TADZHACONINE – A NEW C-20 DITERPENE ALKALOID FROM Aconitum zeravschanicum

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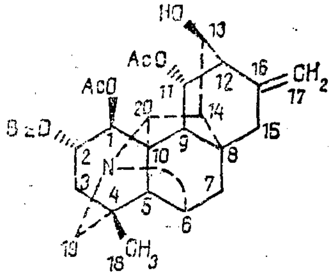
The new alkaloid tadzhaconine has been isolated from the roots of the plant Aconitum zeravschanicum and its structure has been established by the x-ray structural method as 1β-acetoxy-11-acetyl-2-benzoylhetisine. The characteristics of the compound investigated are given.

Continuing a study of the alkaloids of Aconitum zeravschanicum Steinb. [1, 2], from the roots of the plant collected in the environs of Tadzhikabad (Tadzhikstan, Peter I range) in the building stage we have isolated a new base with the composition $C_{31}H_{35}NO_7$ (I), mp 236-237°C (decomp., ethanol) which we have called tadzhaconine.

The IR, mass, PMR, and ^{13}C NMR spectra of (I) (see the Experimental part) showed that tadzhaconine was a C_0 diterpene alkaloid of the hetisine type and enabled its formula to be developed in the form of $C_{20}H_{23}N(OH)(OCOCH_3)_2(OCOC_6H_5)$.

In the weak field of the PMR spectrum of (I) at 4.08 and 5.26 ppm there were one-proton signals in the form of a broadened doublet with J = 9.0 Hz and an ordinary doublet with J = 9.0 Hz. These signals, which have also been found in the PMR spectra of 11-acetylhetisine and 2,11-diacetylhetisine [3], showed the presence of a β-hydroxy group at C13 and of an α-acetoxy group at C11.

In addition to those mentioned above, in the weak field of the spectrum of (I) there were one-proton signals at 5.46 and 5.77 ppm in the form of a multiplet and a doublet with J 3.0 Hz, respectively. In view of this and also of the results of a comparison of the ^{13}C NMR spectra of hetisine and its acetyl derivatives [3, 4], torokonine [5] and hypognavine [6] it was possible to conclude that the two other substituents in (I) were present in ring A and were located at C1 and C2 axially-equatorially or axially-axially. The question of what were the substitutents at C1 and C2 and their configuration was answered with the aid of an x-ray structural investigation (XSI). The results of the XSI confirmed the presence in (I) of a tetisine skeleton and showed that tadzhaconine is 1β-acetoxy-11-acetyl-2-benzoylhetisine.



A comparison of the PMR spectra of (I) and of a number of hetisine alkaloids showed that in the case of (I) the one-proton singlet relating to the H atom at C-20 resonated in a weaker field at 4.21 ppm. A consideration of the conformation by rotating the plane of the benzoyloxy group around the C2-O1 bond (calculation by the MM2 method) showed that in (I) H-20 can be present at the distance of an ansiotropic influence of the benzene ring of the 2α-benzyloxy group (distance of H-20 to the center of the benzene nucleus 4.30 Å), which explains the paramagnetic shift of the H-20 signal by 0.6 ppm from the usual value, even though according to the XSI results this distance was 4.75 Å.

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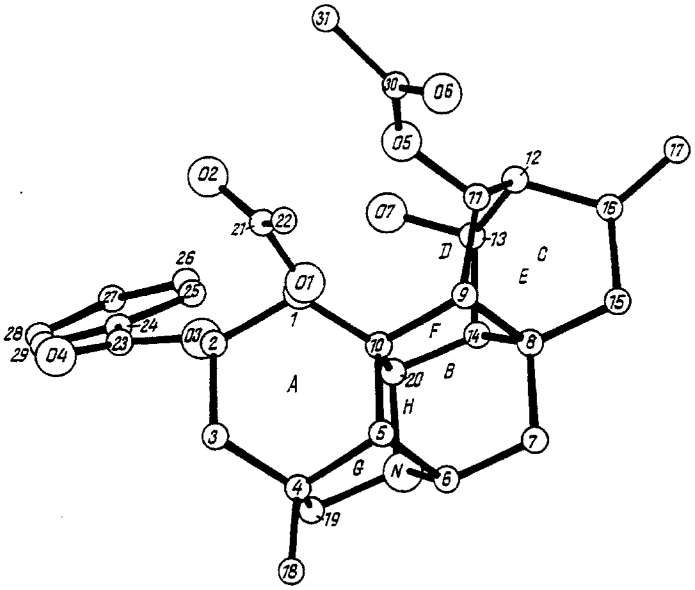

Fig. 1. Structure of the tadzhaconine molecule.

