Chemistry of Natural Compounds, Vol. 30, No. 5, 1994

AKIRAN — A NEW BISNORTERPENE ALKALOID FROM *Aconitum kirinense*

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UDC 547.944/945+548.737

The new bisnorditerpene alkaloid akiran has been isolated from the epigeal part of Aconitum kirinense. *The structure of akiran has been shown on the basis of x-ray analysis (diffractometer, CuK_α radiation, 1755 reflections, direct method, R = 0.064) and a study of spectral characteristics. A possible scheme of the biosynthesis of the bisnorterpene alkaloids of* Aconitum kirinense *is proposed.*

In the course of a further study of the alkaloids of the epigeal part of *Aconitum kirinense* Nakai [1-3] we have isolated a new alkaloid and have called it akiran (1).

Akiran (1) has the composition $C_{26}H_{43}NO_7$ (HRMS M^+ 479.2883). In the IR spectrum there were absorption bands of a hydroxy group (3520 cm^{-1}), an ester group (1740 cm^{-1}), and ether bonds (1100 cm^{-1}). According to its PMR spectrum the base contains N-ethyl, acetoxy, and four methoxy groups. A comparison of its empirical formula and functional composition permitted it to be assigned to the bisnorditerpene alkaloids. The maximum peak in the mass spectrum of akiran was that of the $M^+ - 60$ ion and there were also intense peaks of $M^+ - 91$ ($M^+ - 60 - 31$) and $M^+ - 75$ ($M^+ - 60 - 15$) ions. Analogous peaks are observed in the spectrum of lappaconine 4-monoacetate, which permits the assumption of the presence of an acetoxy group at C-4 and a methoxy group at C-1 in akiran.

The PMR spectrum of (1) also contained the signals of methine protons. A triplet at 3.49 ppm (J = 5 Hz) showed the presence of an α-oriented methoxy group at C-14, and a doublet at 3.93 ppm (J = 7 Hz) that of a β-oriented methoxy group at C-6.

In order to establish its constitution reliably and to confirm suggestions concerning its structure, compound (1) was subjected to an x-ray investigation.

On the whole, the spatial structure of akiran, which is shown in Fig. 1 confirms that proposed on the basis of spectral characteristics (1). Akiran contains a lycoctonine carbon skeleton with the following positions and orientations of the substituents: α-methoxy groups at C1 and C14 and β-methoxy groups at C6 and C16 and a β-oriented OAc group at C4. The linkages of the main rings are *A/E trans* (torsional angle C17C11C5H5 159.7°), *B/C cis* (C14C9C10H10 85.8°, and *B/D trans* (C15C8C9H9 152.8°).

The molecule has a rigid bridge structure consisting of six main rings. The conformations of the rings can be judged from the values of the intracyclic torsional angles. The six-membered rings *A* (the C1-C5 and C11 atoms) and *F* (the C4, C5, C11, C17, C18, and N atoms) have chair conformations (with accuracies of ±0.022 Å and ±0.036 Å, respectively), while ring *B* (the C7-C11 and C17 atoms) assumes the chair form with a slight distortion (±0.063 Å). Ring *D* (the C8, C9,and C13-C16 atoms) is present in the boat form (±0.012 Å) flattened at the C15 atom. The five-membered rings *E* and *C* assume envelope conformations: in the former, the C17 atom departs by 0.77 Å in the α-direction from the plane (±0.04 Å) of the C5, C6, C7, and C11 atoms, and in the latter the C14 atoms departs by 0.73 Å in the β-direction from the plane (±0.014 Å) of the C9, C10, C12, and C13 atoms.

In the molecule there is an intramolecular hydrogen bond of the O—H···O type between the hydroxy group at C8 and the methoxy group at C6, as is shown by the O4···O5 distance of 2.69 Å and the H···O4 distance of 2.01 Å, and also by the O—H—O angle of 119°.

