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STRUCTURE OF DIMETHYLAMINODIHYDROARGLABIN HYDROCHLORIDE

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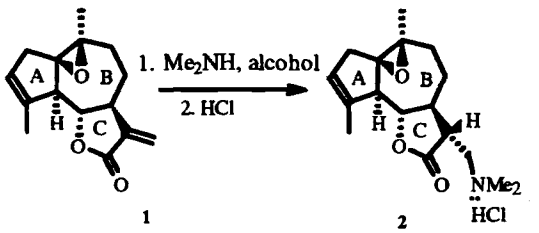
The structure of dimethylaminodihydroarglabin hydrochloride has been determined on the basis of the results of an x-ray structural investigation.

The Michael addition of secondary amines to an α,β-unsaturated double bond of the γ-lactone ring of a sesquiterpene lactone is specific for this class of sequiterpenoids and is used for obtaining water-soluble derivatives [1-3].

The hydrochlorides of the amino derivatives synthesized possess antitumoral activity [4]. Thus, for example, by the Michael reaction followed by quaternization, a sesquiterpene lactone of the guaiane type, arglabin (**1**), isolated from *Artemisia glabella* [5], has given the hydrochloride of its amine derivative (**2**), from which the antitumoral drug Arglabin has been created [6]. However, the configuration of the C11 atom in the lactone ring of (**2**) has not been strictly established. The literature contains only reports of the determination of this chiral center by the PMR method using the NOE procedure of Michael adducts of germacranolides with proline [7].



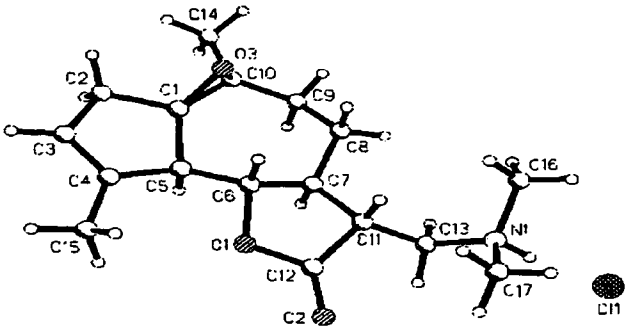


Fig.1

To determine the spatial structure of compound (**2**) we have subjected it to an x-ray structural investigation. The structure of the (**2**) molecule is shown in Fig. 1. As follows from this figure, rings *A* and *B* and rings *B* and *C* are linked in the *trans*- manner (torsion angles O3C1C5H5 = -141.7° and H6C6C7H7 = -172.3°). The conformation of the five-membered ring *A* is a 1β-envelope (ΔC_s^1 = 2.3 Å), the C2, C3, C4, and C5 atoms are coplanar to within ±0.2 Å, and the Cl atom departs from this plane by 0.39 Å in the β-direction. The seven-membered ring *B* has a 7α,1,10β-chair conformation (ΔC_S^7 = 1.5 Å). The methyl group at the C10 atom is α-oriented. The conformation of the lactone ring *C* is a 7α-envelope, the C6, O1, C11, and C12 atoms being coplanar to within ±0.01 Å and the C7 atom departing from this plane by 0.68 Å in the α-direction. The C-13 atom has the α-orientation. On the basis of the facts given above, for the (**2**) molecule we propose the structure of the hydrochloride of 13-dimethylamino-1(10)β-epoxy-5,7α,6,11β(H)-guai-3(4)-en-6,12-olide.

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TABLE 1. Intracyclic Torsional Angles in the Molecules (1) and (2)

	1a	1b	2
		Ring *A*	
C1C2C3C4	-14.3	-12.1	-13.4
C2C3C4C5	-2.2	-0.4	-2.2
C3C4C5C1	17.5	13.0	16.5
C4C5C1C2	-25.4	-19.1	-24.2
C5C1C2C3	24.3	19.1	23.4
		Ring *B*	
C10C1C5C6	45.3	50.3	49.7
C1C5C6C7	-68.9	-73.9	-71.1
C5C6C7C8	79.8	79.3	75.4
C6C7C8C9	-76.5	-72.9	-72.9
C7C8C9C10	67.5	68.2	71.2
C8C9C10C1	-44.9	-47.9	-48.9
C9C10C1C5	-0.4	-1.3	-2.0
		Ring *C*	
C6C7C11C12	27.2	27.1	41.1
C7C11C12O1	-12.4	23.5	-26.6
C11C12O1C6	-9.2	-6.5	-0.5
C12O1C6C7	26.9	23.5	27.9
O1C6C7C11	-32.1	-30.3	-42.0