The spatial structure of (I) in projection on the plane of the C1, C4, and C9 atoms is shown in Fig. 1. The (I) molecule has a rigid bridge structure consisting of nine rings with the following substituents: two acetyl groups (1β and 11α), a hydroxy group (13β), and a benzoyloxy group (2α, orientation of the latter being the same as in sadosine and ignavine, studied previously [7, 8].

The six-membered rings A and B have the chair conformation (ring B with slight distortion) while rings C, D, and E form a bicyclo[2.2.2]octane system in which they have the boat form (ring E approximates to the ideal, while C and D are slightly distorted). The observed distortions of the rings are connected with the strain existing in the molecule. The five-membered rings F, G, and H have the envelope conformation, in the first of which the C atom deviates from the plane of the C9, C10, C14, and C20 atoms (±0.01 Å) by −0.80 Å, in the second the C6 atom deviates from the plane of the C4, C5, C19 and N atoms (±0.01 Å) by −0.82 Å, and in the third there is an ideal envelope form with the departure of the C6 atom from the plane of the C5, C10, C20, and N atoms by 0.83 Å. Heterocycle K has the ideal boat form. The conformations of the rings agree completely with those observed in other compounds of the hetisine type that we have studied [9, 10]. The linkages of the main rings are: A/B-trans (the C20C10C5H5 torsional angle is −161.9°), and B/C-trans (C14C8C9H9 172.9°).

The lengths of the ordinary Csp^3-Csp^3 bonds range from 1.51 to 1.59 Å, but their mean value of 1.53 Å agree with the standard values [11] and also with the values observed in related alkaloids [9, 10]. The pronounced variation in the valence angles at the tetrahedral carbon atoms is due to the sttrains present in the bridge fragments of the molecule. The values of the valence angles in the rings were determined with an error of not more than 0.6°.

The crystal structure of (I) is shown in Fig. 2 in a bc projection, from which it can be seen that in the packing of the structure of (I) a molecule of the crystallization solvent — ethanol — participates, so that the crystals investigated consisted of a 1:1 solvate. The molecule of (I) lined by 2 (x, 3/4, 0) and 2 (x, 1/4, 1/2) screw axes through O7—H...N hydrogen bonds (the O...N and H...N distances are 2.84 and 2.19 Å, respectively, and the O—H...N angle 167°) form infinite helices along the *a* axis. The molecule of the ethanol of crystallization, located in the interhelix space apparently forms a weak H-bond, O...H—O (O6...O8 2.90 Å), with the (I) molecule.

EXPERIMENTAL

The homogeneity of the substances was checked by chromatography in a thin layer of KSK silica gel in the benzene—methanol (4:1). chloroform—methanol (20:1), and chloroform—ethanol (9:1) systems and in a thin layer of alumina of "for chromatography" brand in the chloroform—methanol (50:1), benzene—ethanol (9:1), and ether—hexane (3:1) systems. The IR spectrum

TABLE 1. Interatomic Distances (r, Å) and Valence Angles (ω, degrees) of the Tadzhaconine Molecule