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0009-3130/94/3005-0603$12.50

TABLE 1. Bond Lengths (r, Å) and Valence Angles (ω, degrees) in the Akiran Structure

Bond	r	Bond	r	Angle	ω	Angle	ω
C1-C2	1.53(1)	C13-C14	1.54(1)	C2-C1-C11	116.8(5)	C2-C1-O1	108.4(5)
C1-C11	1.55(9)	C13-C16	1.51(7)	C11-C1-O1	108.1(5)	C1-C2-C3	113.8(7)
C1-O1	1.42(7)	C14-O6	1.42(1)	C2-C3-C4	108.7(6)	C3-C4-C5	110.0(6)
C2-C3	1.53(1)	C15-C16	1.53(1)	C3-C4-C18	115.4(7)	C5-C4-C18	108.2(5)
C3-C4	1.52(1)	C16-O7	1.42(8)	C3-C4-O2	107.6(5)	C5-C4-O2	102.9(7)
C4-C5	1.53(1)	C17-N	1.48(8)	C18-C4-O2	112.1(5)	C4-C5-C6	108.5(5)
C4-C18	1.53(8)	C18-N	1.47(9)	C4-C5-C11	108.8(7)	C6-C5-C11	105.5(5)
C4-O2	1.48(1)	C19-C22	1.49(2)	C5-C6-C7	105.1(6)	C5-C6-O4	115.4(5)
C5-C6	1.54(1)	C19-O2	1.34(1)	C7-C6-O4	112.7(6)	C6-C7-C8	113.2(6)
C5-C11	1.55(1)	C19-O3	1.19(1)	C6-C7-C17	100.7(5)	C8-C7-C17	112.4(6)
C6-C7	1.54(9)	C20-C21	1.52(1)	C7-C8-C9	109.0(5)	C7-C8-C15	113.2(6)
C6-O4	1.44(1)	C20-N	1.43(7)	C9-C8-C15	113.1(6)	C7-C8-O5	107.4(6)
C7-C8	1.53(9)	C23-O1	1.41(1)	C9-C8-O5	110.1(6)	C15-C8-O5	103.7(6)
C7-C17	1.55(1)	C24-O7	1.41(1)	C8-C9-C10	111.9(6)	C8-O9-C14	111.5(5)
C8-C9	1.53(8)	C25-O4	1.43(1)	C10-C9-C-14	101.8(6)	C9-C10-C11	116.9(5)
C8-C15	1.55(1)	C26-O6	1.38(1)	C9-C10-C12	104.0(6)	C11-C10-C12	116.7(7)
C8-O5	1.45(1)			C1-C11-C5	115.1(5)	C1-C11-C10	107.7(50
C9-C10	1.56(1)			C5-C11-C10	109.9(6)	C1-C11-C17	115.2(6)
C9-C14	1.52(9)			C5-C11-C17	97.8(5)	C10-C11-C17	110.9(5)
C10-C11	1.56(9)			C10-C12-C13	106.4(7)	C12-C13-C14	100.4(6)
C10-C12	1.56(1)			C12-C13-C16	111.4(6)	C14-C13-C16	111.3(7)
C11-C17	1.51(7)			C9-C14-C13	101.9(6)	C9-C14-O6	111.5(6)
C12-C13	1.53(1)			C13-C14-O6	118.0(6)	C8-C15-C16	118.3(5)
				C13-C16-C15	115.6(6)	C13-C16-O7	113.0(5)
				C15-C16-O7	105.5(6)	C7-C17-C11	101.4(6)
				C7-C17-N	116.1(5)	C11-C17-N	109.1(5)
				C4-C18-N	113.7(5)	C22-C19-O2	110.1(8)
				C22-C19-O3	124.9(9)	O2-C19-O3	124.9(9)
				C21-C20-N	114.8(6)	C17-N-C18	117.4(6)
				C17-N-C-20	114.8(5)	C18-N-C20	109.6(5)
				C1-O1-C23	114.2(5)	C4-O2-C19	120.9(8)
				C6-O4-C25	112.6(6)	C14-O6-C26	113.1(7)
				C16-O7-C24	112.8(7)		

