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The Steric Structure of Multiflorine Methylation Products

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Summary. Multiflorine (**1**) – a minor lupine alkaloid – treated by methyl lithium or methyl magnesium iodide affords 4*S*-4-hydroxy-4-methyl-2,3-didehydrosparteine (**2**) and 2*S*-2-methyl-4-oxosparteine (**3**), respectively, as the dominating products. Their steric structure, determined by ^{1}H and ^{13}C NMR techniques, points to stereospecific preferences of these reactions. The observed nucleophilic 1,2- and 1,4-additions indicate that regiospecificity of the action of MeLi or MeMgI on multiflorine is different from that of the so far known similar alkylation of other enamino ketones.

Keywords. Enaminoketones; Lupin alkaloid; Multiflorine; NMR; Nucleophilic methylation; Stereospecificity.

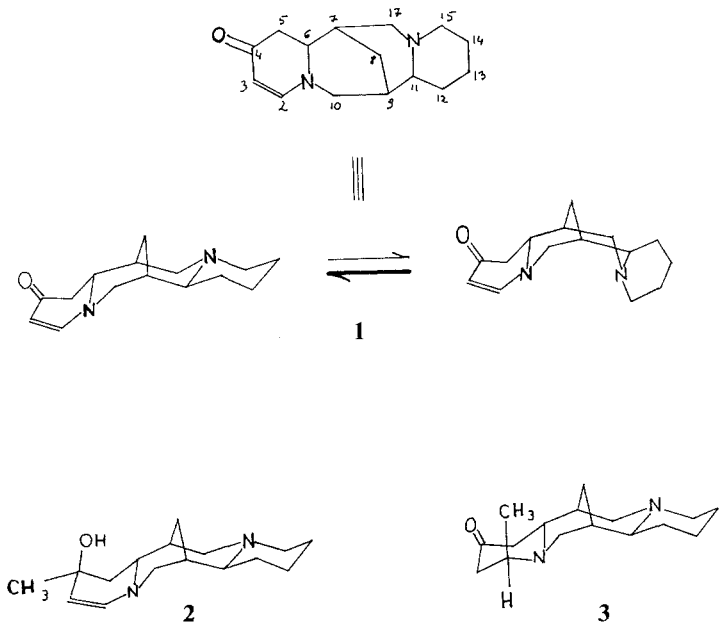
Die räumliche Struktur von Methylierungsprodukten des Multiflorins

Zusammenfassung. Multiflorin (**1**), ein Lupin–Nebenalkaloid, ergibt bei Umsetzung mit Methyllithium oder Methylmagnesiumiodid 4*S*-4-Hydroxy-4-methyl-2,3-didehydrospartein (**2**) und 2*S*-2-Methyl-4-oxospartein (**3**) als Hauptprodukte. Ihre NMR-spektroskopisch (^{1}H und ^{13}C) aufgeklärte räumliche Struktur weist auf eine Stereoselektivität der erwähnten Reaktionen hin. Die beobachteten nucleophilen 1,2- und 1,4-Additionen zeigen, daß sich die Regiospezifität der Einwirkung von MeLi oder MeMgl auf Multiflorin von jener bis jetzt bekannter Alkylierungen von Enaminoketonen unterscheidet.

Introduction

Multiflorine (**1**) comprises a γ-keto-α,β-enamine fragment in ring A of its molecule. This moiety contains three nucleophilic and two electrophilic reaction centers. Thus, one could expect electrophilic alkylating agents causing C-[1], O-[1,2], and N-alkylation [2,3], while alkylating nucleophiles would undergo 1,2- and/or 1,4-addition [4].

In the case of **1**, such an addition would introduce an axial or equatorial alkyl substituent at the newly formed chiral carbon atom. This provides an alternative alkylation procedure since it avoids the generation of an asymmetric carbon atom during the subsequent hydrogenation of the products (*e.g.* 2-methyl-2-dehydrosparteine) obtained from the reaction of the sparteine lactams and methyl lithium [5].



Scheme

In order to obtain information about the steric course of the reaction, it is necessary to know the steric structure of the products of the above addition. This is also important for an estimation of the influence of alkyl substituents on the conformational equilibrium between *boat* and the *chair* forms of ring C in sparteine type alkaloids.

The presented results enable the determination of the steric structure of products resulting from action of methyl lithium or the corresponding *Grignard* reagent on multiflorine.

