X-Ray Structure Study of an Unusual 13,14,15,16-Tetranorlabdane Derivative Obtained in the Synthesis of (7*α*)-7,8-Dihydroxy-14,15-dinorlabdane-11,13-dione

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Dedicated to the memory of *Yurii A. Simonov*

The unconventional (5*S*,7*R*,8*S*,9*R*,10*S*)-configurated (−)-7-(acetyloxy)-12,12-dichloro-8-hydroxy-13,14,15,16-tetranorlabdan-11-one (**2**) was synthesized *via* the HCl-promoted hydrolysis of (7*α*)-7,8-(isopropylidenedioxy)-14,15-dinorlabdan-11,13-dione (**5**). Possible mechanistic pathways of the reaction are considered. Crystal and molecular structures of the isolated compound **2** were determined by single-crystal X-ray structure analysis.

Introduction. – Natural halogen-containing labdane diterpenoids are rather scarcely cited in the literature, being mainly isolated from marine organisms but rarely found in plants [1]. In the majority of these compounds, the halogen atom (mostly Br-atom) is positioned at ring *A*, reflecting its implication as initiator of the cyclization reaction in the course of their biogenesis. In continuation of our recently reported work on the synthesis of the novel metabolite (7*α*)-12-chloro-8,13-epoxy-7-hydroxy-14,15-dinorlabd-12-en-11-one[1]) (**1**) and of the uncommon, (5*S*,7*R*,8*S*,9*R*,10*S*)-configurated (−)-7-(acetyloxy)-12,12-dichloro-8-hydroxy-13,14,15,16-tetranorlabdan-11-one[1]) (**2**) [2], we here present the data regarding the crystal structure and absolute configuration of **2**. Formation of the latter under the reported reaction conditions was quite unexpected. Furthermore, the presence of a dichloroacetyl moiety at C(9) is inconsistent with the structures of all the known halo-labdanes, which motivated us to study the structure of **2** in more detail. An X-ray structure investigation of **2** became possible once the appropriate conditions for its crystallization from hexane were elaborated. Compounds **1** and **2** present interest as being potentially endowed with bioactivity since a series of biologically active forskoline (**3**) derivatives, containing halogen atoms (F, Cl, Br, and I) at C(12), was patented some time ago [3].

Results and Discussion. – In the course of our investigations on the synthesis of polyfunctional dinorlabdane derivatives related to sclareoloxide (**4**), (7*α*)-7,8-(isopro-

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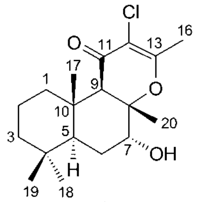
[1]) Trivial atom numbering; for systematic name of **2**, see *Exper. Part.*



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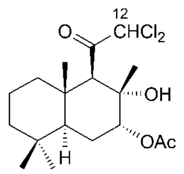

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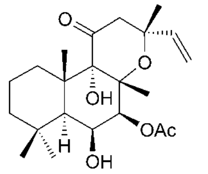

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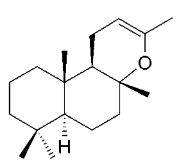

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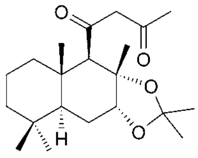

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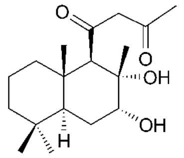

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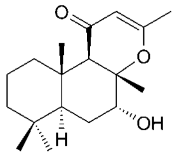

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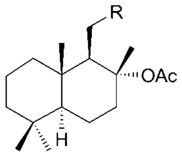
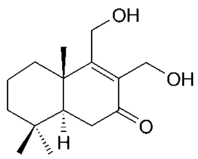


13 R = HOCH2
14 R = OH



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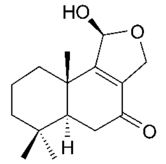

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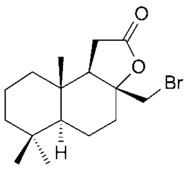