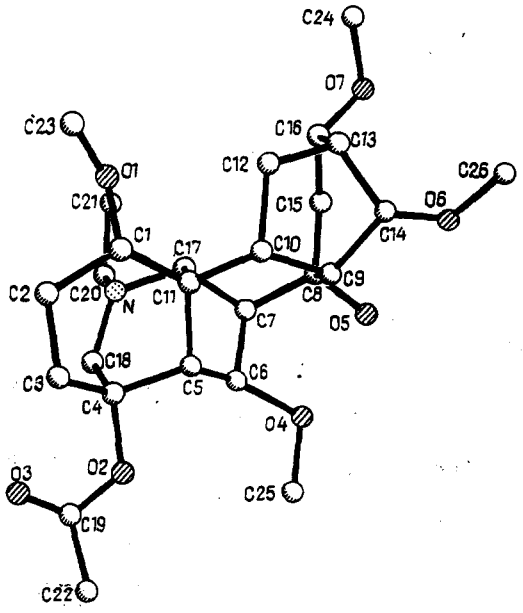


Fig. 1

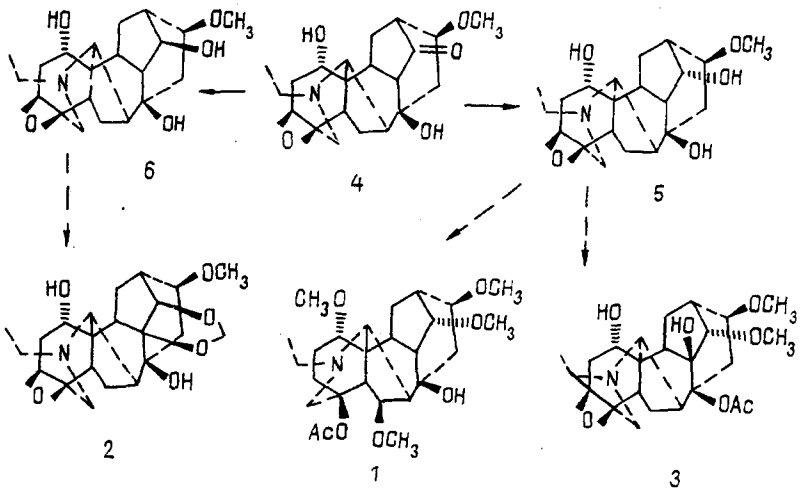
Bond lengths and valence angles are given in Table 1. The lengths of the ordinary C_{sp^3}-C_{sp^3} bonds range between 1.51 and 1.56 Å, and the lengths of the C—O bonds between 1.41 and 1.48 Å, which, within the 3σ limits, agree with those generally accepted [4] and are close to those observed in akirine [2]. The considerable variation in the valence angles at tetrahedral carbon atoms is connected with the stress in the bridge fragments that exists in the molecule (Table 1).

There are no intermolecular hydrogen bonds, since the results of an analysis of intermolecular contacts did not reveal any shortening of intermolecular distances due to H-bonds.

Akiran is the first representative of the bisnorditerpene alkaloids of the aconitine type with an acetoxy group at C-4.

We are the first to have isolated from the epigeal part of *Aconitum akirinense* the bisnorditerpene alkaloids akiran (1), akirine (2) [2], and 8-acetylexcelsine (3) [1]. Akirine was the first alkaloid having a lycoctonine skeleton with a β-oriented substituent at C-14. The simultaneous isolation of the alkaloids suggests certain biogenetic hypotheses. It may be assumed that biosynthesis takes place with the participation of precursor (4) having a keto function at C-14 the enzymatic reduction of which can lead to both the α- and the β-epimers, (5) and (6), respectively (scheme 1).

Scheme 1. Possible scheme of the biosynthesis of the bisnorditerpene alkaloids of *Aconitum kirinense*



The subsequent hydroxylation of the β-epimer in position 9 followed by the formation of a methylenedioxy group leads to akirine (2). In the case of the α-epimer, the analogous hydroxylation followed by C-14 methylation and acylation of the hydroxy group at C-8 gives 8-acetylexcelsine (3). Akiran is obviously synthesized from (5) as the result of successive reactions of 6β-hydroxylation, methylation of the secondary hydroxy groups, opening of the epoxy function, and acylation of the C-4 hydroxy group.

EXPERIMENTAL

For chromatography we used type KSK silica gel and deactivated alumina. PMR spectra were taken on a Tesla BS 567 A 100 MHz instrument, mass spectra on a MKh-1310 spectrometer with a system for the direct injection of the sample into the ion source, and IR spectra on a UR-20 spectrophotometer in tablets with KBr.

Isolation of Akiran (1). The extraction and preliminary separation of the total alkaloids has been reported in [1]. When the hexane material was eluted with benzene—ethyl acetate (1:1), a fraction enriched with akiran was obtained. This was rechromatographed on a column of silica gel, and elution with benzene—methanol (50:1) yielded 0.07 g of chromatographically pure akiran (1).

