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ARCUTIN - A NEW TYPE OF DITERPENE ALKALOIDS

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The structure of the diterpene alkaloid arcutin, which is isolated from Aconitum arcuatum *Maxim. (Ranunculaceae), is solved by x-ray methods. Arcutin represents a new type of diterpene alkaloids containing a C5–C20 bond instead of the traditional C10–C20 bond in the carbon backbone.*

Key words: *Aconitum arcuatum*, Ranunculaceae, new diterpene alkaloid arcutin, x-ray structure analysis.

Diterpene alkaloids (DA), the main component of almost all studied species of *Aconitum* and *Delphinium* (Ranunculaceae), are interesting owing on one hand to their wide variation and complicated carbon backbones and, on the other, to the valuable pharmacological properties and sometimes high toxicity.

In continuation of research on wild and cultivated *Aconitum* and *Delphinium* species [1, 2], we studied alkaloids of the aerial portions of *A. arcuatum* Maxim. The plant exhibits antibacterial activity and is used in folk medicine as a narcotic for rheumatism and radiculitis [3]. It was found earlier that they contain the nor- and bisnorditerpene alkaloids talatisamine and aconosine [4].

The aerial portion of *A. arcuatum* was collected near the village Starovarvarovka, Anuchinsk Region, Primorskii Krai and contains 0.38% (of dry mass) mixed alkaloids. We isolated a new compound that we call arcutin in addition to talatisamine.

DAs have a rigid three-dimensional carbon backbone and are divided into two large groups. These are lycoctonines and alkaloids with the perhydrophenanthrene nucleus. The absolute configuration is determined by the fusion of rings *A*, *B*, and *C* of the perhydrophenanthrene nucleus. The fusions *A*/*B*-*trans* and *B*/*C*-*cis* are invariant over all known DAs.

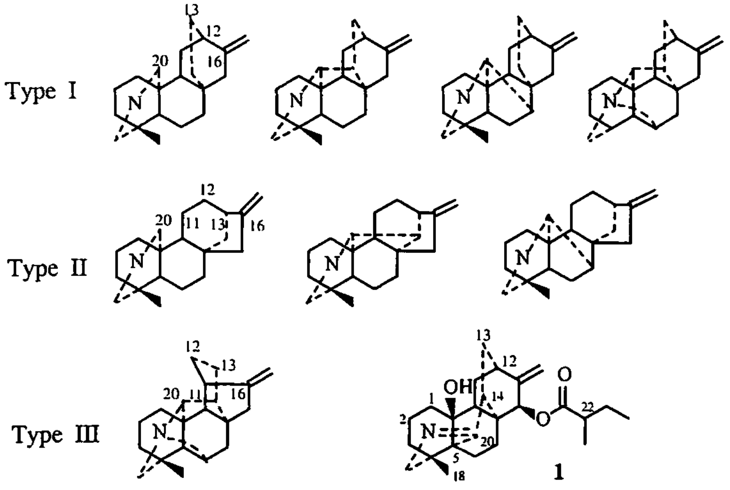

Fig. 1. Carbon backbones in diterpene alkaloids with the perhydrophenanthrene nucleus.

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TABLE 1. Torsion Angles (φ, deg) in Rings of Arcutin (**1**)

Ring	Atom Nos.	φ	Ring	Atom Nos.	φ
A	1-2-3-4	62.6	*B*	5-6-7-8	2.1
	2-3-4-5	-47.9		6-7-8-9	57.9
	3-4-5-10	36.6		7-8-9-10	-56.3
	4-5-10-1	-38.6		8-9-10-5	-3.1
	5-10-1-2	52.0		9-10-5-6	62.3
	10-1-2-3	-63.8		10-5-6-7	-61.9
C	8-9-11-12	12.3	*D*	8-9-11-12	12.3
	9-11-12-13	53.7		9-11-12-16	-66.3
	11-12-13-14	-66.6		11-12-16-15	53.5
	8-14-13-12	9.9		12-16-15-8	10.2
	13-14-8-9	53.8		16-15-8-9	-63.4
	14-8-9-11	-67.3		15-8-9-11	50.3
E	8-14-13-12	9.9	*F*	4-5-20-N	-20.3
	14-13-12-16	53.8		5-20=N-19	4.2
	13-12-16-15	-66.8		20-N-19-4	14.4
	12-16-15-8	10.2		N-19-4-5	-25.5
	16-15-8-14	53.4		19-4-5-20	25.5
	15-8-14-13	-64.9			
G	5-10-9-8	-3.1	*H*	5-6-7-8	2.1
	10-9-8-14	63.3		6-7-8-14	-60.2
	9-8-14-20	-70.0		7-8-14-20	49.8
	8-14-20-5	15.4		8-14-20-5	15.4
	14-20-5-10	45.0		14-20-5-6	-71.3
	20-5-10-9	-50.4		20-5-6-7	58.1

