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CRYSTAL STRUCTURE 2,4-DIDEACETYLDIHYDROXYINUCHINENOLIDE C. EFFECT OF PSEUDOROTATION IN THE SEVEN-MEMBERED RING OF LINEAR trans,trans-CONJUGATED PSEUDOGUANOLIDES

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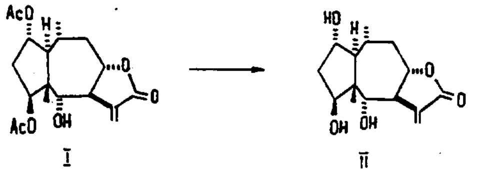
The spatial structure of 2,4-dideacetyldihydroxyinuchinenolide C has been established by the x-ray structural method. On the basis of an analysis of known crystal structures of linear trans, trans-conjugated pseudoguanolides using the method of molecular mechanics it has been shown that a partial pseudo-rotation of the seven-membered carbocycle in these compounds is possible.

The isolation of the sesquiterpene lactone inuchinenolide C (I) from the epigeal part of Caspian inula *Inula caspica* Blume and the determination of its spatial structure have been reported previously. With the aim of a further analysis of the stereochemistry of this class of compound, we have made an x-ray structural investigation of 2,4-dideacetyldihydroxyinuchinenolide C (II), the product of the hydrolysis of (I):



I II

The general form of the (II) molecule is shown in Fig. 1. The bond lengths (Table 1) and valence angles (Table 2) are close to the usual ones [2] within the limits of accuracy, with the exception of somewhat lengthened C1−C2, C1−C5, and C1−C10 bonds at 1.556(5), 1.562(6), and 1,556(4) Å, respectively, and the distorted valence angles C5C1C10 117.3(3)°, C1C5C4 99.2(3)°, C1C5C6 115.9(3)°, C6C7C11 116.8(3)°, C8C7C11 103.5(3)°, and C8C9C10 116.9(3)° differing considerably from the ideal tetrahedral angle (109.5°). However, we may note that the lengthening of the bonds and the distortion of the valence angles at the positions of ring linkage are also observed in other pseudoguanolides (see, for example, [1, 3, 4])

The A/B and B/C ring linkages are trans (the torsional angles H1C1C5C15 and H7C7C8H8 are 168(1)° and 156(1)°. Ring A has an almost ideal 4α,5β-half-chair conformation ($\Delta C_2^2 = 1.4°$), while ring C is intermediate between a 7α-envelope and 7α,8β-half-chair ($\Delta C_s^7 = 5.0°$ and $\Delta C_2^{12} = 4.6°$). The cyclopentane ring B assumes the conformation of a considerably distorted 1,10α,8,9β-twist-chair ($\Delta C_2^6 = 16.0°$ and $\Delta C_s^9 = 28.9°$) (the torsional angles are given in Table 3). The estimate $\Sigma_2/(\Sigma_s + \Sigma_2)$ characterizing the degree of deviation of the cyclopentane ring from the ideal twist-chair (TC) and chair (C) conformations, for which $\Sigma_2/\Sigma_s + \Sigma_2) = 0$ and 1, respectively has a value of 0.27 for ring B.

Analysis of literature information on the crystal structure of trans,trans-conjugated pseudoguanolides has shown that various conformations are realized for the seven-membered ring from 1,10α,8,9β-TC in bromoisotenulin (III) [5], amblyodiol (IV) [6], (±)-decahydro-4-hydroxy-4α,8-dimethylazuleno[6,5-b]furan-2,5(3H)-dione (V) [3], diacetylspathulin (VI) [7], and britanin (VII) [8] to 9α,5,6β-C in (±)-decahydro-4,5-dihydroxy-4α,8-dimethylazuleno[6,5-b]furan-2(3H)-one (VIII) [4] and 11,13-dibromopulchellin (IX) [9].

