predominating. The structures of the germacrane esters chimganidin 8-O-angelate [13] and shiromodiol (ugamdiol) 8-O-angelate [14], each with a β-OH group at C-6, also confirm our hypothesis concerning the realization of conformation C.

Thus, the mutual transition A ↔ B, i.e., from the chair-chair conformation to the boat-boat conformation or conversely in the compounds under investigation is determined by the conformational mobility of the C9-C10-C1-C2 section. While in the case of laurenobiolide such an A ↔ B transition takes place readily [10], in compounds (II), (III), and (IV) it is hindered because of the presence of a substituent in position 1 (in the case of (II) there is an epoxide ring in the 1,10 position, in (III) there is an OH group in position 1, and in (IV) a keto group in this position). Consequently, a section with restricted mobility in the molecules of (II), (III), and (IV) is the C1-C4 fragment, because of which the torsion angles at the C1-C2, C2-C3, and C3-C4 bonds may differ substantially, as can be seen from Table 1.

In conclusion, it may be mentioned that the conformation of the 10-membered ring in mucrin, tanachin, and tamarin is less mobile than in the case of laurenobiolide, and the boat-boat conformations found in the crystalline state must correspond to the conformations realized in solution.

In each of these molecules, the lactone ring has a conformation close to planar with an accuracy of 0.05 A. However, it may be mentioned that in the values of the torsion angles of the lactone ring slight regular changes are observed in the direction of the half-chair conformation (with C_2 symmetry) in tanachin and in the direction of an envelope conformation (with C_s symmetry) in tamirin (see Table 1) [15].

