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The Stereochemistry of the Reduction of Cyclic Enaminones

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Summary. The stereo- and regiochemistry of di-, tri-, and tetracyclic enaminones upon catalytic hydrogenation on Pd and Pt catalysts seems to be mainly a function of the catalyst and the medium. The highest stereoselectivity was observed for multiflorine on Pd/C in which 99% of equatorial alcohol were formed in this case, the formation of alcohols proceeds *via* a ketonic intermediate. On platinum, irrespective of the solvent used (EtOH, H_2O, AcOH, HCl), the hydrogenation reaction proceeds through ketonic (piperidone system) and dehydro (pyridone system) intermediates. In EtOH or H_2O solution, the dehydro product remains unchanged, whereas the ketonic intermediate is reduced to a mixture of epimeric alcohols. In HCl and acetic acid, both intermediates are hydrogenolyzed to a product with a methylene group, but the ketonic one is additionally reduced to a mixture of epimeric alcohols. Reductions with complex metal hydrides provide mixtures of epimeric alcohols with a predominance of equatorial orientation. The structures of products were determined by NMR spectroscopy and/or by GC-MS analysis.

Keywords. Multiflorine; *Seco*-(11,12)-12,13-didehydromultiflorine; 3,4-Didehydro-2-quinolizidone; NMR; GC-MS.

Introduction

Recently, the enaminoketone moiety has received great attention because of its usefulness in pharmacology [1, 2]. In continuation of our studies of the physical, chemical, and biological properties of enaminoketones [3–7] we have studied the stereochemistry of the reduction of some selected enaminones. Little is known on the stereo- and regiochemistry of the reduction of the β-amino-vinyl ketone system, and literature information, limited mostly to multiflorine, is not well resolved [8–11].

This paper reports new observations on the catalytic hydrogenation and complex hydride reduction of multiflorine (**1**) along with some preliminary results of reduction of *seco*-(11,12)-12,13-didehydromultiflorine (**2**) and 3,4-didehydro-2-qinolizidone (**3**).

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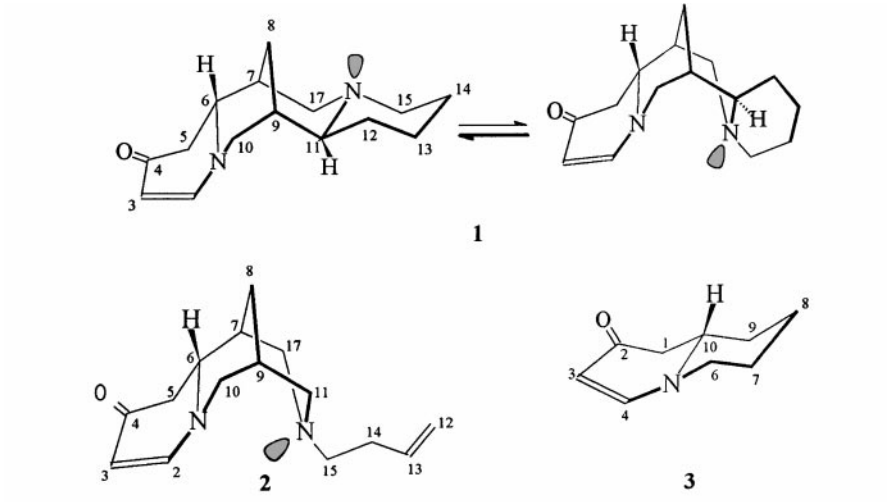
Results and Discussion

Multiflorine (**1**) and *seco*-(11,12)-12,13-didehydromultiflorine (**2**) were isolated from *L. albus* [12, 13]. 3,4-Didehydro-2-quinolizidone (**3**) was obtained according to the method described in literature [14–16]. Catalytic hydrogenation was carried out in the presence of various catalysts (*Adam*'s Pt, $Pd/CaCO_3$, $Pd/BaSO_4$, Pd/C) and in different solvents (water (Pt), hydrochloric acid (Pt), glacial acetic acid (Pt), ethanol (Pt, $Pd/CaCO_3$, $Pd/BaSO_4$, Pd/C)).



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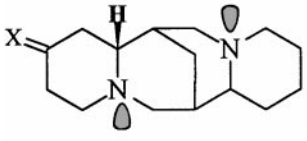
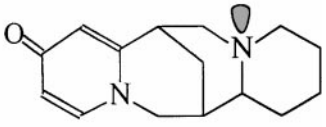


4: X = OH, H
5: X = H, H
6: X = O



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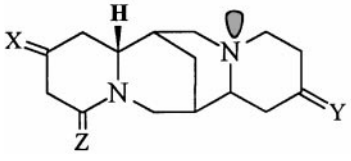


8: X = $OCOCH_3$, Z = H_2, Y = H_2
9: X = H_2, Z = H_2, Y = OH, H
10: X = H_2, Z = O, Y =OH, H
11: X = H_2, Z = H_2, Y = O

Reactions and Products

Reaction conditions and product distribution established for **1** are listed in Table 1. In all experiments, the hydroxy derivative **4** was formed as the main product. In the resulting post-hydrogenation mixture of **1** in aqueous solution and in absolute ethanol (entries 1, 2), the didehydro product **7** was additionally formed (78 and 27%). Hydrogenation of **1** in HCl or glacial acetic acid resulted in the formation of **4** and sparteine (**5**), a product of hydrogenolysis, in ratios 1:1 (HCl) and 1:4 (CH_3COOH).