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TABLE 1. Bond Lengths (Å) in the Structure of (II)

O1—C8	1,476(4)	C4—C5	1,551(4)
O1—C12	1,318(5)	C5—C6	1,552(4)
O2—C12	1,211(5)	C5—C15	1,546(6)
O3—C2	1,431(7)	C6—C7	1,536(5)
O4—C4	1,427(5)	C7—C8	1,538(4)
O5—C6	1,432(4)	C7—C11	1,501(5)
C1—C2	1,556(5)	C8—C9	1,495(6)
C1—C5	1,562(6)	C9—C10	1,536(5)
C1—C10	1,556(4)	C10—C14	1,538(8)
C2—C3	1,540(6)	C11—C12	1,503(4)
C3—C4	1,502(6)	C11—C13	1,297(5)

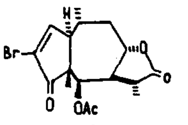
TABLE 2. Valence Angles (degrees) in the Structure of (II)

C8O1C12	111,6(2)	O5C6C7	107,4(3)
C2C1C5	105,8(3)	C5C6C7	114,0(3)
C2C1C10	111,4(3)	C6C7C8	114,5(3)
C5C1C10	117,3(3)	C6C7C11	116,8(3)
O3C2C1	112,8(3)	C8C7C11	103,5(3)
O3C2C3	112,9(3)	O1C8C7	104,6(3)
C1C2C3	105,9(3)	O1C8C9	107,6(3)
C2C3C4	104,6(3)	C7C8C9	113,6(4)
O4C4C3	114,5(3)	C8C9C10	116,9(3)
O4C4C5	112,3(3)	C1C10C9	114,9(3)
C3C4C5	105,5(2)	C1C10C14	111,0(4)
C1C5C4	99,2(3)	C9C10C14	106,5(4)
C1C5C6	115,9(3)	C7C11C12	105,6(3)
C4C5C6	111,2(2)	C7C11C13	132,7(3)
C1C5C15	111,5(3)	C12C11C13	121,7(3)
C4C5C15	109,2(3)	O1C12O2	123,1(3)
C6C5C15	109,4(3)	O1C12C11	110,4(3)
O5C6C5	113,9(3)	O2C12C11	126,5(4)

TABLE 3. Torsional Angles (degrees) in the Rings of Structure (II)

C1C2C3C4	—13,8	C8C9C10C1	—47,8
C2C3C4C5	36,8	C9C10C1C5	68,8
C3C4C5C1	—44,1	C10C1C5C6	—81,7
C4C5C1C2	34,8	O1C8C7C11	20,4
C5C1C2C3	—13,7	C8C7C11C12	—18,4
C1C5C6C7	26,3	C7C11C12CO1	9,8
C5C6C7C8	51,0	C12CO1C8C7	3,9
C6C7C8C9	—94,2	C11C12O1C8	—15,6
C7C8C9C10	67,9		

In a number of compounds a conformation of ring B intermediate between 1,10α,8,9β-TC and 9α,5,6β-C is observed: (II), geigerinin (X) [10], spathulin (XI) [11], graveolide (XII) [12], and allodeacetylconfertiflorin (XIII) [13] with different degrees of distortion from the ideal TC and C. It has also been found that in the structure of pulchelloid C (XIV) [14] ring B assumes a conformation intermediate between 9α,5,6β-C and 7,8α,9,10β-TC.



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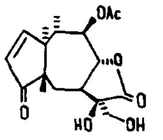

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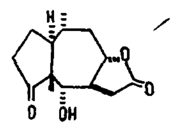

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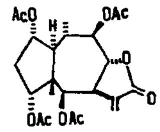

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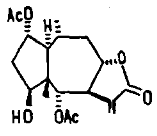

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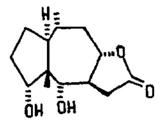

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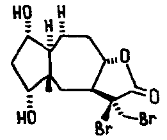

IX

As follows from the values of the estimate $\Sigma_2/\Sigma_s + \Sigma_2$ and the torsional angles in rings B of compounds (I)-(XIV) (Table 4), in the linear trans,trans-conjugated pseudoguanolides an effect of partial pseudorotation in ring B between 1,10α,8,9β-TC and 9α,5,6β-C is observed. In this case, complete pseudorotation of the seven-membered ring is impossible because of its conjugation with the two five-membered rings A and C.

