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A Stereostructural Study of 17-Hydroxylupanine and its Perchlorate

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Summary. The bisquinolizidine carbinolamine 17-hydroxylupanine was synthesized *de novo* from lupanine using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; its structure was established by NMR techniques. The equatorial position of the hydroxy group as well as the prevailing boat form of ring C were determined. As expected, the carbinolamine converted into the C17=N16 anhydronium perchlorate upon treatment with $HClO_4$. NMR analysis of the salt revealed a conformational equilibrium within rings A and D, whereas rings B and C remain rigid.

Keywords. Bisquinolizidine alkaloids; Configuration; Conformation; NMR spectroscopy; *DDQ* oxidation.

Introduction

In continuation of our research on the stereochemistry of conformationally labile lupine alkaloids [1, 2] we took interest in the analogous features of their carbinolamine derivatives. To the best of our knowledge, due to their low stability the spatial structures of these compounds have not yet been investigated. In the so far described compounds 17-hydroxysparteine [3], (+)-2-hydroxy-17-oxo-β-isosparteine (lupanoline) [4], and 17-hydroxylupanine [5] only the locations of the OH groups have been determined, whereas their configurations, not to mention their conformational equilibria, remain unknown. 17-Hydroxylupanine is a particular case, since even its isolation have not been reported yet. *Edwards* and coworkers have described the formation of this compound during action of silver oxide on lupanine [5]. Similarly, *Wiewiórowski* and *Legocki* [6] have postulated the generation of 17-hydroxylupanine during oxygenation of the parent alkaloid by means of a mercuric acetate/*EDTA* complex. These authors as well as *Edwards* and his collaborators settled for isolation of 17-hydroxylupanine as its perchlorate, which in fact is the 17-dehydrolupaninium salt [5, 6].

Since isolation of 17-hydroxylupanine was not feasible by the above methods, it was necessary to find another access to this carbinolamine. For this purpose, *DDQ* (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) seemed promising because of its oxygenating properties [7, 8]. According to Refs. [9, 10] it could be expected

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that *DDQ* would dehydrogenate lupanine at carbon atoms C-17 and/or C-11, where then a hydroxyl group might be introduced.

Results and Discussion

Action of *DDQ* on lupanine (in dioxane and under argon) causes precipitation of a crude product which upon treatment by hydrochloric acid, aqueous NaOH, and ethyl ether gave the expected alkaloid as the free base. ^{1}H and ^{13}C NMR as well as IR spectra of the perchlorate of the product were identical with those of 17-dehydrolupaninium perchlorate synthesized according to *Marion* and *Leonard via* oxidation of lupanine by *NBS* [9]. Due to severe signal overlapping, most of the δ_H values had to be taken from DQF-COSY, HMQC, HETCOR and (in the case of the perchlorate) NOESY spectra. The NMR data of compounds **3** and **4** are presented in Tables 1 and 2.

The above-mentioned overlap of the proton signals also obscured the DQF-COSY spectra, making it difficult to detect all linkages between protonated carbon atoms. Carbon-carbon bonds firmly established by 2D NMR spectroscopy are

Table 1. NMR data of 17-hydroxylupanine (**3**); for numbering, see Scheme 1; δ in ppm J in Hz

