

CONFORMATIONAL ANALYSIS OF 4-METHYLRaucubainium AND 4-METHYLSTRICTAMINIUM CHLORIDES

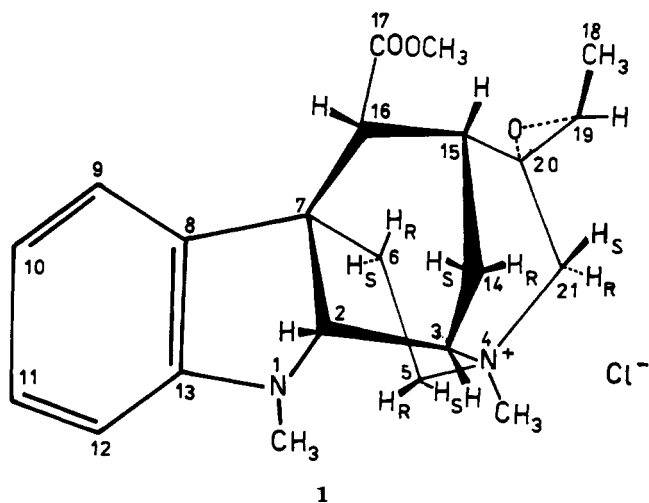
DUŠAN UHRÍN and BOHUMIL PROKSA*

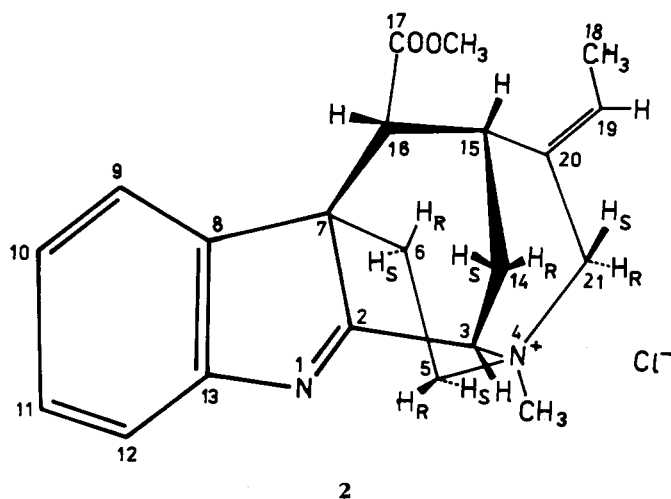
Institute of Chemistry, Slovak Academy of Sciences, 84238 Bratislava, Czechoslovakia

ABSTRACT.—The conformation of 4-methylraucubainium chloride and 4-methylstrictaminium chloride, new alkaloids from leaves of *Vinca minor*, have been elucidated by ^1H -nmr methods.

So far more than fifty alkaloids have been isolated from leaves of the lesser periwinkle (*Vinca minor* L.), but only a few of them are quaternary salts. Recently, we have isolated three new quaternary alkaloids from this plant and identified them as 4-methylakuammicinium chloride, 4-methylraucubainium chloride [**1**], and 4-methylstrictaminium chloride [**2**] (1); the latter two compounds belong to the picaline group. We report herein the results of conformational analysis of these pentacyclic molecules by ^1H -nmr spectroscopy. The ^{13}C -nmr spectral data of **1** and **2** were published in our previous paper (1), and therefore, all proton signals were assigned according to the ^{13}C - ^1H heterocorrelated experiment. Assignment of protons (*R/S*) at prochiral carbons was backed by the coupling constant analysis and nOe difference spectroscopy. The absolute configuration at C-7 (i.e., *7S*) of **1** was based

on a strong positive dichroic band at 248 nm in the cd spectrum, similar to that of raucubaine, raucubaine or (+)-vindoline (**2**), all having the same spatial arrangement at C-7 [erroneously, the configuration of raucubaine and raucubaine in Sierra *et al.* (2) was printed as *7R*]. The configuration at the other carbons of ring C, namely C-2, C-3, C-15, and C-16, and the conformation of this ring were deduced from the nOe experiment. After irradiation of the proton H-2 an enhanced intensity of H-3 (proton at the adjacent carbon), H-14_S, and H-16 (1,3-diaxial arrangement) signals was observed, thus indicating the chair conformation of ring C with absolute configuration *2S*, *3S*, *7S*, *15R*, *16R*. An opposite configuration at C-2 (i.e., *2R*) is excluded, as irradiation of H-2 would bring about an nOe at H-3 and H-5_R. Rings D (N-4, C-3, C-2, C-7, C-6, C-5) and E (N-4, C-3, C-14, C-15, C-20, C-21) in **1** appear





in boat conformation with a joint C-3–N-4 bond. This arrangement is characterized by a four-bond W-connectivity between H-21_S and H-5_R, possibly only providing mutual *cis* arrangement of rings D and E. The last two chiral centers in **1**, at C-19 and C-20, participate in an oxirane ring. After irradiation of C-18 methyl protons, an nOe effect was observed at H-19 and H-15 only; as a consequence, the absolute configuration at C-19 and C-20 has to be 19*S*,20*R*. Any other possible configurations (i.e., 19*R*,20*R*; 19*R*,20*S*; or 19*S*,20*S*) would show after irradiation of H-18 an enhanced intensity at H-21_R and H-6_R or H-5_S, H-6_R, and H-21_S, respectively. It follows that the absolute configuration of 4-methylraucubaininium chloride [**1**] is 2*S*,3*S*,7*S*,15*R*,16*R*,19*S*,20*R*.