TABLE 2. Coordinates of the Atoms ($\times 10^4$) in the (2) Molecule

Atom	*x*	*y*	*z*
O1	4487 (4)	6832 (3)	1561 (2)
O2	2229 (5)	8519 (4)	1783 (2)
O3	7914 (4)	2948 (3)	2737 (2)
N1	1072 (4)	7071 (4)	4071 (2)
C1	7051 (6)	2956 (5)	1706 (3)
C2	8487 (6)	2564 (4)	1068 (3)
C3	8765 (6)	4056 (4)	616 (3)
C4	7431 (6)	5111 (5)	740 (3)
C5	5980 (5)	4421 (4)	1281 (3)
C6	5289 (5)	5394 (4)	2023 (3)
C7	3600 (5)	4766 (4)	2425 (3)
C8	4116 (6)	3482 (4)	3156 (3)
C9	4522 (6)	1963 (4)	2710 (3)
C10	6391 (6)	1830 (4)	2344 (3)
C11	2937 (5)	6268 (4)	2825 (3)
C12	3113 (5)	7370 (5)	2026 (3)
C13	973 (5)	6314 (5)	3113 (3)
C14	7097 (7)	198 (5)	2311 (3)
C15	7260 (7)	6659 (6)	317 (4)
C16	2184 (6)	6183 (5)	4890 (3)
C17	1823 (6)	8691 (5)	4108 (4)
Cl1	-2859 (1)	7209 (1)	4534 (1)

It must be mentioned that the conformations of the five-membered ring *A* and of the seven-membered ring *B* in the (2) molecule agree with the corresponding conformations in the two crystallographically independent molecules of the previously studied arglabin [8] (the intracyclic torsional angles of the (1) and (2) molecules are given in Table 1). However, the lactone ring *C* in the (2) molecule adopts a conformation close to an ideal 7α-envelope, while in the arglabin molecule the conformation of ring *C* is 6β,7α-half-chair (ΔC_2^{12} = 3.0 Å) in the first independent molecule and intermediate between a 7α-envelope and a 6β,7α-half-chair (ΔC_s^7 = 6.6 Å, ΔC_2^{12} = 8.6 Å) in the second.

EXPERIMENTAL

Melting points were determined on a Kofler stage. TLC was conducted on Silufol plates.

13-Dimethylamino-1(10)β-epoxy-5,7α,6,11β(H)-guai-3(4)-en-6,12-olide Hydrochloride. A solution of 1 g of arglabin in 10 ml of alcohol was treated with 10 ml of aqueous dimethylamine until the initial substance had disappeared (monitoring by TLC). The alcohol was distilled off under vacuum and the residue was extracted with $CHCl_3$ (3 × 100 ml). The chloroform layer was dried over Na_2SO_4 and evaporated in a rotary evaporator. The oily mixture obtained was dissolved in alcohol (10 ml), and HCl was bubbled through the solution until the pH was 5.3, after which ethyl acetate was added. The resulting precipitate was filtered off and dried under vacuum. About 1 g was obtained of a colorless substance with mp 183—185°C (alcohol—EtOAc), and this was recrystallized from $CHCl_3$.

X-Ray Structural Experiment. The cell parameters and the intensities of 3246 independent reflections were measured on a Siemens SMART CCD diffractometer (MoK_α, graphite monochromator, ω-scanning, $2\theta \leq 60°$). The crystals were monoclinic, a=6.979(3), b=8.707(4), c=14.070(6)Å, V=836.3(6)Å^3, d_{calc}=1.310 g/cm^3, z=2($C_{17}H_{26}ClNO_3$), sp. gr. $P2_1$. The structure was interpreted by the direct method and was refined by full-matrix MLS in the anisotropic approximation for the nonhydrogen atoms. All the hydrogen atoms, with the exception of the hydrochloride H atom, which was found from a difference synthesis, were given geometrically and were fixed. In the calculations we used 2683 reflections with $I \geq 2\sigma(I)$. The final discrepancy factors were R = 0.0681 and R_w = 0.0605.

The coordinates of the atoms are given in Table 2. All the calculations were made on a Pentium-150 PC by the SHELX93 program packet.

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