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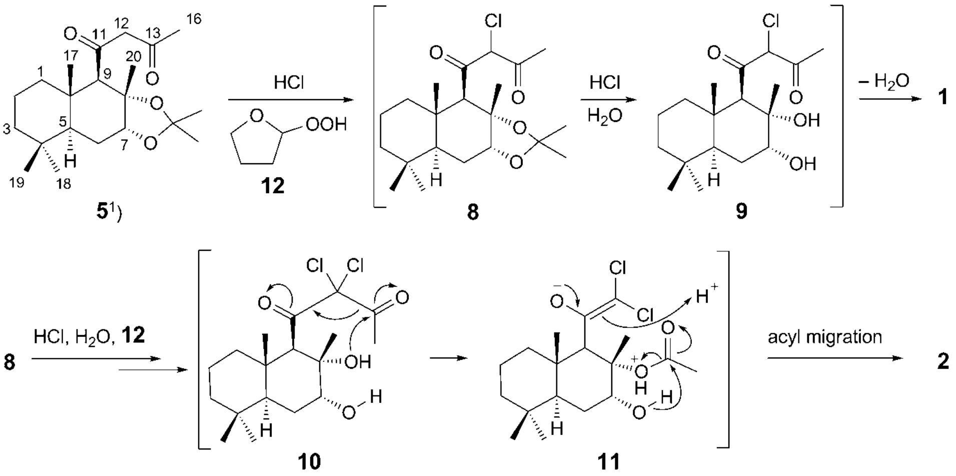
pylidenedioxy)-14,15-dinorlabdan-11,13-dione1) (**5**) was prepared recently as an intermediate [2]. During the following step we intended to remove the acetonide protecting group from **5** to get access to (7α)-7,8-dihydroxy-14,15-dinorlabdan-11,13-dione (**6**) or to the derivative **7** for further transformations, characteristic for such 14,15-dinorlabdane compounds. This conversion, which occurs with elimination of H_2O and subsequent closing to a pyran ring, is well-documented for 14,15-dinorlabdane-type compounds [4][5]. Thus, (7α)-7,8-(isopropylidenedioxy)-14,15-dinorlabdan-11,13-dione (**5**) was treated with a solution of HCl in THF [2]. As a result, a mixture of two compounds was obtained, which was separated *via* flash chromatography. However, both products turned out to contain Cl-atom(s), with the structures differing from the expected products **6** and/or **7**. According to the spectral data, the products obtained from **5** have the structures **1** and **2**. Their formation points to the fact that in this case, HCl acts not only as catalyst for the removal of the protective group but also as precursor of a reagent that converts the primary reaction product **6** or a precursor thereof into the Cl-containing final products **1** and **2** in 30 and 53% yield, respectively [2].

A plausible pathway for the formation of compounds **1** and **2** from **5** is shown in the *Scheme*. Accordingly, we assume that the Cl-containing intermediates **8**–**11** can act as crucial precursors for chloro compounds **1** and **2**. It is known that β-diketones interact with halogenated acids in the presence of hydroperoxides by radical substitution of the H-atoms of the active CH_2 group through halogen atoms [6]. We suspect that tetrahydrofuran hydroperoxide (**12**) acted as the hydroperoxide source in our case: it was most likely generated during treatment of compound **5** with HCl in THF under rather harsh conditions in the presence of air and light [7].

Scheme. *Possible Routes for Obtaining the Chlorinated Products* **1** *and* **2** *from Compound* **5**



The formation of dichloro ketone **2** deserves a special attention because it is an atypical degradation product of the 14,15-dinorlabdane C-atom skeleton. It represents a unique norlabdane compound containing a $CHCl_2$ group bound to C(11). Our now presented results corroborate our previous report, establishing that compounds of this kind are formed in the series of 13,14,15,16-tetranorlabdane derivatives [2]. Another interesting detail that characterizes the structure of **2** is related to the acetyloxy group at C(7). Taking into consideration the absence of any potential acetyl sources in the reaction medium, this functional group can only result from an unprecedented intramolecular *C* → *O*-acetyl migration in the dichlorinated intermediate **10**, as suggested in the *Scheme*. It should be mentioned that the migration of an acetyl group from O–*C*(8) to O–*C*(12) has been described in the series of homodrimanes for compound **13** [8], as well as for the related drimane analog **14** (O–*C*(8) → O–*C*(11) migration) [9][10].

To clarify the structural details of **2**, the crystal and molecular structure, as well as the absolute configuration of **2** were determined by single-crystal X-ray analysis. Compound **2** crystallizes in the noncentrosymmetric orthorhombic $P2_12_12_1$ space group. The molecular structure with absolute configuration of compound **2** is shown in *Fig. 1*. Both cyclohexane rings have a chair conformation. Atoms C(1), C(2), C(4), and C(5) are coplanar within ± 0.022 Å. The displacements of atoms C(3) and C(10) from this plane are – 0.629(3) and 0.672(3) Å, respectively. The *Cremer–Pople* (*CP*) puckering parameters [11] for this cycle are: $\Theta = 4.0(3)°$, $\varphi = 11(3)°$, and $Q = 0.554(2)$ Å. In the C(5) to C(10) moiety, the ring atoms C(5) and C(8) are displaced by – 0.732(3) and 0.654(3) Å out of the plane defined by C(6), C(7), C(9), and C(10), which are coplanar within ± 0.008(1) Å. *CP* Parameters for this ring are $\Theta = 7.33(19)°$, $\varphi = 341.2(19)°$, and $Q = 0.595(2)$ Å. The Me groups at C(8) and C(10) reside in *axial* positions, and at C(4), one Me group (C(17)) is in axial and the other (C(16)) in an equatorial position (arbitrary atom numbering; see *Fig. 1*). Such an arrangement of the Me groups leads to stressed 1,5-intramolecular contacts C(17) ··· C(18) = 3.22 Å and C(13) ··· C(18) =

