TRITERPENE GLYCOSIDES OF Thalictrum squarrosum.

II. MOLECULAR AND CRYSTAL STRUCTURE OF SQUARROFURIC ACID

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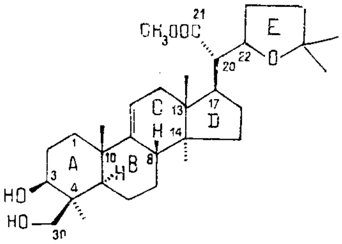
The structure of squarrofuric acid (an artifactual genin from Thalictrum squarrosum) has been confirmed by x-ray structural analysis and the configurations of the C13, C14, C17, C20, and C22 asymmetric centers have been established, which has enabled this compound to be assigned to the lanostane series with the following structure: 3β,30-dihydroxy-20(S),22(S)-22,25-epoxylanost-9(11)-en-21-oic acid.

The isolation of squarrofuric acid (I) — the predominating artifactual sapogenin obtained by the acid hydrolysis of an extract of Thalictrum squarrosum Stephan ex Willd. (nodding meadow rue) — and the determination of its structure by chemical and spectral methods have been considered previously [1]. Although the proposed structure was not a matter of doubt, questions of the conformation of the rings and of the conformations of the C13, C14, C17, C20, and C22 asymmetric centers, and, consequently, whether compound (I) belonged to the lanostane, the euphane, or the tirucallane [2] series remained open. To answer these questions, we have performed an x-ray structural analysis of methyl squarrofurate (Ia).



I

TABLE 1. Torsional Angle in the Rings, τ, deg

Ring	Angle	τ	Ring	Angle	τ
A	C1 C2 C3 C4	59,7	*D*	C13 C14 C15 C16	−34,0
	C2 C3 C4 C5	−52,0		C14 C15 C16 C17	7,8
	C3 C4 C5 C10	47,1		C15 C16 C17 C13	21,3
	C4 C5 C10 C1	−46,7		C16 C17 C13 C14	−42,0
	C5 C10 C1 C2	50,9		C17 C13 C14 C15	46,9
	C10 C1 C2 C3	−58,7			
B	C5 C6 C7 C8	57,0	*E*	C22 C23 C24 C25	35,9
	C6 C7 C8 C9	−47,7		C23 C24 C25 O3	−27,1
	C7 C8 C9 C10	43,6		C24 C25 O3 C22	5,5
	C8 C9 C10 C5	−47,9		C25 O3 C22 C23	18,3
	C9 C10 C5 C6	57,5		O3 C22 C23 C24	−33,1
	C10 C5 C6 C7	−62,9			
C	C8 C9 C11 C12	−0,9			
	C9 C11 C12 C13	−15,9			
	C11 C12 C13 C14	48,0			
	C12 C13 C14 C8	−67,6			
	C13 C14 C8 C9	50,1			
	C14 C8 C9 C11	−16.4			

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The conformation of the molecule and the interatomic distances are shown in Fig. 1. Rings A and B have the chair form (trans-linkage) while ring C has the half-chair form because of the presence of the C9—C11 double bond in it. The C8, C9, C11, and C12 atoms are located in practically one plane — the torsional angle is less than 1° (Table 1). Ring D is present in trans-linkage with ring C and has an intermediate conformation between a ^{13}E envelope and a $^{13}T_{14}$ twist form, the C14—C15—C16—C17 torsional angle being 7.8°.

The interatomic distance in the molecule agrees well with the lengths of the corresponding bonds in related compounds [3, 4]. The range of variation of the C_{sp^3}—C_{sp^3} bonds in the polycyclic part of the molecule is 1.513 to 1.570 Å, which is characteristic for strained steroid systems [5]. As compared with cyclohexane, there is an increase in the C4—C5 interatomic distance (1.570 Å). The range of variation of the extra- and intracyclic interatomic C—O distances is 1.38-1.46 Å and these distances are close to the standard lengths of an ordinary bond.

In the crystal, the two hydroxy groups form an intramolecular O1...O2 (2.70 Å) and an intermolecular O1...O2' ($\frac{1}{2} - x$, $\frac{1}{2} - y$, $1 - z$), (2.71 Å) hydrogen bond.