TABLE 4. Torsional Angles (degrees) in Rings B of the trans-trans-Linked Linear Pseudoguanolides Investigated Structurally

Structure	Angles at these bonds							$\frac{\Sigma_2}{\Sigma_s+\Sigma_2}$
	1—5	5—6	6—7	7—8	8—9	9—10	1—10	
IIIa*	—95,1	39,8	38,4	—93,8	73,7	—44,0	68,9	0,07
IIIb*	—94,1	37,8	40,8	—91,5	71,5	—49,9	73,3	0,07
IV	—86,7	35,8	38,8	—84,4	66,6	47,8	69,2	0,09
V	—85,6	34,0	41,9	—89,7	69,9	—50,0	69,2	0,13
VI	—85	39	37	—90	75	—53	68	0,16
VII	—85,0	34,1	45,5	—93,6	67,0	—45,0	66,8	0,17
I	—81,7	26,3	51,0	—94,2	67,9	—47,8	68,8	0,27
Xa*	—77,0	22,2	50,7	—92,2	70,5	—51,4	69,8	0,33
Xb*	—77,5	17,9	55,5	—92,7	68,6	—52,2	73,0	0,43
II	—80	22	57	—97	68	—52	73	0,40
XI	—81,0	21,1	53,1	—91,6	68,1	—53,9	77,7	0,48
XII	—75,4	13,1	57,9	—90,0	66,4	—54,7	76,5	0,56
XIII	—74,0	12,1	59,5	—98,8	71,1	—49,8	71,3	0,48
VIII	—68,4	0,9	66,9	—91,4	64,8	—54,2	77,5	0,80
IXa*	—64,0	—4,4	61,9	—76,0	56,5	—62,9	86,1	0,85
IXb*	—69,4	—4,4	66,5	—90,2	66,1	—58,6	90,5	0,90
XIV	—59,1	—18,0	77,6	—84,8	61,6	—62,9	87,7	0,64
XV	—77	19	54	—94	71	—53	73	0,41
XVI	—72	11	57	—94	72	—54	73	0,52

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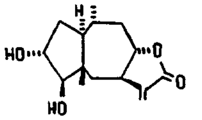
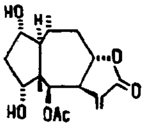
*Crystallographically independent molecules.



X



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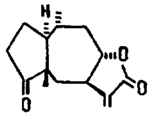
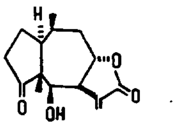
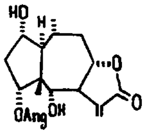


XII



XIII



XIV

It is quite natural to assume that the reason for the considerable differences in the experimentally observed conformations of rings B is the presence of different substituents in them and their type, number, and orientation. However, a detailed comparison of the structures of the molecules of the compounds under consideration showed no clear correlation between the type of substitution and the conformation of ring B. Thus, when the hydroxy groups at the C2 and C4 atoms in (I) were replaced by acetoxy groups in (II) or the same substitution at the C2 and C6 atoms in (VII), the ratio $\Sigma_2/(\Sigma_s + \Sigma_2)$ changed from 0.27 to 0.17 and 0.48, respectively. Likewise, when the two OH groups at C2 and C4 in (XI) were replaced by OAc groups in (VI), the value of $\Sigma_2/(\Sigma_s + \Sigma_2)$ changed from 0.40 to 0.16. Particularly indicative is the marked change in the conformation of ring B from C in (VIII) to TC in (V) on the oxidation of the OH group in ring A to a keto group ($(\Sigma_2/(\Sigma_s + \Sigma_2) = 0.80$ and 0.13, respectively).

The considerable change in the conformation of ring B from intermediate between 9α,5,6β-C and 1,10α,8,9β-TC in (II), to intermediate between 9α,5,6β-C and 7,8α-TC in (XIV) also took place when the hydroxy group was replaced by an angeloyloxy group and its orientation was changed from the α- to the β-direction ($(\Sigma_2/(\Sigma_s + \Sigma_2) = 0.48$ and 0.64). It follows from this that it does not yet appear to be possible to establish unambiguously an influence on the conformation of ring B for such substituents as OH, keto, or ester groups.

Earlier, on the basis of a consideration of the structure of (IX) [12] Appendino et al. had suggested that a chair conformation of ring B, energetically less favorable than the twist-chair conformation, can be realized through the formation

TABLE 5. Coordinates of the Atoms ($\times$ 10^4, for H $\times$ 10^3) in Structure (II)