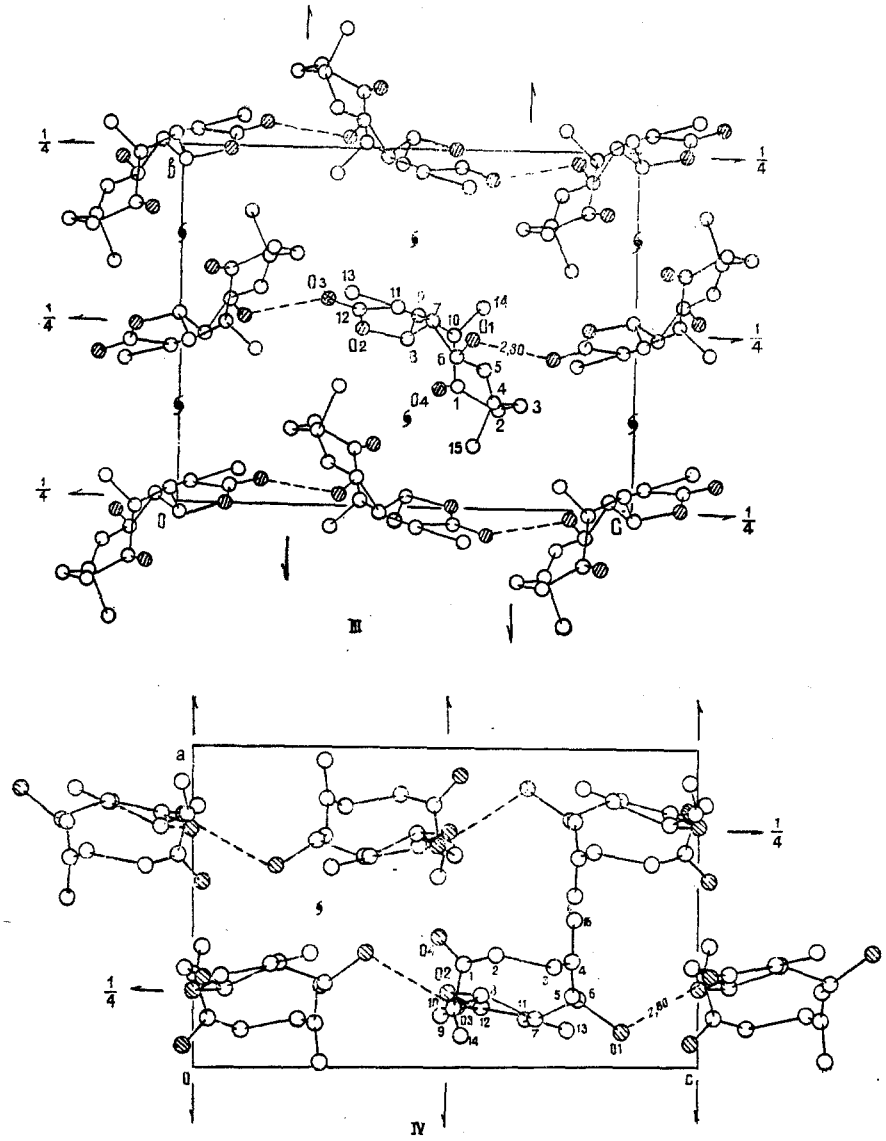


Fig. 2. Packing of the tanachin (III) and tamirin (IV) molecules.

TABLE 2. Valence Angles (deg) of the Tanachin (III) and Tamirin (IV) Molecules

Angle	III	IV	Angle	III	IV
2—1—10	117,1	120,6	7—8—9	116,3	118,3
10—1—04	108,3	117,2	7—8—02	107,2	105,5
2—1—04	108,9	122,1	9—8—02	106,6	104,7
1—2—3	112,7	112,0	8—9—10	116,4	115,9
2—3—4	112,3	111,5	1—10—9	115,0	117,9
3—4—5	117,9	118,9	9—10—14	122,8	122,9
3—4—15	120,4	115,5	1—10—14	121,7	118,9
5—4—15	121,7	125,6	7—11—12	107,9	106,9
4—5—6	128,6	129,4	7—11—13	131,9	131,9
5—6—7	106,9	109,8	12—11—13	120,2	121,2
5—6—01	111,5	109,8	11—12—02	109,8	111,9
7—6—01	107,0	106,4	02—12—03	121,1	119,5
6—7—8	111,4	118,2	11—12—03	129,1	128,6
6—7—11	113,3	113,8	8—02—12	111,6	110,8
8—7—11	102,9	103,5			

TABLE 3. Coordinates of the Atoms (× 10^4; for H, × 10^3) in the Structures of Tanachin (III) and Tamirin (IV)

Atom	III			IV		
	x	y	z	x	y	z
C1	6750 (7)	3446 (6)	6106 (4)	3299 (5)	4761 (5)	5295 (4)
C2	6640 (8)	2837 (6)	7002 (4)	3632 (6)	5890 (5)	5977 (5)
C3	8213 (8)	2949 (6)	7535 (3)	3190 (7)	5680 (5)	7115 (5)
C4	9631 (8)	2898 (6)	6955 (3)	3362 (5)	4293 (5)	7445 (4)
C5	10350 (7)	3957 (6)	6783 (3)	2303 (5)	3560 (4)	7545 (4)
C6	11530 (6)	4218 (6)	6101 (3)	2205 (6)	2143 (5)	7645 (4)
C7	10842 (6)	5247 (5)	5494 (3)	1600 (5)	1575 (4)	6653 (4)
C8	9440 (6)	4754 (6)	4979 (3)	2362 (5)	1929 (4)	5654 (3)
C9	7863 (6)	5288 (5)	5225 (3)	1760 (6)	2899 (5)	4906 (4)
C10	7180 (7)	4851 (6)	6075 (3)	1953 (5)	4285 (5)	5184 (4)
C11	11955 (7)	5666 (5)	4783 (3)	1583 (4)	125 (4)	6636 (3)
C12	11137 (8)	5559 (6)	3940 (3)	2030 (5)	−269 (4)	5607 (4)
C13	13367 (8)	6076 (7)	4811 (4)	1300 (5)	−720 (5)	7357 (4)
C14	6815 (8)	5623 (5)	6709 (4)	965 (5)	5113 (5)	5222 (4)
C15	10075 (10)	1706 (6)	6521 (4)	4750 (5)	3841 (5)	7547 (4)
O1	12935 (4)	4723 (4)	6471 (2)	1333 (3)	1820 (3)	8484 (2)
O2	9707 (4)	5075 (4)	4067 (2)	2450 (3)	726 (3)	5045 (2)
O3	11589 (6)	5808 (5)	3230 (3)	2045 (4)	−1350 (3)	5221 (3)
O4	5302 (5)	3287 (5)	5669 (2)	4170 (3)	4155 (3)	4847 (3)
H1	760	300	570			
H2.1	627	185	692	462	609	582
H2.2	556	309	733	379	675	559
H3.1	829	376	796	375	621	756
H3.2	827	222	803	207	583	707
H5	1000	481	717	126	396	739
H6	1172	325	566	320	178	774
H7	1034	604	582	74	200	648
H8	951	371	504	338	213	594
H9.1	698	525	468	214	274	408
H9.2	805	635	517	75	274	483
H13.1	1391	627	430	97	−55	805
H13.2	1391	615	546	113	−170	715
H14.1	706	658	661	99	614	537
H14.2	681	514	733	8	485	508
H15.1	1021	171	582	513	368	676
H15.2	974	92	678	507	420	831
H15.3	873	125	755	480	292	728
HO1	1315	474	715	205	155	908
HO4	405	341	569	—	—	—