Distance	r	Distance	r	Angle	ω	Angle	ω	Angle	ω
C1—C2	1,53(1)	C13—C14	1,54(1)	C10—C1—C2	114,9	C15—C8—C14	111,5	C17—C16—C15	126,2
C1—C10	1,51(1)	C13—O7	1,44(1)	O1—C1—C2	106,3	C10—C9—C8	100,5	N—C19—C4	106,9
C1—O1	1.47(1)	C14—C20	1,51(1)	O1—C1—C10	102,6	C11—C9—C8	106,4	C14—C20—C10	106,2
C2—C3	1,51(1)	C15—C16	1,51(1)	C3—C2—C1	113.5	C11—C9—C10	121,9	N—C20—C10	105,4
C2—O3	1,47(1)	C16—C17	1,37(2)	O3—C2—C1	103,8	C5—C10—C1	112,9	N—C20—C14	108,0
C3—C4	1,54(1)	C19—N	1,48(1)	O3—C2—C3	112,4	C9—C10—C1	114,3	O1—C21—C22	110,3
C4—C5	1,55(1)	C20—N	1,49(1)	C4—C3—C2	115,9	C9—C10—C5	106,8	O2—C21—C22	125,8
C4—C18	1,56(1)	C21—C22	1,52(1)	C5—C4—C3	114,5	C20—C10—C1	118,5	O2—C21—O1	123,9
C4—C19	1,56(1)	C23—C24	1,52(1)	C18—C4—C3	106,5	C20—C10—C5	99,8	O3—C23—C24	110,1
C5—C6	1,52(1)	C24—C25	1,40(1)	C18—C4—C5	112,7	C20—C10—C9	102,8	O4—C23—C24	123,7
C5—C10	1,53(1)	C24—C25	1,39(1)	C19—C4—C3	113,2	C12—C11—C9	111,7	O4—C23—O3	126,2
C6—C7	1,53(1)	C24—C29	1,33(1)	C19—C4—C5	99,5	O5—C11—C9	118,0	C25—C24—C23	122,2
C6—N	1,49(1)	C25—C27	1,37(1)	C19—C4—C18	110,5	O5—C11—C12	105,8	C29—C24—C23	117,0
C7—C8	1,50(1)	C26—C28	1,27(2)	C6—C5—C4	100,8	C13—C12—C11	111,6	C29—C24—C25	120,7
C8—C9	1,57(1)	C30—C31	1,51(1)	C10—C5—C4	109,9	C16—C12—C11	104,3	C27—C25—C24	120,7
C8—C14	1,56(1)	C32—C33	1,38(2)	C10—C5—C6	101,8	C16—C12—C13	107,6	O5—C30—C31	111,7
C8—C15	1,54(1)	O1—C21	1,33(1)	C7—C6—C5	114,6	C14—C13—C12	110,5	O6—C30—C31	126,5
C9—C10	1,60(1)	O2—C21	1,22(1)	N—C6—C5	96,6	O7—C13—C12	112,2	O6—C30—O5	121,8
C9—C11	1,53(1)	O3—C23	1,32(1)	N—C6—C7	110,7	O7—C13—C14	109,4	O8—C33—C32	117,5
C10—C20	1,59(1)	O4—C23	1,20(1)	C8—C7—C6	111,2	C13—C14—C8	110,1	C19—N—C6	100,3
C11—C12	1,54(1)	O5—C30	1,33(1)	C9—C8—C7	110,9	C20—C14—C8	100,6	C20—N—C6	109,6
C11—O5	1.48(1)	O6—C30	1,23(1)	C14—C8—C7	109.3	C20—C14—C13	114,8	C20—N—C19	108,4
C12—C13	1,52(1)	O8—C33	1,32(2)	C14—C8—C9	98.4	C16—C15—C8	110,2	C21—O1—C1	119,7
C12—C16	1,52(1)			C15—C8—C7	112,0	C15—C16—C12	112,2	C23—O3—C2	116,8
				C15—C8—C9	113.9	C17—C16—C12	121.6	C30—O5—C11	119,1