Interest is presented by a comparison of the results obtained with the analogous figures for 3β,16β,29-trihydroxy-22,25-epoxylanost-9(11)-ene (II) [6]. The lengths of the bonds in the steroid skeletons of (Ia) and (II) coincide to within 3 σ, with the exception of C5—C6 and C16—C17, which are 1.550(8) and 1.53(1) Å in (Ia) and 1.514(6) and 1.582(5) Å in (II). These deviations can be explained for the C5—C6 bond by the opposite configurations of the voluminous constituents at C4 in (Ia) and (II) and, for the C16—C17 bond, by the presence of an OH group at C16 in compound (II).

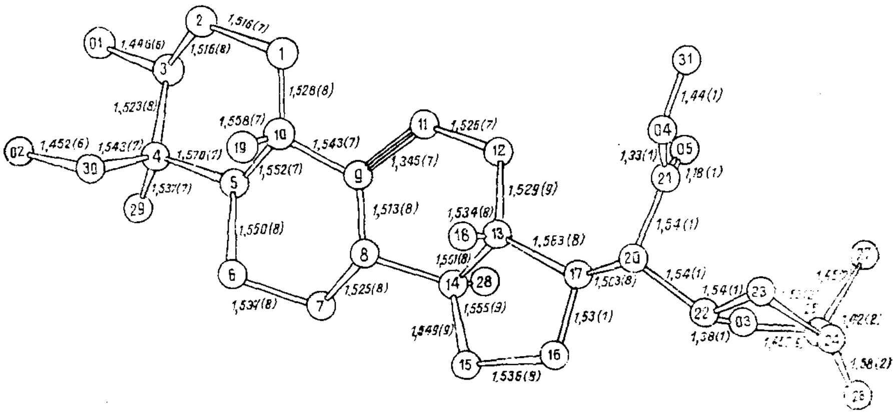
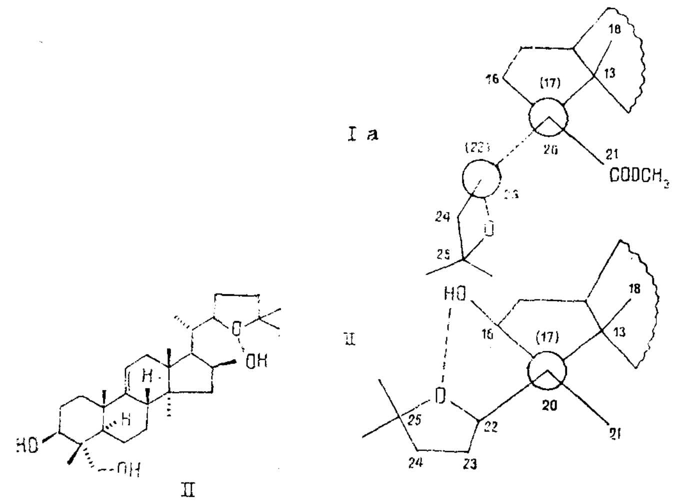


Fig. 1. Conformation of squarrofuric acid.



II

Fig. 2. Newman projections of the lateral fragment for compounds (Ia) and (II).

TABLE 2. Coordinates of the Nonhydrogen Atoms (× 10^4).

Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
C1	0790 (5)	−1731 (6)	3572 (2)	C2	127[illegible] (5)	−2441 (7)	4[illegible]2 (2)
C3	2372 (5)	−1541 (6)	4211 (1)	C4	2[illegible]77 (5)	0128 ([illegible])	43[illegible] (2)
C5	1447 (5)	0842 (6)	3868 (2)	C6	1[illegible]88 (6)	2546 (7)	3016 (2)
C7	09[illegible]3 (6)	3257 (7)	3462 (2)	C8	−[illegible]71 (5)	242[illegible] (6)	3159 (2)
C9	0091 (5)	0760 (7)	3162 (1)	C10	0384 (5)	−0[illegible]65 (6)	36[illegible]8 (1)
C11	−0151 (5)	−0142 (7)	28[illegible]1 (2)	C12	−[illegible]623 (6)	04[illegible]1 (7)	2356 (2)
C13	−1128 (5)	2114 (7)	2397 (2)	C14	−[illegible]155 (5)	3042 (7)	2691 (2)
C15	−068[illegible] (6)	468[illegible] (7)	2639 (2)	C16	−1278 (7)	4756 (8)	2169 (2)
C17	−1258 (6)	3138 (8)	1982 (2)	C18	−2[illegible]38 (5)	2[illegible]14 (8)	2589 (2)
C19	−085[illegible] (4)	−0[illegible]4[illegible] (7)	3824 (2)	C20	−24[illegible]2 (7)	2787 (9)	1647 (2)
C21	−2243 (8)	1175 (10)	1456 (2)	C22	−2587 (8)	4[illegible]11 (11)	1288 (2)
C23	−3678 (9)	3606 (15)	0943 (3)	C24	−3226 (11)	4584 (19)	0568 (3)
C25	−1918 (12)	4375 (16)	0613 (3)	C26	−1118 (14)	5787 (19)	0487 (3)
C27	−1411 (14)	−3151 (19)	0366 (3)	C28	1154 (6)	−3[illegible]1 (8)	2521 (2)
C29	3314 (5)	0961 (7)	4426 (2)	C30	1231 (5)	0272 (6)	467[illegible] (1)
C31	−3255 (11)	−112[illegible] (13)	1265 (13)	O1	2918 (4)	−2310 (0)	4596 (1)
O2	1889 (4)	−0191 (4)	5081 (1)	O3	−1536 (5)	41[illegible]7 (8)	1[illegible]70 (1)
O4	329[illegible] (6)	0366 (7)	1463 (2)	O5	−133[illegible] (5)	0723 (7)	1322 (1)