No anomalies are observed in the values of the valence angles and distances. The bond lengths and valence angles are given in Fig. 1 and Table 2, respectively (mean square deviations not more than 0.009 Å, and 0.6°, respectively).

The packing of the tanachin and tamirin molecules is shown in Fig. 2 as projections on the bc and ac planes, respectively. The hydroxy and carbonyl groups participate in the formation of intermolecular H-bonds, the O1-H···O3 distance in tanachin and tamirin being 2.80 A. The tanachin and tamirin molecules, being bound by 2_1 [1/4, 0, Z] and [0, 1/4, Z], axes, respectively, form continuous chains along the c-axis.

EXPERIMENTAL

Colorless crystals of tanachin (III) and tamirin (IV) of acicular and tabular form, respectively, were grown from ethyl acetate–hexane (1:1) and were subjected to preliminary examination by the photo method. The space groups and parameters of the elementary cells were established from precession x-ray patterns. Subsequently, these parameters were refined in a Syntex-$P2_1$ diffractometer using CuKα radiation: for (III) a = 8.611(5), b = 10.709(5), c = 15.381(9) Å, d_{calc} = 1.24 g/cm³, and for (IV) a = 10.207(1), b = 10.416(2), c = 12.826(3) Å; d_{calc} = 1.24 g/cm³; space groups $P2_12_12_1$, Z = 4.

The intensities of the reflections were measured on the same diffractometer. In the primary treatment of the group, weak reflections with $I \leq 2\sigma$ were excluded. The final groups of structural amplitudes contained 845 (III) and 981 (IV) independent non-zero values. The structures were determined by the direct method using the Rentgen-75 program [16] in the automatic regime and were refined by the method of least squares (MLS) with allowance for the anisotropic thermal vibrations of the nonhydrogen atoms to R = 0.087 (III) and 0.083 (IV). At this stage, difference electron density syntheses were calculated and

the positions of all the H atoms were found. The final values of the divergence factors after four cycles of MLS with allowance for the H atoms but without refining their positions were 0.064 (III) and 0.065 (IV). Coordinates of the atoms are given in Table 3.

SUMMARY

The stereochemistries of the sesquiterpene lactones tanachin and tamirin have been established unambiguously by the x-ray structural method; they are 1,6-dihydroxy-1α,6α,-7α(H),8β(H)-germacra-4,11(13),10(14)-trien-8,12-olide and 6-hydroxy-1-oxo-6α,7α(H),8β(H)-germacra-4,11(13),10(14)-trien-8,12-olide, respectively. Boat-boat conformations of the ten-membered rings with configuration of the $^{1}D_{14}$ and $^{15}D_{5}$ types have been established for both molecules.

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