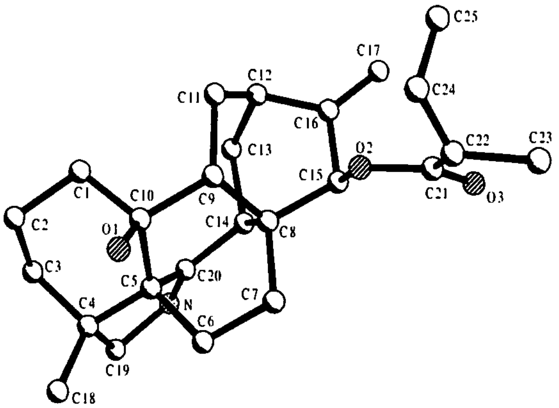

Fig. 2. Structure of arcutin (**1**).

Three classes of alkaloids with the perhydrophenanthrene nucleus are known. These differ in the bonding of the C15–C16 bridge to C11, C12, and C13. Depending on the mode of bonding, the alkaloids are classed as atisine (Type I) (ring *D* is six-membered, the bridge closes at C12), veatchine (Type II), and delnudin (Type III) (ring *D* is five-membered, the bridge closes at C13 and C11, respectively). Structures of class **I**, **II**, and **III** alkaloids also vary by the presence or absence of bridges between C7–C20, C14–C20, and N–C6. Figure 1 shows the carbon backbones of plant alkaloids with the perhydrophenanthrene nucleus of the atisine, veatchine, and delnudin classes. The atisine class is illustrated most clearly. Alkaloids of the veatchine class with C13–C20 and N–C6 bridges have not yet been observed in nature. The third class has a single representative, delnudin, which has C14–C20 and N–C6 bridges [5].

TABLE 2. Bond Lengths (*r*, Å) and Angles (ω, deg) in Arcutin (**1**)

Bond	*r*	Angle	φ	Angle	φ
N-C20	1.259(8)	C20-N-C19	106.9(5)	C12-C11-C9	108.9(6)
N-C19	1.496(8)	C21-O2-C15	117.7(6)	C16-C12-C11	109.8(6)
O1-C10	1.450(7)	C10-C1-C2	111.1(5)	C16-C12-C13	109.1(6)
O2-C21	1.347(9)	C3-C2-C1	107.9(6)	C11-C12-C13	109.7(5)
O2-C15	1.457(9)	C2-C3-C4	114.1(6)	C12-C13-C14	108.0(6)
O3-C21	1.185(10)	C19-C4-C3	107.4(6)	C20-C14-C8	106.0(5)
C1-C10	1.528(9)	C19-C4-C18	111.2(6)	C20-C14-C13	114.0(6)
C1-C2	1.528(10)	C3-C4-C18	110.4(5)	C8-C14-C13	110.1(5)
C2-C3	1.500(11)	C19-C4-C5	101.2(5)	O2-C15-C16	109.4(6)
C3-C4	1.529(9)	C3-C4-C5	111.2(5)	O2-C15-C8	107.1(6)
C4-C19	1.526(10)	C18-C4-C5	114.9(5)	C16-C15-C8	108.2(6)
C4-C18	1.530(9)	C20-C5-C10	113.5(5)	C17-C16-C12	125.4(7)
C4-C5	1.552(9)	C20-C5-C6	102.3(5)	C17-C16-C15	122.7(7)
C5-C20	1.504(9)	C10-C5-C6	108.2(5)	C12-C16-C15	111.8(6)
C5-C10	1.541(9)	C20-C5-C4	100.3(5)	N-C19-C4	106.9(6)
C5-C6	1.546(8)	C10-C5-C4	117.9(5)	N-C20-C5	116.9(5)
C6-C7	1.548(8)	C6-C5-C4	113.6(5)	N-C20-C14	126.8(6)
C7-C8	1.536(8)	C5-C6-C7	109.0(5)	C5-C20-C14	115.0(6)
C8-C15	1.536(9)	C8-C7-C6	111.4(5)	O3-C21-O2	123.3(8)
C8-C14	1.536(10)	C15-C8-C14	108.4(6)	O3-C21-C22	125.3(8)
C8-C9	1.536(9)	C15-C8-C9	110.1(6)	O2-C21-C22	111.3(8)
C9-C11	1.546(9)	C14-C8-C9	107.1(5)	C24-C22-C23	115.4(11)
C9-C10	1.592(9)	C15-C8-C7	111.1(5)	C24-C22-C21	115.2(11)
C11-C12	1.513(10)	C14-C8-C7	109.9(5)	C23-C22-C21	114.1(9)
C12-C16	1.478(10)	C9-C8-C7	110.2(6)	C22-C24-C25	111(2)
C12-C13	1.532(11)	C8-C9-C11	109.6(6)		
C13-C14	1.554(9)	C8-C9-C10	109.5(6)		
C14-C20	1.521(9)	C11-C9-C10	117.8(6)		
C15-C16	1.526(10)	O1-C10-C1	106.9(5)		
C16-C17	1.321(9)	O1-C10-C5	105.3(4)		
C21-C22	1.480(12)	C1-C10-C5	112.1(5)		
C22-C24	1.30(2)	O1-C10-C9	107.8(5)		
C22-C23	1.453(13)	C1-C10-C9	115.0(5)		
C24-C25	1.35(2)	C5-C10-C9	109.2(5)		