Table 1. Catalytic hydrogenation and reduction with complex hydrides of multiflorine (**1**) (yield in % by GC-MS)

Entry	Catalyst	Medium	t/h	**7**	**5**	**6**	**4b**	**4a**
1	PtO_2	H_2O	23	78	–	–	11	11
2	PtO_2	EtOH (anhydrous)	20	27	–	–	40	33
3	PtO_2	1 *M* HCl	23	–	52	–	45	3
4	PtO_2	CH_3COOH (glacial)	24	–	21	–	62	17
5	$Pd/BaSO_4$	EtOH (anhydrous)	22 days	–	–	–	93	7
6	$Pd/CaCO_3$	EtOH (anhydrous)	48	–	–	70	29	1
7	$Pd/CaCO_3$	EtOH (anhydrous)	7 days	–	–	–	97	3
8	Pd/C	EtOH (anhydrous)	24	–	–	85	15	–
9	Pd/C	EtOH (anhydrous)	27 days	–	–	–	99	1
10	$NaBH_4$	MeOH	0.5	–	–	–	90	10
11	$NaBH_4$	CH_2Cl_2	1	–	–	–	88	12
12	$LiALH_4$	Diethyl ether (anhydrous)	19	–	–	30	57	13
13	$LiALH_4$	Diethyl ether (anhydrous)	43	–	–	–	81	19
14	$LiAlH_4$	*THF*	24	–	–	–	77	23

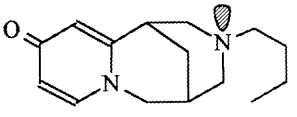
In the presence of $Pd/CaCO_3$, $Pd/BaSO_4$, and Pd/C, the hydrogenation rate of **1** was very low, and it was possible to separate 4-oxosparteine (**6**) along with the alcohols **4** after 48 h ($Pd/CaCO_3$) and 24 h (Pd/C), whereas after 7 or 27 days only the alcohols **4** were found (Table 1, entries 5–9). After separation from 5,6-didehydromultiflorine and/or sparteine, the TLC of the hydroxylic product **4** revealed only one spot. However, the ^{13}C NMR spectrum of **4** proved the existence of a mixture of two epimers. Two signals assigned to carbon C-4 bearing the hydroxy group were observed (64.65 and 69.33 ppm). Separation of the epimers by GC-MS was possible after conversion into the O-acetyl derivatives **8a** and **8b** under mild acetylation conditions ($[M^{+\cdot}]$: $m/z = 292$; R_t: 19 min 55 s (**8a**), 20 min 10 s (**8b**)).

Preparative separation of the 4-O-acetyl derivatives of hydroxysparteine was achieved by short column chromatography [17] on Al_2O_3 with ethyl acetate/methanol. Alkaline hydrolysis of **8a** and **8b** afforded two alcohols characterized by a molecular mass of 250; they were assigned to the epimeric alcohols **4a**, **b**.

The stereochemistry of **4a**, **b** was established by analysis of their ^{13}C and ^{1}H NMR spectra (Tables 2 and 3) using two-dimensional techniques (HMQC, DQF-COSY, NOESY, *J*-resolved spectroscopy) as well as by comparison of the spectra with those of model compounds (13α-hydroxysparteine (*ax*) (**9**), 13α-

hydroxylupanine (*ax*) (**10a**), 13β-hydroxylupanine (*eq*) (**10b**) (Table 2)). The structures of 4-oxosparteine (**6**) and 5,6-didehydromultiflorine (**7**) were also determined on the basis of their spectroscopic data (^{13}C NMR, DEPT, ^{1}H NMR, HMQC, DQF-COSY; Tables 4 and 5).

The preliminary chromatographic investigation (TLC, GC-MS) of the products resulting from catalytic hydrogenation of **2** and **3** (Tables 6 and 7) pointed to the dominance of the equatorial alcohols. The hydrogenation of **2** and **3** on Pt in aqueous solution resulted in the formation of alcoholic and dehydro products (48% yield of dehydro moiety in the case of **2** (Table 6) and 58% for **3** (Table 7). In ethanolic solution, the hydrogenation of **2** and **3** led to the dehydro products in 44 and 5% yield (Tables 6 and 7). In 1 *M* HCl solution, the hydrogenation of **6** and **7** gave *seco*-(11,12)-sparteine (**15**) and quinolizidine (**17**) along with the alcoholic products **14** and **20a**,**b**. Though TLC and GC-MS of **2** revealed only one product with a hydroxy group, the ^{13}C and ^{1}H NMR spectra of 4-hydroxy-*seco*-(11,12)-sparteine (**14**) proved it to be a mixture. However, attempts to separate it by conversion into 4-acetyl- or 4-*tert*-butyl-dimethyl-silyl derivatives failed.