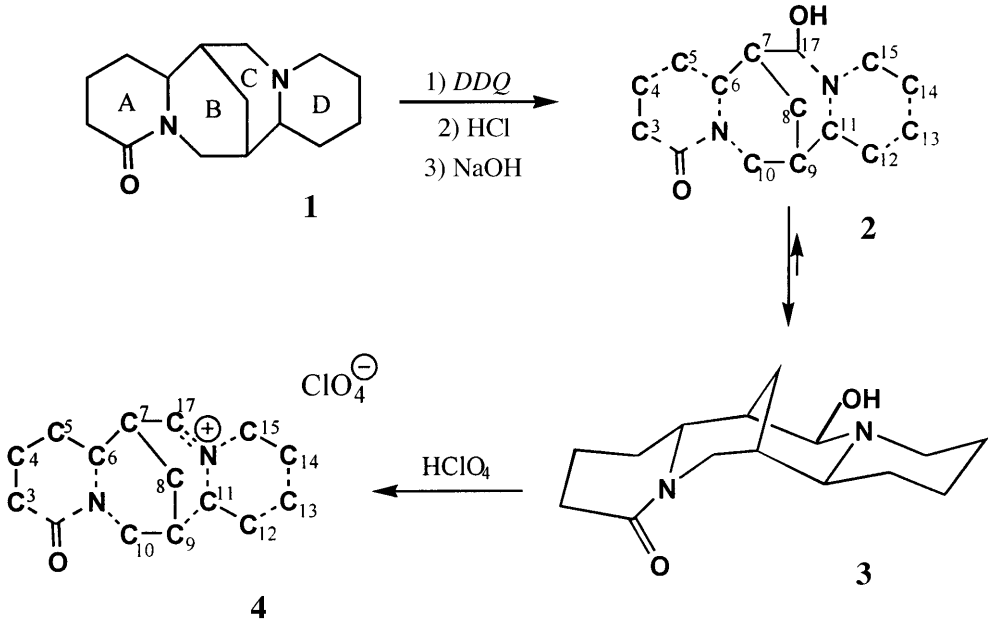
Carbon atom	^{13}C-^{1}H correlations (HMQC, HETCOR)		^{1}H-^{1}H correlations (DQF-COSY)
	δ_C (DEPT)	δ_H, multiplicity, J	
2	170.69		
3	32.98 (CH_2)	2.44, m	1.64, 1.86, 2.28
		2.28, m	1.64, 1.86, 2.44
4	19.86 (CH_2)	1.64, m	2.28, 2.44, 1.86
		1.86, m	2.28, 2.44, 1.88(?), 1.64
5	26.97 (CH_2)	1.88, m	1.86 (?)
		1.88, m	
6	59.52 (CH)	3.34, dd ?	1.84, 1.88
7	43.46 (CH)	1.84, ddddd ?	3.76, 3.34, 2.35, 1.28, 1.65
8	25.02 (CH_2)	2.35, m (*eq*)	1.84, 4.50, 1.28, 1.65
		1.28, dt, 12.3, 2.4, 2.4 (*ax*)	2.35, 1.84, 1.65
9	34.84 (CH)	1.65, m	4.50, 2.51, 2.35, 1.28, 1.84, 1.92
10	47.22 (CH_2)	4.50, dt, 13.1, 2.4, 2.4 (*eq*)	2.51, 1.65, 2.35
		2.51, dd, 13.2, 2.4 (*ax*)	4.50, 1.65
11	60.41 (CH)	1.92, m	1.65, 1.52
12	33.74 (CH_2)	1.52, m	1.92
		1.52, m	
13	25.25 (CH_2)	1.76, dm, ~12.0	1.35
		1.35, dt ?, 12.0, 3.9, 3.9	1.76
14	25.76 (CH_2)	1.57, m	3.35
		1.57, m	
15	51.62 (CH_2)	3.35, m (*eq*)	2.00, 1.57
		2.00, td, 12.0, 12.0, 3.0 (*ax*)	3.35, 1.57
17	85.75 (CH)	3.76, bs	1.84

Table 2. NMR data of 17-dehydrolupaninium perchlorate (**4**); for numbering, see Scheme 1; δ in ppm, J in Hz