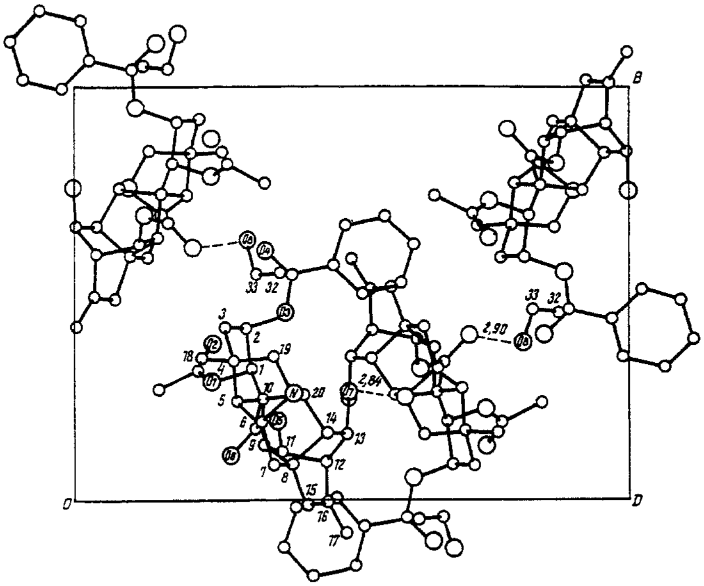

Fig. 2. Packing of the tadzhaconine molecules.

was taken on a UR-20 instrument in a KBr table; the PMR spectrum on a BS-567 A NMR isntrument (Tesla, Czechoslovakia) at a frequency of 100 MHz in $CDCl_3$ solution with HMDS as internal standrd (the chemical shifts are given in the δ scale; the ^{13}C NMR spectrum on the same instrument at a frequency of 25 MHz in $CDCl_3$–CD_3OD (9:1) solution with TMS as internal standard; and the mass spectrum on a MKh-1310 instrument fitted with a system for direct introduction into the ion source.

Isolation of Tadzhaconine from the Roots of *A. zeravchanicum*. The comminuted dry roots of the plant (0.6 kg) were extracted with chloroform. The chloroform extract was concentrated by evaporation and was treated with 5% H_2SO_4 and was then washed with water and dried with sodium sulfate. After the solvent had been distilled off and the residue had been dried in vacuum, 17.0 g of a mixture of substances was obtained. This was chromatographed on a column of Al_2O_3 (1:20) with elution by chloroform and the collection of 100 ml fractions. On treatment with chloroform, fractions 2-3 yielded 2.4 g of tadzhaconine.

Tadzhaconine – transparent crystals in the form of prisms changing on storage into a fine powder. IR spectrum, ν_{max}, cm^{-1}): 3070, 1660, 860 (terminal methylene group); 1600, 1585, 720 (aromatic ring). Mass spectrum (m/z): 533 (M^+), 490, 474, 430, 414, 368, 352, 310, 292, 282, 264, 207, 122, 105 (100%). PMR spectrum (δ, ppm): 0.94 (3H, s, $C18{-}H_3$), 1.93 and 1.94 (each 3H, 2s, $2OCOCH_3$), 2.39 (1H, d, J = 12.9 Hz, C19–Hb), 2.79 (1H, d, J = 12.0 Hz, Ha), 3.18 (1H, br. s, C6–H), 4.08 (1H, br. d, J = 9.0 Hz, C13–αH), 4.21 (1H, s, C20–H), 4.67 and 4.78 (each 1H, 2s, $C17{-}H_2$), 5.26 (1H, d, J = 9.0 Hz, C11–βH), 5.46 (1H, m, C2–βH), 5.77 (1H, d, J = 3.0 Hz, C1–αH), 7.28–8.12 (5H, m, $OCOC_6H_5$).

^{13}d NMR spectrum (δ, ppm): 71.63 (C-1); 68.87 (C-2); 36.68 (C-3), 36.15 (C-4); 57.96 (C-5); 64.31 (C-6); 34.04 (C-7); 43.99 (C-8); 51.91 (C-9); 54.68 (C-10); 76.11 (C-11); 49.37 (C-12); 70.36 (C-13); 51.46 (C-14); 33.15 (C-15); 144.61 (C-16); 108.91 (C-17); 29.35 (C-18); 63.64 (C-19); 65.66 (C-20); 165.90 (C_2–OCO–); 130.34; 129.97; 128.70; 133.26 (C atoms of a benzene ring), 172.02 and 21.59 ($C1{-}OCO{-}CH_3$); 170.53 and 21.36 ($C11{-}OCOCH_3$).