Atom	x	y	z	Atom	x	v	z
O1	3516(3)	3244	−516(2)	HO4	445(4)	434(6)	678(4)
O2	5604(3)	3300(6)	−1350(2)	HO5	594(4)	219(5)	400(4)
O3	1318(3)	−392(6)	4852(3)	H1	295(4)	86(5)	337(3)
O4	4191(3)	4547(6)	6097(2)	H2	23(3)	173(4)	443(3)
O5	5846(2)	3105(5)	4020(2)	H3a	142(4)	347(6)	589(3)
C1	2163(3)	1851(6)	3386(3)	H3b	230(4)	183(6)	647(4)
C2	1341(4)	1421(7)	4570(3)	H4	433(3)	216(4)	542(3)
C3	2113(4)	2492(7)	5771(4)	H6	471(3)	494(4)	309(3)
C4	3520(3)	3099(6)	5356(3)	H7	437(3)	158(5)	194(3)
C5	3118(3)	3487(6)	3834(3)	H8	277(3)	452(5)	90(3)
C6	4524(3)	3712(6)	3194(3)	H9a	229(4)	100(5)	67(4)
C7	4429(3)	2846(6)	1815(3)	H9b	101(4)	240(5)	6(4)
C8	3039(4)	3311(7)	804(3)	H10	39(3)	296(5)	204(3)
C9	1806(4)	2043(7)	779(3)	H13a	761(4)	332(7)	236(4)
C10	1072(4)	1959(7)	2032(3)	H13b	773(4)	356(6)	85(3)
C11	5666(4)	3207(7)	1058(3)	H14a	62(5)	−78(8)	177(5)
C12	4966(5)	3254(7)	−397(3)	H14b	−66(5)	48(7)	94(5)
C13	7076(5)	3405(9)	1434(4)	H14c	−72(5)	28(7)	246(4)
C14	33(6)	386(9)	1848(5)	H15a	278(4)	609(6)	393(4)
C15	2185(5)	5160(6)	3628(4)	H15b	113(5)	500(6)	386(4)
HO3	217(4)	−76(6)	504(4)	H15c	190(5)	550(7)	273(5)

of hydrogen bonds in the crystal. However, it must be mentioned that a substantial difference in the conformations of rings B is also observed in those molecules that are incapable of forming H-bonds (since they do not contain proton-donating groups). Thus, the conformation of ring B changes from almost symmetrical chair in (III) to a somewhat distorted one in (VI) and to a conformation intermediate between C and TC in (XII) (Table 4). This shows the possibility of an influence of the conformation of ring B not only of comparatively strong (H-bonds) but also of comparatively weak intermolecular interactions. In this connection, it may be assumed that for this type of carcass one broad potential trough exists within which a comparatively easy transition from 9α,5,6β-C to 1,10α,8,9β-TC is possible, taking place even with small changes in the energy of the crystal field. In actual fact, the torsional angles in rings B of compound (I)-(XIV) are fairly remote from the values of 0 and 120° corresponding to the maxima of the barrier to rotation around ordinary bonds, with the exception of the C1C5C6C7 torsional angle in some molecules, and does not pass through these maxima. Changes in the torsional angles in the C7...C10−C1 section of the molecule take place within the range of 10-20° and in the C1−C5...C7 section within the range of 30-40°.

To confirm the possibility of an influence of crystal packing on the conformation of ring B we modeled pseudorotation for the molecules (VII) (TC), (IX) (C), and (I) and (VIII) (intermediate conformations) by the method of molecular mechanics. Figure 2 shows the dependence of the conformational energy E (kcal/mole) on the C1C5C6C7 intracyclic torsional angle ($\varphi_{5,6}$). The value of the angle $\varphi_{5,6}$ for the ideal 9α,5,6β-C is 0°, for 10α,5,6β-C it is 66°, and for the 1,10α,8,9β-TC and 7,8α,9,10β-TC conformations it is 39 and −39°, respectively [15].

As follows from Fig. 2, for the molecules in this section of pseudorotation a barrier-free transition from the TC conformation to C is in fact possible. The difference in the conformational energy (ΔE) for the C and TC conformers changes in this case from 0.3 kcal/mole in (IX) to 1.6 kcal/mole in (VIII), and for the (IX) molecule the chair conformation proves to be somewhat more favorable than the twist-chair conformation. As was to be expected, the real minima for all the molecules under consideration are located in the region intermediate between 9α,5,6β-C and 1,10α,8,9β-TC, being concentrated in the region of $\varphi_{5,6}$ values of 20-30°. The difference between the conformation of ring B observed in the crystals (the values of $\varphi_{5,6}$ in the crystal structures are marked in the graph by asterisks) and the calculated position of the minimum for the (IX) molecule ($\varphi_{5,6}$ = 26°) is particularly pronounced. However, the difference in energy due to the slope of the potential trough is only 0.2 kcal/mole.