Appreciable discrepancies in the lengths of the bonds are observed in the heterocyclic moiety. However, the shortening, as compared with the usual values, of the C24—C25 bond to 1.42(2) Å and of the C25—C27 bond to 1.45(2) Å in (Ia) apparently takes place because of the high temperature factors of the atoms of this moiety [for example, $B_{22}(C24)$ = 19 $Å^2$].

The conformations of the rings in the polycyclic part of the molecule of squarrofuric acid are the same as in (II) the difference in the intracyclic torsional angles not exceeding 3°. This fact indicates a rigidity of the given tetracyclic system, since a change in the C4 configuration and even the introduction of an OH group at C16 and the formation of an intramolecular hydrogen bond (intra-HB) with its participation does not change the conformation of the rings.

The heterocycle in (Ia) has an envelope conformation with a bent-back C23 atom, while in (II) it is the C25 atom that is bent back for this form of the ring. This difference is of no great importance, since the pseudorotation barrier in tetrahydrofuran does not exceed 1 kcal/mole [7].

There are conformational differences between (Ia) and (II) in the lateral fragment. Thus, the absence of an hydroxy group at C16 in squarrofuric acid and, consequently, of an intra-HB between this group and the oxygen atom of the heterocycle apparently made the rotation of the heterocycle around the C20—C22 bond possible. The orientation of the side chain along the C20—C17 bond for compounds (Ia) and (II) is shown in Newman projections in Fig. 2.

It must be mentioned that in [8], on the basis of ^{13}C NMR spectra, a semiempirical calculation of chemical shifts [9], and an analysis of Dreiding models, for the same side chain (in compound VII) [8] with no intra-HB a conformation was proposed which coincides with that which we have found by x-ray structural analysis.

This, on the one hand, is a confirmation of the possibility of the correct determination of the conformations of side chains in phytosteroids and tetracyclic triterpenoids by ^{13}C spectroscopy and, on the other hand, makes it possible to speak of the dominating influence of an intra-HB on the conformation of the side chain in such a compound and of the possibility of the retention of its orientation of passing from the crystal into solution.

EXPERIMENTAL

The preparation of methyl squarrofurate was described in the preceding communication [1]. The crystals for analysis were grown from acetonitrile.

The x-ray structural study of methyl squarrofurate was performed on a Syntex $P2_1$ diffractometer (Mo radiation with a graphite monochromator; ω-scanning, $2\theta < 50°$). The crystal taken for the experiment had the form of a plate with dimensions of 1.1 × 2.0 × 0.03 mm^3. Crystallographic characteristics: a = 10,791(4), b = 8.738(3), c = 31,049(13) Å, β = 95.70(3)°; space group C2, Z = 4, d_{calc} = 1.14 g/cm^3. The structure was interpreted by the direct method in the RANTAN variant [10]. Refinement was carried out by the SHELZ 76 method of least squares in the block-diagonal anisotropic approximation to R = 0.071 for 2119 reflections with $I > 2\sigma$. In each cycle of calculation the positions of the hydrogen atoms were refined geometrically. The coordinates obtained for the nonhydrogen atoms are given in Table 2.

CONCLUSION

The structure of squarrofuric acid has been confirmed by x-ray structural analysis, and the configurations of the C13, C14, C17, C20, and C22 asymmetric centers have been established, and this has permitted this compound to be assigned to the lanostane series.

Thus, squarrofuric acid is 3β,30-dihydroxy-20(S),22(S)-22,25-epoxylanost-9(11)-en-21-oic acid.

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