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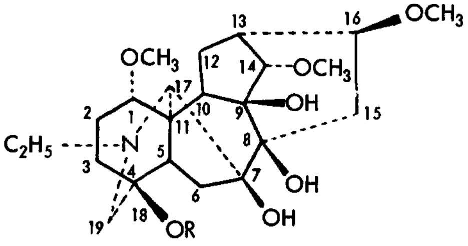
THE STRUCTURE OF RANACONITINE, A NEW DITERPENOID ALKALOID OF ACONITUM RANUNCULAEFOLIUM

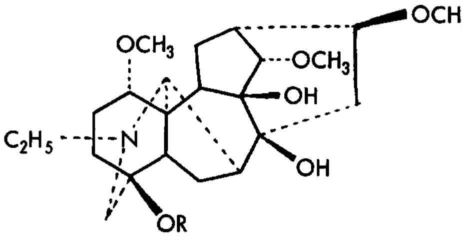
S. William Pelletier*, Naresh V. Mody, Atanas P. Venkov[1]
Institute for Natural Products Research and the Department of Chemistry
University of Georgia, Athens, Georgia 30602 U.S.A.

Nikola M. Mollov*
Department of Chemistry, University of Plovdiv
4000 Plovdiv, Bulgaria

We wish to report the structure determination of ranaconitine (1), a C_{19}-diterpenoid alkaloid occurring in Aconitum ranunculaefolium, a plant native to Bulgaria. In 1964 Mollov and coworkers[2] isolated two related diterpenoid alkaloids, ranaconitine and lappaconitine, from this plant. On the basis of extensive chemical studies Marion and coworkers[3] later elucidated the structure of lappaconine (4), a hydrolysis product of lappaconitine. Subsequently, Birnbaum[4] confirmed the structure 4 for lappaconine by an X-ray analysis of lappaconine hydrobromide. Due to its instability in solution and the unavailability of sufficient sample for degradative work, the structure of ranaconitine remained unknown even after the structure of the related alkaloid, lappaconitine (3), had been established.[5]



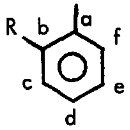
1 R = CO-C_6H_4-o-NHAc
2 R = H



3 R = CO-C_6H_4-o-NHAc
4 R = H

Ranaconitine, $C_{32}H_{44}N_2O_9$, mp 132-134°C, $[\alpha]^{27}$ D + 33.2° (c = 0.5, $CHCl_3$) shows IR absorption at 3510 and 3275 (OH and NH), 1700 and 1680 (carbonyls), 1605 (aromatic) and 1085 (ether) cm^{-1}. The ^1H NMR spectrum of ranaconitine in $CDCl_3$ exhibits signals at δ 1.13 (3H, t, N-CH_2-$C\underline{H}_3$), 2.24 (3H, s, NHCO$C\underline{H}_3$), 3.28, 3.33, 3.43 (each 3H, s, -O$C\underline{H}_3$), 7.13, 7.53, 7.95, 8.68 (aromatic protons) and 11.07 (1H, broad s, N$\underline{H}$COCH_3) ppm. Treatment of ranaconitine with 5% KOH in methanol at 25°C yielded an amino alcohol, ranaconine (2), $C_{23}H_{37}NO_7$, mp 107-109°C, and N-acetylanthranilic acid.

Table 1. ^{13}C Chemical Shifts and Assignments for Ranaconitine (1) and Lappaconitine (3)[†]

Carbon	1	3	Carbon	1	3	Carbon	1	3
1	83.5	84.2	12	25.9	24.2	16	56.3	56.1
2	26.5	26.2	13	49.8	49.0	-C=O	167.7	167.5
3	31.6	31.9	14	90.0	90.2		a 115.9	115.8
4	84.4	84.7	15	37.8	44.9		b 141.8	141.7
5	51.1	48.6	16	82.9	82.9		c 120.4‡	120.3‡
6	32.5	26.8	17	63.1	61.5		d 134.6*	134.4*
7	77.9	47.6	19	55.2	55.5		e 122.6‡	122.3‡
8	85.7	75.6	-NCH_2	48.7	49.9		f 131.3*	131.1*
9	78.4	78.6	CH_3	14.4	13.5	R=NHCO	169.5	169.0
10	36.6	36.4	1'	56.3	56.5	CH_3	25.6	25.5
11	51.4	51.0	14'	58.0	57.9			

[†] In ppm downfield to TMS. Solvent, $CDCl_3$. ‡,* Values within any vertical column are interchangeable.

A correlation of the ^{13}C NMR spectrum of ranaconitine was made with lappaconitine (3), and other published[6] ^{13}C NMR data of lycoctonine-type alkaloids. The pattern of ^{13}C chemical shifts in ranaconitine is similar to that of the known alkaloid lappaconitine except for a few changes. The appearance of a new singlet and disappearance of a doublet (47.6 ppm) in the ^{13}C NMR spectrum (SFORD) of ranaconitine in comparison with that of 3 suggested the presence of a tertiary hydroxyl group at the C-7 position in ranaconitine. The presence of C-7 hydroxyl group was confirmed by observing the downfield change in the ^{13}C chemical shifts of the adjacent C-6, C-8, and C-17 carbons when compared with lappaconitine. All other signals are also in agreement with the assigned structure (1) for ranaconitine.

The occurrence together in the same plant of ranaconitine, a lycoctonine-type alkaloid, and lappaconitine, an aconitine-type alkaloid,is perhaps unique. In this respect, in recent work aconitine-type alkaloids with a C-7 hydroxy group and lycoctonine-type alkaloids with hydroxy, methoxy or other oxygenated group at C-7 have not been detected together in the same plant.[7]

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