Arcutin differs from known alkaloids in lacking a C10–C20 bridge, which is characteristic of all DA. Instead, it has an unusual C5–C20 bridge and an azomethine N=C20. Therefore, arcutin is the first representative of a new class of DA with the perhydrophenanthrene nucleus in which the C15–C16 bridge is bonded to C12, like in atisine alkaloids, and C20 is single-bonded to C5 and C14 and double-bonded to the N atom. Figure 2 shows the three-dimensional structure of arcutin from an x-ray structure analysis. It can be seen that the fusion of the principal perhydrophenanthrene rings is unchanged: *A/B-trans* and *B/C-cis*. However, chiral centers C5 and C10 change sign compared with known DA with the perhydrophenanthrene nucleus. This causes the OH on C10 to be β-axial and C5–C20 to be α-axial. As usual, the C18-methyl is β-axial. The ester on C15 is β-axial. The asymmetric center C22 in the 2-methyl fatty acid has the R-configuration.

The new six-membered rings *G* (C5, C10, C9, C8, C14, C20) and *H* (C5—C8, C14, C20) are formed by the bonds of C20 to C5 and C14 and the N atom. Rings *G* and *H* have slightly distorted 5,8α-boat conformations. They share atoms with rings *B* (C5—C10), *C* (C8, C9, C11—C14), *D* (C8, C9, C11, C12, C16, C15), and *E* (C8, C15, C16, C12—C14). The torsion angles (Table 1 and Fig. 2) show that six-membered rings *A* and *B* in arcutin have the 2β,5α-chair and 5,8α-boat conformations, respectively, whereas rings *C*, *D*, and *E* have the 8,12α-boat conformation. Rings *C*, *D*, and *E* for one and rings *B*, *G*, and *H* for another are mutually fused bicyclo-[2.2.2]-octanes. Therefore, the rings involved in these systems are constrained to adopt the boat conformation. The bicyclo-[2.2.2]-octane formed by rings *C*, *D*, and *E* is slightly twisted as indicated by the approximately equally positive torsion angles C8—C9—C11—C12 (12°), C8—C14—C13—C12 (10°), and C8—C15—C16—C12 (10°). The other bicyclooctane formed by rings *B*, *G*, and *H* is less twisted and unevenly, as indicated by the torsion angles C5—C6—C7—C8 (2°), C8—C9—C10—C5 (3°), and C8—C14—C20—C5 (15°) (Table 1). The five-membered ring *F* (C4, C5, N, C20, C19) has the flattened 4β-envelope conformation.

The Csp^3–Csp^3 bond lengths in the carbon backbone average near the usual value 1.540 Å and vary in the range 1.500-1.592 Å (Table 2). However, the relatively fluxional ester on C15 is unusual. The Csp^3–Csp^3 bonds C22–C24 [1.30(2) Å], C24–C25 [1.35(2) Å], and C22–C23 [1.453(13) Å] are significantly shortened. This is probably due to the relatively strong anisotropic thermal vibrations of C22, C23, C24, and C25 (Table 3). The lengths of the double bonds are N=C20, 1.259(8); C16=C17, 1.321(9); and C21=O3, 1.185(10) Å. These lengths are close to the usual values (within experimental uncertainty) [6]. Anomalies were not observed in the values of other types of bonds. The distortion of the bond angles in arcutin is apparently due to the formation of rigid condensed rings.

The packing and intermolecular contacts are consistent with N...H–O hydrogen bonds. For example, unit translations along the *a* axis give an intermolecular N...O1 distance of 2.82 Å. Otherwise, van-der-Waals interactions are found.

EXPERIMENTAL

General. Melting points were determined on a Boetius RNMK 05 apparatus. Mass spectra were obtained on an MX-1310 spectrometer. TLC on aluminum oxide (LCL 5/40, neutral) using hexane—ethylacetate (10:3), $CHCl_3$, $CHCl_3$—CH_3OH (100:1) and on silica gel using ethylacetate—CH_3OH (5:1) and $CHCl_3$—CH_3OH (3:1) was used to monitor the reactions. Silica gel (L 100/160) was used for column chromatography.