Results and Discussion

The action of methyl lithium on multiflorine of temperatures above 0°–5 °C resulted in the formation of product mixtures which were hard to separate. Reducing the temperature of the reaction mixture to −60 °C resulted in the formation of only two compounds. Attempts of separation by chromatographic methods as well as by crystallization of their perchlorates also failed. This salt, as indicated by its ^{13}C NMR spectrum, underwent a undetermined transformation. Elemental analyses of the above substances indicated that they were products of 1,2- or 1,4-addition, while the mass spectrum suggested 1,2-addition.

The ^{13}C NMR spectrum in $CDCl_3$ showed that one of the obtained alkaloids predominates (80–85%). The resonances of the dominating alkaloid establish the presence of an enamine fragment [6] formed at carbon atoms C(2) and C(3) (see Table 1).

At the same time, the spectrum reveals the resonances of a quaternary carbon atom and of the introduced methyl group, while no carbonyl signal can be observed. The presence of the methyl substituent causes the expected downfield shift of the C(5) signal (see Table 1) [7].

Table 1. ^{13}C chemical shifts (relative to intend *TMS*) of multiflorine and the methyl lithium addition product

Carbon atom	δ (ppm, C_6D_6)			δ (ppm, $CDCl_3$)		
	1	**2**	"epimer"	**1**	**2**	"epimer"
2	154.68	137.74		154.44	137.61	139.67
3	100.77	107.57		98.77	105.68	103.73
4	191.20	68.82		192.34	68.53	~70.3
5	40.85	43.83	44.64	39.39	42.66	43.96
6	61.16	60.62		60.30	59.67	57.10
7	32.05	32.93[a]	33.34	31.09	31.72[d]	32.20
8	26.54	28.02[b]	27.19[c]	25.84	27.06	26.16
9	35.78	36.93	37.10	34.57	35.48	35.63
10	57.61	58.10	57.74	57.49	57.35	
11	64.12	64.82		63.55	64.28	64.38
12	32.97	35.44		31.48	34.35	34.56
13	25.25	26.02[b]	26.16[c]	23.79	24.80	
14	26.02	26.92[b]	26.86[c]	24.92	25.69	25.83
15	55.81	56.30	56.42	55.16	55.52	55.63
17	52.05	53.63	53.91	51.09	52.73	49.10
CH_3	–	32.93[a]	–	–	31.72[d]	–

[a,d] assigned on the basis of a DEPT experiment;
[b,c] interchangeable

The assignment of the remaining ^{13}C resonances could be only partially supported by H,H-COSY and H,C-COSY techniques because of severe overlapping of the ^1H NMR signals. Hence, resonances for carbon atoms in rings B, C, and D were compared with those of multiflorine [8]. The ^{13}C NMR spectrum of the discussed alkaloid was also recorded in benzene-d_6 giving results similar to those obtained from the measurements in $CDCl_3$ (see Table 1).

The data of Table 1 clearly show that methyl lithium and multiflorine reacted according to the 1,2-addition scheme, leading to the formation of a tertiary enamino alcohol. The known instability of this class of compounds [4] explains why the above mentioned separation of the predominant alkaloid *via* chromatography or crystallization of its salt was unsuccesful.

The spectrum of the discussed alkaloid shows a considerable ^{13}C chemical shift of its methyl group. Two β substituents (the hydroxyl group and the olefinic fragment of the restored enamine) contribute to the magnitude of this effect. The deshielding influence of a β-hydroxyl group amounts to +10 ppm [7], while the double bond in the model 2,3-didehydrosparteine [9] shields a β-carbon atom by −2.9 ppm. Substraction of these increments from the chemical shift of the methyl group gives $\delta = 25.3$ ppm.

The latter value is closer to the ^{13}C chemical shifts of the equatorial methyl groups in the models 2-methylquinolizidine (22.17 ppm, [10]), 2-, 3-, and 6-methyldecahydroquinoline (22.95, 19.61 and 22.43 ppm, respectively, [11]), and 2-methyl-

sparteine (21.3 ppm, [12]) than to their axial counterparts appearing within the range of 12.62–18.62 ppm [10, 11]. The above result (given the fact that the ring A cannot adopt the *chair* conformation but rather approximates to the "half-*chair*" form of the similar fragment in multiflorine [13]) allows us to ascribe an equatorial position to the discussed methyl group.

As a consequence, the distance of the methyl group from the hydrogen atom at C(6) is larger than in the case of the axial arrangement. This agrees with the absence of an *Overhauser* enhancement of the methyl proton signal upon ppm irradiation of H-C(6) at $\delta = 2.71$. Thus, the *S*-configuration can be attributed to the newly formed asymmetric carbon atom and, consequently, structure **2** (see Scheme) can be ascribed to the dominating product of the 1,2-addition. The minor component accompanying compound **2** is probably its C(4)-epimer (see Table 1).