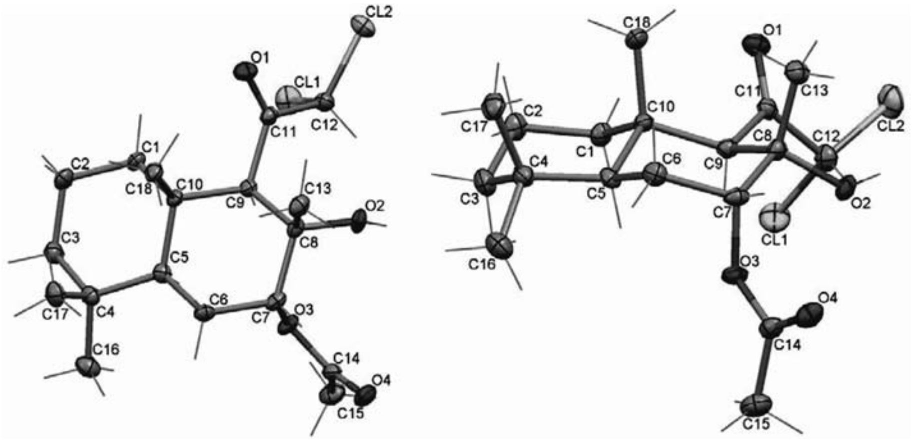


Fig. 1. *Top view perpendicular to the best plane of the molecule* **2** (left) *and side view* (right), *illustrating the configuration (5*S*,7*R*,8*S*,9*R*,10*S*) of* **2**. *Arbitrary atom numbering.*

3.15 Å. Similar intramolecular contacts have been found in the molecular structures of 11,12-dihydroxydrim-8-en-7-one (**15**) [12], (11*β*)-11,12-epoxy-11-hydroxydrim-8-en-7-one (**16**) [13], and especially in 17-bromonorambreinolide (**17**) [14], which have the same basic skeleton. The flat acetate group (O(3), O(4), C(14), and C(15)) is approximately perpendicular to the C(6),C(7),C(9),C(10) plane with a dihedral angle of 81.50(8)°. The torsion angle O(4)–C(14)–O(3)–C(7) equals $-3.4(3)°$. The mutual arrangement of the dichloroacetyl group relative to the proximate cyclohexane ring is defined by torsion angles O(1)–C(11)–C(9)–C(8) $= -100.8(3)°$ and O(1)–C(11)–C(9)–C(10) $= 31.8(3)°$. Atom Cl(1) is *gauche*- and atom Cl(2) *cis*-situated with respect to O(1). The corresponding torsion angles O(1)–C(11)–C(12)–C(11) and O(1)–C(11)–C(12)–Cl(2) amount to $-99.8(2)°$ and 20.7(3)°, respectively. Such an arrangement leads to a short O(1)$\cdots$Cl(2) intramolecular contact of 2.888(2) Å and results in an increased bond angle C(11)–C(12)–Cl(2) of 111.4(2)° compared to C(11)–C(12)–Cl(1) (= 106.8(2)°). Bond lengths of C-atoms with heteroatoms are: Cl(1)–C(12) 1.786(2) Å, Cl(2)–C(12) 1.770(2) Å, O(1)–C(11) 1.204(3) Å, O(2)–C(8) 1.441(3) Å, O(3)–C(14) 1.338(3) Å, O(3)–C(7) 1.459(3) Å, and O(4)–C(14) 1.209(3) Å. The bond lengths of single C–C bonds are in the expected range. In the crystal, the H-bond O(2)–H$\cdots$O(4) = 2.879(2) Å (O(2)–H = 0.840 Å, H$\cdots$O(4) = 2.043 Å, and angle O(2)–H$\cdots$O(4) = 172. 8°) links two-fold-screw-axis-related molecules ($x - 1/2$, $-y + 3/2$, $-z + 1$) related molecules into a zigzag chain along the *a* crystallographic axis, see *Fig. 2*.