The ¹H-nmr spectrum of 4-methylstrictaminium chloride [**2**] (Tables 1,2) differs from that of strictamine by clearly resolved signals, especially of protons bound to carbons adjacent to N-4, which appeared as undistinguishable multiplets in the spectrum of strictamine (3,4). The presence of an sp² carbon (C-2) and replacement of the epoxide grouping by an ethylidene moiety in **2** in comparison with **1** caused differences in chemical shifts of several protons. In addition to the expected changes of proton signals bound to car-

bons in α positions to C-2, C-19, and C-20, two effects having a through-the-space character were observed: shielding of H-5_R (δ 4.43 ppm in **1** vs. 3.07 in **2**) and deshielding of H-6_R (δ 2.98 ppm in **1** vs. 3.86 in **2**). The first is due to a shielding effect of the indolenine N=C bond; the other depends on a shielding effect of the epoxide ring in **1** which is

TABLE 1. ¹H-nmr Chemical Shifts of Quaternary Alkaloids from *Vinca minor*.

Proton	Compound	
	1	2
H-2	3.10 s	—
H-3	4.60 d	5.06 dd
H-5 _R	4.43 dddd	3.07 dddd
H-5 _S	3.41 dd	3.65 dd
H-6 _R	2.98 ddd	3.86 ddd
H-6 _S	2.02 dd	2.16 dd
H-9	7.06 ddd	7.49 d
H-10	6.78 ddd	7.30 dd
H-11	7.17 ddd	7.45 dd
H-12	6.76 d	7.70 d
H-14 _R	2.88 ddd	3.12 ddd
H-14 _S	2.24 d	2.16 dd
H-15	2.85 dd	3.75 dd
H-16	3.30 d	2.38 d
H-18	1.31 d	1.67 dd
H-19	3.34 q	5.92 q
H-21 _R	3.26 d	4.28 d
H-21 _S	3.83 dd	4.51 ddd
N-1--Me	2.79 s	—
N-4--Me	3.35 s	3.40 s
OMe	3.80 s	3.78 s

TABLE 2. ^1H - ^1H Coupling Constants (Hz).

Protons	Compound	
	1	2
H-2,3	^a	—
H-3,14R	5.0	4.9
H-3,14S	^a	1.6
H-5R,5S	12.0	13.2
H-5R,6R	14.6	14.6
H-5R,6S	5.3	5.6
H-5R,21S	2.5	2.5
H-5S,6R	6.1	5.8
H-5S,6S	^a	^a
H-6R,6S	17.1	16.2
H-9,10 ^b	7.7	7.8
H-9,11 ^b	1.5	^a
H-9,12 ^b	0.4	^a
H-10,11 ^b	7.6	7.4
H-10,12 ^b	1.0	1.2
H-11,12 ^b	7.7	7.3
H-14R,14S	15.0	15.1
H-14S,15	^a	2.7
H-14R,15	2.7	2.7
H-15,16	3.5	3.6
H-18,19	5.7	7.2
H-18,21S	—	2.8
H-21R,21S	14.3	15.6

^aSmall, unresolved coupling.^bIn first order approximation.

stronger than the shielding effect of the ethylidene double bond in **2**. A similar strong effect of the epoxide grouping was encountered also in spectra of the 15,16-epoxybeyerols (**5**). A rather high shift value of H-6R in both **1** and **2** is associated with deshielding effect of the C-16 methoxycarbonyl group at an *R* absolute configuration at this atom. In the opposite configuration (i.e., 16S) an additional shift of methoxyl group protons into a higher magnetic field should be observed (**6**) due to a shielding effect of the benzene ring. The difference in chemical shift of H-16 in **1** (3.30 ppm) and **2** (2.38 ppm) can be explained by deformation of ring C in **2** caused by the indolenine double bond. Similar values of particular coupling constants (Table

2) together with the chemical shift analysis discussed above lead to the conclusion that the conformation of **2** is quite similar to that of **1**.

EXPERIMENTAL

^1H - and ^{13}C -nmr spectra were recorded in CD_3OD with TMS as internal standard on a Bruker AM-300 spectrometer at 300 MHz and 75 MHz, respectively. The pulse sequence with proton decoupling in F_1 (7) was used for ^{13}C - ^1H heterocorrelated experiment. The delays within the pulse sequence including BIRD pulse were optimized to $1/J(^{13}\text{C}-^1\text{H})$ of 150 Hz. Other parameters were as follows: spectral width 9750 Hz (^{13}C axis), 750 Hz (^1H axis); number of data points 4K in F_2 , 256 in F_1 ; size of final matrix after zero-filling to 512 in F_1 1M; number of transients 32; relaxation delay 3 sec. The total acquisition time was 8 h for the solution containing 30 mg of **1** or **2** in 2 ml of CD_3OD .

Parameters of the steady-state difference nOe experiment (**8**) were as follows: relaxation, preirradiation, and acquisition times 5 sec; preirradiation frequency changed every one scan; decoupler power 2.5 Hz; frequency between individual transients in doublet of C-18 methyl group in **1** switched in 150 msec intervals; sample concentration 10 mg of **1** or **2** in 0.5 ml of CD_3OD ; temperature 298°.

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