The reaction of methyl magnesium iodide with **1** is another example of the nucleophilic alkylation under investigation. Two alkaloids resulted from this process. One of them, making up to *ca.* 20% proved to be identical with by its

Table 2. ^{1}H and ^{13}C NMR chemical shifts (relative to internal *TMS*) of 2*S*-2-methyl-4-oxosparteine (**3**)

Carbon atom	δ_C (ppm)	δ_H (ppm)	mode of splitting	J_{HH} (Hz)	
2	56.70	2.83	m	2.3, 5.7, 6.6	
3	49.02	2.48	d d q	12.9, 5.8, ~0.5	ax
		2.03	d d d(?)	12.9, 2.4, 2.5	eq
4	207.34	–	–	–	
5	44.00	1.83	d d d	2.5, 4.4, 14.4	eq_a
		2.06	m	11.0, 14.4	ax
6	57.10	2.31	d d d	11.0, 4.3, 2.1	
7	32.65	1.53	m		
8	26.34	0.72	d d d	11.8, 2.6, 2.6	ax
		2.15	m		eq
9	36.43	1.32	m		
10	56.70	2.17	m		
		2.12	m		
11	64.22	1.94	m		
12	35.05	1.41	m		
		1.34	m		
13	26.45	1.50	m		
		1.65	m		
14	25.42	1.23	m		
		1.67			
15	55.80	2.74	d m	11.2,	
		1.94	d d	11.4, 11.4	
17	53.29	2.46	d d	10.8, 10.8	eq
		2.21	d d	10.8, 3.4	ax
CH_3	10.39	0.67	d d	6.7; ~0.5	

[a] assigned on the basis of a H,H-COSY experiment

^{13}C NMR spectrum. The chromatographic separation of that mixture on alumina allowed us to isolate only the more abundant (*ca.* 80%) of the two components. Its ^{1}H and ^{13}C NMR spectral data are presented in Table 2. The assignment of the chemical shifts was performed with the aid of DEPT and H,H- and H,C-COSY (HMQC) experiments.

The data of Table 2 show the absence of the enamine fragment and the presence of a methyl group. The signal of the carbonyl carbon atom is shifted downfield in comparison with its analogue in the parent compound **1** (see Table 1). This shift confirms the disappearance of conjugation between the carbonyl group and the olefinic double bond. At the same time, the carbonyl group at C(4) exerts a deshielding influence to its α carbon atoms, *i.e.* C(3) and C(5). The resonance of C(3) is additionally shifted downfield by the β-effect of the methyl group situated at C(2).

The above results prove that the compound under consideration is a product of an 1,4-addition. Comparison of the chemical shifts of C(6) and C(10) with their analogues in sparteine and 2-methylsparteine (66.3/61.8 ppm and 66.2/57.3 ppm, respectively [12]) shows the shielding effect caused by the *γ-gauche* influence of the methyl group. Such an influence is possible only when the alkyl group is oriented axially at C(2).

The NMR signal of H-C(2) has the form of a complex multiplet resulting from coupling with the adjacent methyl and methylene groups. Homonuclear decoupling of the methyl group by irradiation at 0.67 ppm reveals the interaction between H-C(2) and the two remaining protons at C(3), manifested as coupling constants of 2.3 and 5.7 Hz. These values cannot result from any axial-axial coupling with the protons on carbon atom C(3). Therefore, H-C(2) must occupy the equatorial position. The axial orientation of the methyl group at C(2) is further confirmed by its W-coupling with the axial proton at C(3) (see Table 2).

The above results and considerations allow to ascribe the *S*-configuration to the new chiral atom and structure **3** to the dominating product of the action of the *Grignard* reagent on multiflorine (see Scheme).

The alkaloids **2** and **3** show ^{13}C chemical shifts close to 28.09 ppm for C(8) [9], characteristic of the analogous atom in sparteine with a *boat* conformation of ring C [14]. In turn, chemical shift values of C(12) and C(14) of these alkaloids do not indicate any *γ-gauche* interaction with C(8) and C(17), as well as C(17), respectively. Such an interaction could be expected if ring C in **2** and **3** had to *chair* conformation [15]. Consequently similarly as in the case of **1** [15], the conformer with ring C in the *boat* conformation predominates in alkaloids 2 and 3.