Carbon atom	^{13}C-^{1}H correlations		^{1}H-^{1}H correlations	
	δ_C (DEPT)	δ_H, multiplicity, J	DQF-COSY	NOESY
2	169.33			
3	32.30 (CH_2)	~2.16, m	1.55, 1.66	1.63, 1.55
		~2.16, m	1.55, 1.66	1.63
4	19.49 (CH_2)	1.55, m	~2.16, 2.11	2.11, 1.66
		1.66, m	~2.16, 2.11	2.11, 1.55
5	27.13 (CH_2)	2.11, m	1.63, 3.68, 1.55, 1.66	1.55
		1.63, m	2.11, 3.68	8.94, ~2.16
6	59.17 (CH)	3.68, ddd, 10.2, 5.1, 2.4	3.25, 2.11, 1.63	3.25, 2.71, 2.11, 1.77
				1.63
7	37.63 (CH)	3.25, ddddd ?	8.94, 3.68, 2.10	8.94, 3.68, 2.11
		$\Sigma J = 17.1$	1.99, 1.77	1.99, 1.77, 1.63
8	21.58 (CH_2)	1.99, ddt, 13.2, 3.2, 3.2, 2.6	3.25, 2.10, 1.77, 4.62	3.25, 1.77
		1.77, m	3.25, 2.10, 1.99, 8.94	3.68, 3.25, 2.71, 1.99
9	31.97 (CH)	2.10, m	4.62, 2.71, 1.99	4.62, 3.76, 3.25
			1.77, 3.25	2.71, 1.77
10	46.55 (CH_2)	4.62, dt, 13.4, 2.3, 2.3 (*eq*)	2.71, 2.10, 1.99	3.76, 2.71, 2.10
		2.71, dd, 13.5, 2.7 (*ax*)	4.62, 2.10	4.62, 3.68, 2.10, 1.77
11	66.42 (CH)	3.76, Ψ-dd, ~10.6, ~4.9	1.92, 1.73	3.89, 2.10, 1.92
				1.76, 4.62
12	32.50 (CH_2)	1.92, m	3.76	1.76, 1.73, 3.76
		1.73, m	3.76	3.76, 1.92
13	22.21 (CH_2)	1.76		1.92
		1.76		
14	26.04 (CH_2)	1.88, m	4.16, 3.89	4.16, 3.89
		1.75, m	4.16, 3.89	4.16, 3.89
15	60.58 (CH_2)	4.16, Ψ-dd, ~12.4, ~2.8 (*eq*)	3.89, 1.88, 1.75	8.94, 3.89, 1.88, 1.75
		3.89, Ψ-td, ~12.1, ~3.3 (*ax*)	4.16, 1.88, 1.75, 8.94	4.16, 3.76, 1.88, 1.75
17	177.62 (CH)	8.94, dddd ?, 4.7	3.25, 3.76, 3.89, 1.77	4.16, 3.25, 1.63

shown in Scheme 1 as solid lines; completion of the lacking links, marked as dotted lines in Scheme 1, was performed on the basis of the criteria discussed below.

The discussed alkaloids feature ^{13}C NMR signals which are very close to those of C3, C4, C5, and C10 of rings A and B of the starting lupanine **1** ($\delta_C = 33.0$, 19.6, 26.7, and 46.6 ppm, respectively) [11]. In particular, the resonances at 32.98 (Table 1) and 32.30 (Table 2) ppm belong to α carbon atoms relative to carbonyl groups of δ-lactams, those at 47.22 (Table 1) and 46.55 (Table 2) ppm are characteristic of carbons in position α in relation to a δ-lactam nitrogen atom [11].



Scheme 1. Transformation of lupanine (**1**) into its perchlorate (**4**); solid lines in structures **2** and **4** denote C–C bonds established by 2D NMR techniques; dotted lines show C–C and C–N bonds deduced from the data as discussed in the text

The occurrence of a bicyclic δ-lactam is further supported by the $\nu_{C=O}$ bands at 1636 and 1633 cm^{-1} in the IR spectra of the alkaloid and its perchlorate [12, 13]. Consequently, the above results point to the presence of unchanged rings A and B of the parent lupanine.