Akiran (1) has mp 214-217°C (acetone). IR spectrum (KBr, ν_{max}) 3540, 2950, 2830, 1745, 1475, 1410, 1375, 1275, 1240, 1140, 1100, 1050, 990, 960, 870. Mass spectrum, m/z (%): 479(6), 464(13), 448(28), 446(5), 430(3), 419(100), 404(33), 388(66), 364(4), 362(4), 360(3), 358(4), 356(5), 346(15), 330(5), 288(6), PMR spectrum: ($CDCl_3$, δ): 1.00 (3H, t, J = 7 Hz, N$-CH_2-CH_3$), 1.93 (3H, s, $OCOCH_3$), 3.18, 3.25, 3.33, 3.33 (each 3H, s, 4 × OCH_3), 3.49 (1H, t, J = 5 Hz, H-14β), 3.93 (1H, m, J = 7 Hz, H-6α), 4.33 (1H, br.s).

TABLE 2. Coordinates ($\times 10^4$) of the Nonhydrogen Atoms and Thermal Factors ($Å^2 \times 10^3$) of the Akiran Molecule

Atom	x	y	z	U	Atom	x	y	z	U
C1	4267(6)	8380(6)	7686	46(2)	C18	3551(7)	5102(6)	6772(7)	51(2)
C2	5172(8)	7341(7)	8050(7)	57(2)	C19	6374(8)	4497(8)	5879(8)	67(3)
C3	6051(7)	6761(8)	7283(7)	61(3)	C20	955(7)	4634(6)	7219(7)	52(2)
C4	4968(7)	6194(7)	6483(7)	50(2)	C21	-324(8)	5060(8)	7765(8)	70(3)
C5	4450(6)	7392(6)	5985(7)	45(2)	C22	7458(9)	4338(9)	5119(9)	83(4)
C6	3319(7)	6776(6)	5205(6)	47(2)	C23	3567(9)	9268(8)	9136(7)	68(3)
C7	1752(6)	6904(6)	5587(6)	42(2)	C24	-1941(9)	10821(8)	6995(8)	79(3)
C8	1217(7)	8178(6)	5209(6)	46(2)	C25	4748(11)	6848(9)	3785(8)	88(4)
C9	2507(7)	9471(6)	5306(7)	48(2)	C26	647(11)	12205(8)	4455(8)	85(4)
C10	3321(6)	9516(6)	6282(7)	42(2)	N	2301(5)	5712(5)	7121(6)	43(2)
C11	3542(6)	8091(6)	6690(6)	40(2)	O1	3092(5)	8432(4)	8341(5)	49(1)
C12	2463(7)	10386(6)	6919(7)	54(2)	O2	5856(5)	5662(5)	5743(6)	58(2)
C13	1179(7)	10719(6)	6317(7)	48(2)	O3	6009(8)	3700(7)	6511(7)	97(3)
C14	1909(7)	10804(6)	5335(7)	52(2)	O4	3639(5)	7396(4)	4285(6)	60(2)
C15	-285(7)	8370(6)	5661(7)	53(2)	O5	833(6)	7917(4)	4223(6)	60(2)
C16	-221(7)	9560(6)	6367(7)	45(2)	O6	985(6)	10911(5)	4543(6)	71(2)
C17	2073(6)	7003(5)	6659(6)	40(2)	O7	-1586(5)	10036(4)	6227(6)	60(2)

The x-ray structural experiment with akiran was conducted on a Syntex $P2_1$ diffractometer, using CuK_α radiation: $a = 9.046$ (2), b = 9.820(2), c = 14.190(4) Å, $\gamma = 102.47(1)$, $D_{CALC} = 1.294$ g/cm^3, space group $P2_1$, $z = 2$, $V = 1230.8$. The structure was interpreted by the direct method using the SHELXS-86 program [5]. In the calculation we used 1755 reflections. Refinement of the structure by the method of least squares was done by the SHELX-76 program [6] in the isotropic-anisotropic approximation for all nonhydrogen atoms, $R = 0.064$, $R_w = 0.064$. The hydrogen atoms were placed in the calculated positions and refined in the isotropic approximation. The coordinates of the nonhydrogen atoms are given in Table 2.

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