With an increase in the torsional angle $\varphi_{5,6}$ to 60°, the value of E rises considerably because of steric repulsion between the Me group C15 and the H atom at C8, which makes the 10α,6,7β-C conformation actually impossible. Passage to the 7,8α,9,10β-TC conformer ($\varphi_{5,6}$ = −39°) is also appreciably hindered because of the impossibility of an appreciable increase in the C2C1C5C4 torsional angle in the five-membered ring A.

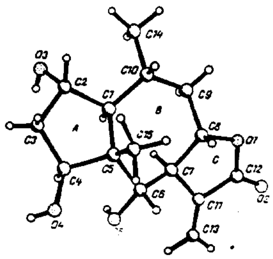


Fig. 1. Structure of the (II) molecule.

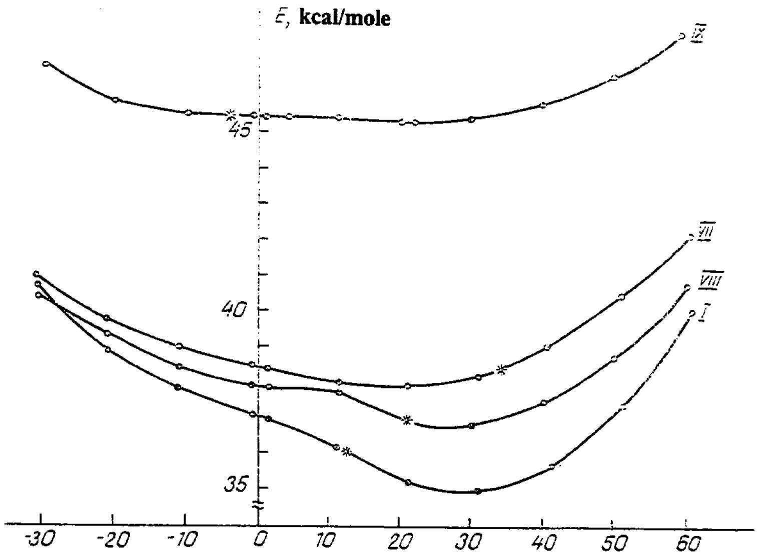


Fig. 2. Dependence of the conformational energy on the C1C5C6C7 torsional angle for the (I) and (VII)-(IX) molecules.

EXPERIMENTAL

Hydrolysis of Inuchinenolide C (I). Compound (I) (5.4 g) was treated dropwise with 60 ml of a 4% solution of NaOH (to pH 11-12). The reaction mixture was stirred vigorously for 2 h, during which the crystals of (I) dissolved completely. The reaction mixture was left for 24 h. In TLC, the spot remained at the start. The reaction mixture was acidified with concentrated HCl to pH 1. Then TLC showed a single spot differing from the initial one, with R_f 0.2 in the ethyl acetate system. The reaction mixture was neutralized with a 4% solution of NaOH to pH 7, whereupon a precipitate deposited. The precipitate was filtered off, and the filtrate was extracted with chloroform (3 × 150 ml). The chloroform extract was separated off, dried over $MgSO_4$, and evaporated. Residue was crystallized from ethanol. The substance obtained had mp 177-178°C. Yield 3.75 g.

x-Ray Structural Investigation. The parameters of the cell and the intensities of 2166 reflections were measured on a Siemens P3/PC automatic four-circle diffractometer (λMoK_α graphite monochromator, $\theta/2\theta$ scanning, $2\theta \leq 60°$). The crystals were monoclinic a = 9.196(2), b = 7.730(2), c = 10.116(2) Å, β = 99.78(3)°, V = 708.7(3) Å^3, M = 282.3, D_{calc} = 1.323 g/cm^3, Z = 2 ($C_{15}H_{22}O_5$), group $P2_1$.

In the calculations we used 1698 independent reactions with $I > 3\sigma$. The structure was interpreted by the direct method and was refined by full-matarix MLS in the anisotropic approximation for the nonhydrogen atoms and in the isotropic approximation for the hydrogen atoms (all the hydrogen atoms were revealed in a difference synthesis). The final discrepancy factors were R = 0.044 and R_w = 0.042. The coordinates of the atoms are given in Table 5. All the calculations were made on a IBM PC/AT computer by means of the Siemens SHELXTL (PC Version) software package.

The calculations by the method of molecular mechanics were performed by means of the MMX program with a standard set of parameters on the IBM PC/AT computer.

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