Apart from the C7 and C9 methine and the C8 methylene groups common with ring B, ring C of the free alkaloid comprises a methine carbon characterized by $\delta_C = 85.75$ ppm. This chemical shift cannot originate from the α-effect of only one electron withdrawing substituent, since methine groups bonded to nitrogen appear within a range of $57 < \delta_C < 68$ ppm, whereas those linked with hydroxylic oxygen resonate between 64 and 70 ppm as observed in model bisquinolizidine alkaloids [11]. Therefore, besides the action of the nitrogen atom, the signal considered is also affected by the influence of the hydroxylic group, whose presence (though attempts towards acetylation failed) is confirmed by the MS data: $m/z = 264$ $M^{+\bullet}$ and 247 (M–OH). The proton from the methine group under consideration is coupled with a proton from a CH group appearing at $\delta_C = 43.46$ ppm. The latter resonance is due to the deshielding effect of the OH group onto the β-carbon atom, *i.e.* on C7 [14] ($\Delta\delta = +11.1$ ppm with respect to unsubstituted lupanine [11, 15]). Such a position of the hydroxyl group simultaneously localizes the second nitrogen atom which links the carbon atoms at 85.75 (C17) and 60.41 ppm (C11), thus closing ring C (see Scheme 1 and Table 1).

Ring D, apart from methylene groups at 33.74 (coupled with C11) and 51.62 (C15); α to N16 and coupled with C14, must contain the CH_2 group at 25.25 ppm, though its connections with the remaining fragments of the molecule remain undetected.

Similarly to other sparteine alkaloids, the δ_C values of C-12 and C-14 in the latter ring depend on the conformational equilibrium between chair and boat form of ring C [16]. In the case of the chair conformer, the above values are shifted upfield due to the γ-*gauche* effect between C8 and C12 and between C17 and C14. Instead, such a shift should not be expected for the boat form for which no *syn*-clinal effect occurs.

The boat form population was estimated using the method of *Eliel* [17] adapted to the case of bisquinolizidine alkaloids by *Wysocka* and *Brukwicki* [16]. Taking into account the chemical shift of C-14 and C-12 (Table 1), the values of 97.2% and 91.7% were found, respectively.

The dominating variety with the boat C ring demands the H-17 hydrogen atom to be situated either *pseudo*-axially or *pseudo*-equatorially. In the latter case, due to an almost zero value (model inspection) of the H-C7-C17-H dihedral angle, one should expect a rather large $^3J_{HH}$ coupling constant. On the other hand, in the case of the *pseudo*-axial orientation, this angle amounts to $\sim -100^\circ$. Hence, small values of the coupling constant can be expected. Based on *Altona*'s dependency [18], $^3J_{HH}$ amounts to 0.88 and 1.06 Hz when the torsinal angle H-C7-C17-H is -90° or -100°, respectively. Therefore, the broadened singlet of H-17 indicates its *pseudo*-axial position (see **3** in Scheme 1).

The conversion of 17-hydroxylupanine into its perchloate (**3** $\rightarrow$ **4**, Scheme 1) not only confirms the location of the OH group at C17 but also offers an opportunity to reinvestigate this salt by means of NMR spectroscopy which, similarly to the parent compound, gives also an insight into subtle structural details which have not been studied so far.

The C7 methine group of ring B (Scheme 1) in the perchlorate is connected to a CH group showing the greatest δ_C value (Table 2). Since the ^{13}C NMR spectrum of the salt does not reveal any other sp^2 methine group, the signal at 177.62 ppm must belong to the HC=N$^+$< moiety which comprises the second (N16) of the two nitrogen atoms. The sp^2 hybridization of N16 increases the ^{13}C chemical shift of its α-carbons. In particular, this concerns C11 and C15; their $\Delta\delta_C$ values relative to the substrate amount to 8.96 and 6.01 ppm. Therefore, the appearance of a methine group at 66.42 ppm as well as an NOE effect between H11 and H9 protons allow a closure of ring C, although the DQF-COSY spectrum exhibits no connection between the corresponding methine groups. It should be added that, in spite of the above, NOEs were found between other vicinal protons which were detected in the DQF-COSY spectrum (Table 2).