The formation of these compound also points to stereospecific preferences of the investigated nucleophilic additions. Similar reactions carried out an other enamino ketones [4] resulted mostly in 1,2-addition along with some 1,4-addition products. The regiospecificity of the described reactions is manifested in the exclusive 1,2-addition for the action of methyl lithium, whereas the *Grignard* reagent cause predominantly 1,4-addition.

Experimental

Elemental analyses were carried out with a Perkin-Elmer 240 CHN analyzer. The NMR spectra were recorded on Varian Gemini 300 VT and Varian Unity 300 spectrometers using solutions in $CDCl_3$

and benzene-d_6 with *TMS* as an internal standard. TLC was performed on silicagel Merck 60 F_{254} (25–100 mm) using a freshly prepared mixture of acetone: methanol: 25% aq. NH_3 = 40:1:1 (v/v) as mobile phase.

Multiflorine (**1**) was extracted from the seeds of *Lupinus albus cul. BAC* according to the method described by *Wysocka et al.* [16].

4S-4-hydroxy-4-methyl-2,3-didehydrosparteine (**2**)

120 mg of **1** dissolved in 6 ml of dry diethyl ether were added dropwise during 25 min to 40 ml of dry Et_2O and 3.5 ml of an 1.6 *M* solution of methyl lithium in Et_2O. The reaction mixutre was kept under passing argon, cooled to −60 °C stirred magnetically and monitored by TLC. Two hours after addition of the aklaloid solution, 20 ml of ice water were added and the mixture stirred for 45 min. The product was exhaustively extracted with Et_2O (*Dragendorff*'s test [17]). The combined extracts were dried over solid KOH and evaporated *in vacuo* to yield 98 mg of a solidifying oil which can be stored below −15 °C for several weeks.

Elemental analysis for $C_{16}H_{26}N_2O$: calc.: 73.28% C, 9.92% H, 10.68% N; found: 72.5% C, 10.11% H, 10.23% N.

^1H NMR (C_6D_6, δ in ppm): 5.49 (d, 8.0 Hz, H–C(2)), 4.56 (dd, 8.0 and 2.1 Hz, H–C(3)), 1.43 (s, CH_3), 1.88 (dd, 11.4 and 2.9 Hz, H_{eq}–C(5)), 0.84 (ddd, 11.8, 2.4, and 2.4 Hz, H_{ax}–C(8)), 1.62 (m, H–C(7)), 1.22 (m, H–C(9)), 2.58 (dd, 11.0 and 11.0 Hz, H_{eq}–C(17)), 2.20 (dd, 11.1 and 3.4 Hz, H_{ax}–C(17)), 2.71 (dm, 11.4 Hz, H–C(6), 2.31 (dd, 11.3 and 2.5 Hz, H_{ax}–C(10)), 2.44 (m, 11.9 and 2.3 Hz, H_{eq}–C(10)); and ^{13}C NMR: see Table 1; MS (*m/e*): 262 (10%, M^+), 244 (8%, M^+-H_2O), 219 (2%), 205 (2%), 191 (3%), 187 (7%), 164 (10%), 150 (18%), 134 (67%), 122 (22%), 110 (28%), 96 (32%), 94 (40%), 80 (35%).

2S-2-methyl-4-oxosparteine (**3**)

50 mg of **1** on 4 ml of Et_2O were added dropwise during 10 min to the *Grignard* reagent which had been prepared by refluxing 100 mg of magnesium, 0.26 ml of methyl iodide and 4 ml of dry Et_2O for 1 h. The reaction mixture was refluxed for 2 h, then cooled and treated by *ca.* 10 g ice water, followed by an excess of 35% aq. NaOH. The product was extracted with Et_2O and dried over KOH pellets for 45 min. 33 mg of the mixture of **2** and **3** (^{13}C NMR) were obtained after removal of the solvent *in vacuo*.

Separation on 4 g of neutral alumina (Woelm, activity grade 2; 25 ml of benzene: ethanol = 75:0.75 and 25:2.5 (ml/ml) and 25 ml of methanol) yielded 25 mg of the oily alkaloid **3**.

^1H and ^{13}C NMR: see Table 2; MS (*m/e*): 262 (14%, M^+), 247 (2.5%, M^+-CH_3), 219 (3%), 205 (2%), 191 (4.5%), 178 (8%), 164 (13%), 150 (23%), 136 (29%), 122 (19%), 110 (20.5%), 98 (34%), 84 (25%).

The second product (6 mg) corresponded to alkaloid **2** (TLC); however, its ^1H NMR spectrum was unreadable, probably due to decomposition caused by the alumina.

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