Experimental Part

General. The synthetic protocol for obtaining homodrimanic dichloride **2** from *β*-diketone **5** is described in [2], $[\alpha]_D^{25} = -75.9$ ($c = 1.00$, CH_2Cl_2).

*X-Ray Crystal Structure Analysis of (–)-(7α)-7-(Acetyloxy)-12,12-dichloro-8-hydroxy-13,14,15,16-tetranorlabdan-11-one (= 1-[(1*R*,2*S*,3*R*,4a*S*,8a*S*)-3-(Acetyloxy)decahydro-2-hydroxy-2,5,5,8a-tetramethylnaphthalen-1-yl]-2,2-dichloroethanone*; **2**). Compound **2** was obtained as a viscous oil [2]. However,

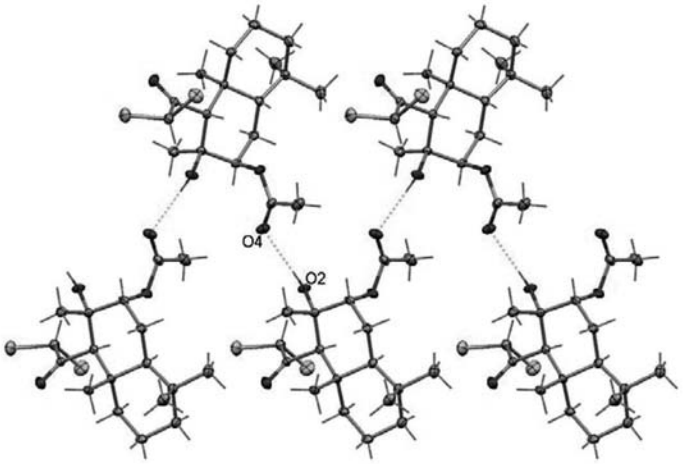


Fig. 2. *H-Bonded chain in the crystal structure of* **2**

Table. *Crystallographic Data and Structure Refinement Details for* **2**

Empirical formula	$C_{18}H_{28}Cl_2O_4$
M_r	379.30
Temperature [K]	100(2)
Wavelength [Å]	0.71073
Crystal system, space group	orthorhombic, $P2_12_12_1$
Unit cell dimensions:	
a [Å]	8.7598(2)
b [Å]	13.0389(4)
c [Å]	17.1880(5)
V [Å^3]	1963.18(9)
Z	4
Density (calc.) [Mg/m^3]	1.283
Absorption coefficient [mm^{-1}]	0.349
F(000)	808
Crystal size	$0.15 \times 0.10 \times 0.06$ mm^3
θ Range for data collection [°]	2.61 to 27.49
Index ranges	$-11 \leq h \leq 11$, $-16 \leq k \leq 16$, $-22 \leq l \leq 22$
Reflections collected	15924
Independent reflections	4503 ($R_{\text{int}} = 0.0612$)
Completeness to $\theta = 27.49°$	99.9%
Max. and min. transmission	0.9794 and 0.9496
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4503/0/223
Goodness-of-fit on F^2	1.004
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0411$, $wR_2 = 0.1201$
R indices (all data)	$R_1 = 0.0492$, $wR_2 = 0.1268$
Absolute-structure parameter	0.05(6)
Largest diff. peak and hole on a difference *Fourier* map	0.293 and –0.209 e Å^{-3}

on long-term storage in a refrigerator, a crystalline precipitate slowly appeared. The colorless single crystals of **2**, m.p. 112–113°, suitable for a single-crystal X-ray investigation, were obtained by recrystallization of **2** from hexane. X-Ray data of a single-crystal sample of the size 0.06 × 0.1 × 0.15 mm were collected at 100 K with a *Nonius-Kappa-CCD* diffractometer and graphite-monochromatized MoK_α radiation. The structure was solved by direct methods and refined by full-matrix least-squares based on F^2 with the program SHELXL97 [15]. All non-H-atoms were refined with anisotropic displacement parameters. The H-atom positions were found in difference *Fourier* maps; however, for further refinement, the H-atoms were included in the models in calculated positions and refined as constrained to the bonding atoms with isotropic temperature factors equal to 1.5 times the value of the equivalent isotropic displacement parameter of the parent atom for Me and OH groups, and with isotropic temperature factors equal to 1.2 times the corresponding value for all other atoms. Crystal data and structure refinement parameters are summarized in the *Table*. The absolute-structure *Flack* parameter 0.05(6) [16] unambiguously shows that the model of the molecular structure corresponds to the true absolute configuration of compound **2**. CCDC-815158 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

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