Apart from C11 and C15 and the corresponding C12 and C14 methylene groups bound to them, the methylene group resonating at 22.21 ppm should be included into ring D; again, DQF-COSY connectivities with the remaining methylenes in β-position relative to N16 remain obscure (see Scheme 1).

The closure of the bisquinolisidine rings A, B, C, and D of **4** which ensues from the analysis of the data from Table 2 is consistent with X-ray results [19]. Moreover, treatment of **4** with aqueous KOH affords the alkaloid **3**.

The above NMR analysis of **4** should be supplemented with a discussion concerning the steric structure of the salt. Its NOESY spectrum shows 1,3-diaxial interactions between protons at C6, C10, and C8 (see Table 3). This testifies to a chair form of ring B. Instead, an NOE appearing between the axial protons H5 and

H3 is not indicative of a chair form of ring A, the more so that the lactam fragment is a factor flattening this ring. However, taking into account the value of $^3J_{HH}$ for the C6-H (10.2 Hz, denoting 1,2-diaxial interaction with C5-H) and also inspecting the model, one may conclude that the C5, C6, N1, C2, and C3 atoms occupy approximately a planar position, whereas C4 rises above this plane towards the C7-C8-C9 bridge. Such an envelope conformer [20] seems to be the dominant form of ring A similar to the analogous fragment of angustifoline [21] for which the corresponding coupling constant amounts to 10.7 Hz. The latter alkaloid, however, features a small contribution of another conformer in which the C4 methylene group is oriented in the opposite direction to that of the C7-C8-C9 bridge. ^3J for the perchlorate under discussion also deviates from the analogous value for sparteine with a rigid chair ring A featuring $^3J_{HH} = 13.2$ Hz [22]. A contribution from another conformer of ring A, similar to that of angustifoline, seems quite probable.

Formation of the double bond between C17 and N16 also induces flattening into ring C, comprising, in particular, C7, C17, N16, and C11 [19]. C9 may also participate in this flattening, since no vicinal coupling of H9 and H11 is observed, whereas an NOE occurs between them (see Table 2). This coupling disappears when the H-C9-C11-H dihedral angle adopts a value of $\sim 90^\circ$, and this corresponds to the molecular model. Besides the NOE mentioned, H11 shows the usual 1,3-diaxial *Overhauser* enhancement with H15$_{ax}$. Unfortunately, due to severe overlapping of the NOESY signals, it was not possible to locate the 1,3-diaxial interactions of H13 proton with H15$_{ax}$ and H11. In other words, the chair form of ring D could not be confirmed by 1,3-diaxial NOEs.

The existence of a chair fragment would have been indicated by signal of H15$_{ax}$ provided that this resonance had appeared as a dtd in the ^{1}H NMR spectrum. Instead, one observes averaged multiplicities of not only H15$_{ax}$ but also of H15$_{eq}$ and H11. The protons appearing in such a form belong to the planar H-C17=N16 < C15,C11 fragment which also participates in ring C together with the chair ring B (*vide supra*), generating a rather rigid 3,7-diazabicyclo [3.3.1]nonane (bispidine) system within the molecule of **4**. Its rigidity is evidenced by multiplicities of H6, H8$_{eq}$, H10$_{eq}$ and H10$_{ax}$ and, in particular, by *W* couplings between H10$_{eq}$ and H8$_{eq}$ as well as between H7 and H9 (see Table 2).

Geometrical stabilization of rings B and C, as deduced from the above data, is additionally confirmed by NOEs of H17 with H5$_{ax}$ and H15$_{eq}$ as well as by *Overhauser* interactions between the pairs H15$_{ax}$ H11 and H10$_{eq}$ H11 (see Table 2). As a consequence, the sp^2 nitrogen N16 from ring C introduces a strain onto the C11-N16-C15 bond angle which amounts to 113.9° in the solid state [19]. Hence, relative to **3**, the geometry of ring D is destablized in **4**. The protons bound to C11 and C15 appear, as mentioned above, in the ^{1}H NMR spectrum in *pseudo*-dd or *pseudo*-dt forms. Such shapes of the resonances should not result from couplings of the allylic type between the H17 and H11, H15$_{ax}$ as detected by means of the DQF-COSY spectrum, since H15$_{eq}$, which does not show this kind of coupling, also appears in a diffuse form. Moreover, a decoupling experiment (irradiating H17 8.94 ppm with different decoupler powers) did not cause any change in the shapes of the resonances of H11, H15$_{ax}$, and H15$_{eq}$. Therefore, since the geometrical stability of the hydrogens at C17, C11, and C15 cannot be the reason for the signal