X-Ray Structural Investigation. The crystals of the ethanol solvate of tadzhaconine (1:1) were obtained from solutions in ethanol. In the air they changed into a white powder in the course of 3-5 min, and therefore the tadzhaconine crystals were isolated and were coated first with vacuum grease and then with an epoxide resin. The recording was carried out by Syntex $P2_1$ diffractometer using CuK_α radiation: (*a* = 11.506(4), b = 13.997(4), c = 19.066 (b) Å), space group $P2_12_12_12_1$, Z - 4. In the calculations we used 1900 independent reflections with $I > 2\sigma$.

The structure was interpreted by the direct method using the SHELXS-86 program [12]. The refinement of the structure by the method of least squares was carried out in accordance with the SHELX-76 program [13] in the isotropic-anisotropic approximation for all the nonhydrogen atoms. In the refinement, the hydrogen atoms attached to the carbon atoms were included in the calculation. The hydrogen atom of the OH group was found from a difference

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

Atom	x	y	z	Atom	x	y	z
C1	—0709 (6)	3144(5)	6779(3)	C22	—2233(9)	2664(7)	8474(4
C2	—0206 (7)	4145(5)	6869(4)	C23	—0129(8)	5428(7)	6047(4)
C3	0912 (7)	4160(6)	7266(4)	C24	—0107(7)	5666(5)	5276(4))
C4	1792 (7)	3364(6)	7108(4)	C25	—0248(9)	4966(6)	4762(5)
C5	1225 (6)	2362(6)	7044(3)	C26	4985(10)	3784(9)	8869(5)
C6	2118 (6)	1853(6)	6579(4)	C27	—0186(10)	5209(7)	4066(5)
C7	1753 (7)	0849(6)	6345(4)	C28	4508(11)	3152(8)	9329(6)
C8	0573 (7)	0861(5)	6018(4)	C29	0119(10)	6587(7)	5091(6)
C9	—0342 (6)	1342(5)	6519(4)	C30	—3337(7)	1715(7)	6709(5)
C10	0164 (6)	2403(5)	6559(4)	C31	—4319(8)	2406(7)	6591(5)
C11	—1536 (7)	1134(5)	6206(4)	N	2066(5)	2541(5)	5988(3)
C12	—1466 (7)	0923(5)	5410(4)	O1	—1044(4)	2820(4)	7485(3)
C13	—0650 (7)	1612(5)	5044(4)	O2	—2664(5)	3714(4)	7491(3)
C14	0553 (6)	1619(5)	5415(4)	O3	—0084(5)	4493(3)	6144(2)
C15	0212 (7)	—133(6)	5749(4)	O4	—0188(7)	6017(4)	6503(3)
C16	—0940 (7)	—082(6)	5372(4)	O5	—2450(4)	1871(4)	6280(3)
C17	—1512 (11)	—820(7)	5025(7)	O6	—3306(6)	1060(5)	7151(3)
C18	2749 (8)	3408(7)	7690(4)	O7	—1101(4)	2552(4)	5004(3)
C19	2337 (7)	3467(6)	6354(4)	C32	—3334(13)	5478(11)	6243(7)
C20	0804 (6)	2527(5)	5818(3)	C33	—4276(15)	5422(11)	6694(9)
C21	—2030 (8)	3118(6)	7763(5)	O8	—4758(11)	6252(9)	6880(5)

synthesis. The H atoms in the ethanol molecule of crystallization were not found. The definitive values of the divergence factors were R = 0.063 and R_W = 0.066. All the calculations were made on a PC of the IBM PC/AT type. The coordinates of the nonhydrogen atoms are given in Table 2.

After the structure of (I) with EtOH had been deciphered, more stable crystals of tadzhaconine were obtained from propanol (the crystals changed into a white powder in the course of 5-7 days). Judging from the parameters of the unit cell (a = 11.648(4), b = 14.362(4), c = 18.902 (b) Å) and the space group $P2_12_12_1$, the crystals of the two forms were isostructural, since, with the same space group, the parameters of the unit cell had scarcely changed. The increase in the size of the solvate molecule in the second case impeded its volatilization and the crystals were more stable in time.

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