Isolation of Alkaloids. Air-dried aerial portions (2 kg) were ground and wetted with 5% Na_2CO_3 solution. The alkaloids were extracted by $CHCl_3$. Bases were extracted from the condensed $CHCl_3$ extract by 5% H_2SO_4. The acidic solution was cooled and made basic with saturated aqueous Na_2CO_3. Alkaloids were extracted with ether and $CHCl_3$. The ether extract yielded 6.54 g; the $CHCl_3$, 1.07 g of alkaloids. The ether fraction was separated into fractions soluble and insoluble (6.40 g) in hexane. Column chromatography with elution by hexane—acetone (1:1) was used to obtain from the soluble fraction a mixture of crystals (8 mg, recrystallized from hexane). Arcutin was separated manually from the crystals. Column chromatography on aluminum oxide with elution by $CHCl_3$ isolated from the hexane-insoluble fraction talatisamine (110 mg, mp 138-140°C), which was identified by its mixed melting point (with an authentic sample), TLC, IR, mass, and PMR spectra.

Arcutin (1). mp 225-226°C (hexane). Mass spectrum *m/z* (%): 397 (M^+, 12), 314 (24), 313 (100), 312 (16), 297 (10), 296 (50), 295 (86), 294 (17), 280 (13), 267 (20), 224 (30), 223 (17), 199 (20), 198 (63), 197 (13), 196 (17), 105 (33), 91 (27), 85 (22), 71 (20). Calc. $C_{25}H_{35}NO_3$, 397.5626. Found, 397.2642.

X-ray Structure Analysis. Cell constants and intensities of 1872 independent reflections were measured on a Nonius CAD-4 diffractometer (Mo Kα-radiation, graphite monochromator, ω/2θ-scanning). Crystals are orthorhombic, a = 7.337(3), b = 11.954(4), c = 24.082 (8) Å, V = 2112.0 (1.3) Å^3, d_{calc} = 1.250 g/cm^3, Z = 4 ($C_{25}H_{35}NO_3$), space group $P2_12_12_1$. The structure was solved by direct methods and refined by anisotropic full-matrix least-squares methods for the nonhydrogen atoms. All H atoms, with the exception of the hydroxyl H, which was found in a difference electron-density synthesis, were assigned geometrically and given fixed in the "riding" model. A total of 1101 reflections with $I > 2\sigma(I)$ were used in the calculations. The final agreement factors were R = 0.072 and R_w = 0.178. Coordinates of nonhydrogen atoms are given in Table 3. All calculations were performed on an IBM-486 PC using the SHELXTL and SHELXL-95 programs.

TABLE 3. Atomic Coordinates ($\times 10^4$) and Equivalent Thermal Parameters ($Å^2 \times 10^3$) in Arcutin (**1**).

Atom	x	y	z	U_{eq}
N	3595(7)	-2753(5)	1258(2)	46(2)
O1	9927(6)	-2818(4)	914(2)	56(1)
O2	8999(7)	1011(3)	1099(2)	57(1)
O3	7887(11)	2681(5)	866(3)	103(2)
C1	8769(10)	-3298(5)	1811(3)	51(2)
C2	8485(11)	-4522(6)	1650(3)	60(2)
C3	6544(11)	-4657(5)	1466(3)	55(2)
C4	6045(9)	-3971(5)	952(3)	42(2)
C5	6702(9)	-2742(5)	1009(2)	34(2)
C6	6740(10)	-2100(5)	451(2)	42(2)
C7	6910(10)	-832(5)	572(2)	45(2)
C8	7059(9)	-601(5)	1197(2)	41(2)
C9	8701(10)	-1227(6)	1442(3)	49(2)
C10	8520(9)	-2528(5)	1311(2)	40(2)
C11	8974(11)	-875(6)	2054(3)	61(2)
C12	7309(11)	-235(6)	2245(3)	59(2)
C13	5592(12)	-930(7)	2135(3)	66(2)
C14	5353(9)	-1037(5)	1496(3)	45(2)
C15	7231(11)	658(5)	1313(3)	54(2)
C16	7175(10)	834(6)	1940(3)	56(2)
C17	7008(12)	1833(7)	2169(4)	76(2)
C18	6680(11)	-4570(6)	425(3)	57(2)
C19	3981(9)	-3819(5)	955(3)	49(2)
C20	5083(10)	-2233(5)	1296(2)	38(2)
C21	9137(14)	2057(7)	896(3)	67(2)
C22	10992(15)	2279(7)	680(5)	90(3)
C23	11196(18)	3365(8)	417(5)	128(4)
C24	12316(22)	1986(19)	1008(8)	193(9)
C25	12255(23)	2578(18)	1486(5)	220(11)

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