deformation discussed, the explanation of this phenomenon should be searched in the interaction with the protons of the methylene chain C12-C13-C14. Hence, the observed spectral picture is due to changes in dihedral angles H-C11-C12-H and H-C15-C14-H which would result from a conformational equilibrium within ring D changing from its chair variety to a twisted chair. To this end it should be mentioned that a conformational disorder of the terminal piperidinium rings is also a feature of the dehydrosparteinium perchlorate crystals [19]. Since their crystal packing forces do not hamper the disorder, then all the more their absence in *DMSO*-d_6 solution should favor the conformational freedom of the piperidinium ring D.

Experimental

The NMR spectra of 17-hydroxylupanine (**3**) and 17-dehydrolupaninium perchlorate (**4**) were obtained on a Varian Unity spectrometer at observation frequencies of 299.949 (^{1}H) and 75.429 (^{13}C) MHz using solutions of ~0.16 *M* **3** in $CDCl_3$ and ~0.2 *M* **4** in *DMSO*-d_6 (internal *TMS*). ^{1}H NMR: spectral width 4000 Hz, acquisition time 3.744 s, 64 transients, 90° pulse widths 20.0 and 21.3 μs for **3** and **4**. ^{13}C NMR: spectral width 16501.7 Hz, acquisition time 1.815 s, 90° pulse width 8.7 μs, 4096 and 1024 transients for **3** and **4**. Phase sensitive DQF-COSY spectra [23]: 1924.5 × 1924.5 and 3146.1 × 3146.1 Hz, acquisition times of 0.532 s and 0.325 μs, 90° pulse widths of 21.4 and 21.3 μs for **3** and **4**, 1.5 s relaxation delay; 2 × 320 FIDs with 32 transients each and 2 × 524 FIDs with 32 transients each were accumulated for **3** and **4** respectively. The NOESY spectrum of **4** was run in the phase-sensitive mode [24] for a spectral width of 3146.1 × 3146.1 Hz, 2 × 262 FIDs with 32 transients each, 90° pulse width 21.3 μs 2.0 s relaxation delay, 0.400 s mixing time, 0.325 s acquisition time. The HMQC spectrum [25] of **3** was acquired with a spectral width of 2706.2 × 8481.8 Hz, 2.0 s relaxation delay, 0.189 s acquisition time, 11 μs 90° pulse width, 128 × 2 FIDs with 128 transients each, optimized for $^1J_{CH} = 132$ Hz. The HETCOR spectrum [26, 27] of **4** was recorded with a spectral width of 16501.7 × 1234.9 Hz collecting 256 FIDs with 128 transients each, 1.5 s relaxation delay, 0.062 s acquisition time, 11.0 μs 90° pulse width, $^1J_{CH} = 135$ Hz. The IR spectra were obtained on a FT-IR Bruker IFS 113v spectrometer using KBr discs. The mass spectra were measured on an AMD 402 instrument (AMD-INTECTRA Germany) using EI ionization with a sample evaporation temperature of 150°C, an ionization potential of 75 eV, and 8 kV accelerating voltage.

17-Hydroxylupanine (**3**; $C_{15}H_{24}N_2O_2$)

A three-necked flask (100 cm^3) equipped with a reflux condenser and magnetic stirrer was flushed for 10 min with Ar passing through a washer with anhydrous benzene as protection against air oxidation prior to addition of 150 mg (0.6 mmol) of lupanine in 12 cm^3 of dioxane freshly distilled from $LiAlH_4$. A slow stream of Ar was passed through the system for 20 min. A solution of 138 mg (0.6 mmol) of *DDQ* in 6 cm^3 of dry dioxane was introduced into the reaction mixture which immediately darkened, soon became opaque, and produced a precipitate. Purging with Ar was continued for 4 h, and the mixture was left stirring over-night. The flow of Ar was then resumed, 139 mg of *DDQ* in 6 cm^3 of dry dioxane were added, and the reaction mixture was refluxed for 4 h. The mixture was allowed to cool and the precipitate was filtered off. The air-dried precipitate was well crushed and treated by 5 cm^3 of ~3 *N* HCl on a sinter funnel. The acidic filtrate was diluted with 5 cm^3 of water and 0.3 cm^3 of 40% aqueous $NaHSO_3$, transferred into a separatory funnel, cooled to ~12°C, and made strongly alkaline by addition of small portions of ~50% aqueous NaOH under cooling. The second ethereal extract showed a negative *Dragendorff* test [28]. The combined ethereal

extracts were dried for 2 h over KOH pellets. Removal of the solvent *in vacuo* gave 89 mg of the alkaloid in a form of a transparent resin. This product was treated with a few droplets of CH_2Cl_2, upon which it crystallized within several minutes. The mother liquor was removed, and the crystals were washed with a small amount of CH_2Cl_2 yielding 70 mg (44%) **3**. The compound can be stored for a week at $-15°C$. The alkaloid dissolved in $CDCl_3$ is stable for ~24 h. After four days, the solution shows considerable changes in its ^1H NMR spectrum.

MS: $m/z = 264$ ($M^{+\bullet}$), 247 (M-OH); IR (KBr): $\nu = 3143$, 2933, 2862, ~2795, ~2765, 1636, 1447, 1422, 1257, 1131, 1091, 1067, 727, 695 cm^{-1}; NMR: see Table 1; the ^{13}C NMR spectrum shows the presence of a small amount of another compound featuring, among others, signals at 91.8 and 15.8 ppm.

The precipitate remaining after the above treatment of the crude product by 3 *N* HCl was again washed with ~1 *N* HCl ($3 \times 5\,cm^3$), 0.3 cm^3 of 40% aqueous $NaHSO_3$, and 15 cm^3 of H_2O. The alkaloids were isolated from the obtained acidic liquid as described above. The yield was 20 mg. TLC (SiO_2; CH_2Cl_2: CH_3OH:CH_3OH saturated with NH_3 =9.5:0.9:0.1 (v/v)) of this product showed, apart from **3** ($R_f \approx 0.11$), some unreacted lupanine ($R_f \approx 0.44$) and a compound of low polarity ($R_f \approx 0.73$).

17-Dehydrolupaninium perchlorate (**4**; $C_{15}H_{23}ClN_2O_5$)

30 mg (0.11 mmol) of **3** were dissolved in several cm^3 of methanol and then treated with a methanolic solution of perchloric acid up to $pH \approx 6$. The solvent was removed *in vacuo*, and the obtained resin treated by a very small amount of methanol gave 19 mg (48%) of crystalline **4**.

IR (KBr): $\nu = 3050$, 3030, 2950, 2876, 1682, 1633, 1457, 1450, 1412, 1370, 1358, 1347, 1332, 1312, 1265, 1173, 919, 623 cm^{-1}; NMR: see Table 2

Hydrolysis of **4**

63 mg (0.17 mmol) **4** were treated with 10 cm^3 of ~20% aqueous KOH and exhaustively extracted with chloroform (*Dragendroff*'s test [28]). Prior to the extraction, the solvent was shaken six times with water to remove the stabilizing ethanol. The combined chloroform extracts (35 cm^3) were filtered through a very small amount of basic alumina (Woelm), and the solvent was removed *in vacuo* to give ~50 mg of slightly contaminated **3**.

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