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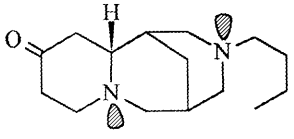

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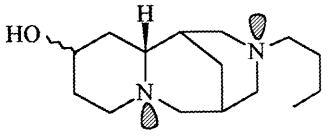

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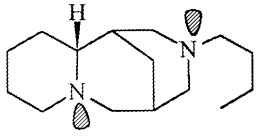

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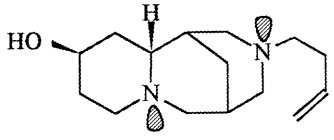

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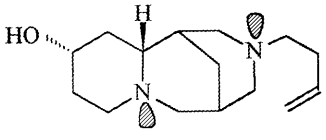

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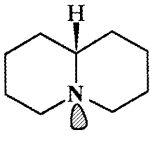

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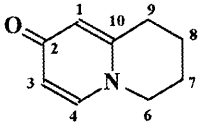

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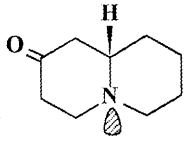

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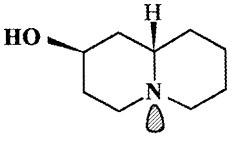
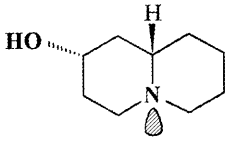


20a



20b

Table 2. ^{13}C NMR chemical shifts of 13α-hydroxysparteine (*ax*) (**9**), 13α-hydroxylupanine (*ax*) (**10a**), 13β-hydroxylupanine (*eq*) (**10b**), 4β-hydroxysparteine (*ax*) (**4a**), and 4α-hydroxysparteine (*eq*) (**4b**) in $CDCl_3$ (ppm from *TMS*)

Carbon	**9**[a]	**10a**[a]	**10b**[a]	**4a**	**4b**
2	56.2	171.0	171.8	*52.58*[b]	*53.81*[b]
3	25.7	32.9	33.0	32.26	34.43
4	24.7	19.6	19.6	*64.65*[b]	*69.33*[b]
5	29.3	26.6	26.7	35.85	38.71
6	66.5	60.8	58.7	*59.17*[b]	*63.78*[b]
7	33.1	31.6	32.6	32.23	32.74
8	27.4	27.3	27.4	27.37	27.14
9	35.6	34.2	34.5	35.55	35.89
10	61.7	46.8	46.9	61.37	60.94
11	*57.2*[b]	*57.0*[b]	*61.3*[b]	64.09	64.30
12	41.7	39.9	41.5	33.37	35.02
13	*64.6*[b]	*64.0*[b]	*69.6*[b]	24.51	24.78
14	32.8	32.4	33.8	24.51	25.71
15	49.2	49.2	51.5	55.19	55.38
17	43.2	52.4	53.0	49.17	53.25

[a] Ref. [18]; [b] numbers in italics indicate the carbon atoms subject to the γ-*gauche* effect

The reduction of **1** with $NaBH_4$ (Table 1) was carried out both in methanol and dichloromethane. It proceeded very smoothyl in 0.5 and 1 h, respectively, whereas the reduction of **1** with $LiAlH_4$ in diethyl ether or *THF* proceeded at a relatively slower rate (43 and 24 h). Both the reactions with $NaBH_4$ and $LiAlH_4$ involved the formation of 4-oxosparteine (**6**, Table 1, entries 12 and 14). The slow conversion of **1** to **4** proceeded *via* an intermediate metal enolate [10].

The chromatographic investigation (TLC, GC-MS) of the products of the reduction of **2** and **3** with complex hydrides (Tables 6 and 7) proved that a mixture of epimeric alcohols was formed in all cases. Thus, the reduction of **2** and **3** with $LiAlH_4$ and $NaBH_4$ resulted in the formation of a mixture of 4β-hydroxy-*seco*-(11,12)-12,13-didehydro-sparteine (**16a**) and 4α-hydroxy-*seco*-(11,12)-12,13-didehydro-sparteine (**16b**) or 4β-hydroxy-quinolizidine (**20a**) and 4α-hydroxy-quinolizidine (**20b**), respectively. They were separated as O-acetyl derivatives, giving two peaks in the GC-MS (**16a**, **b**: $m/z = 292$ [$M^{+\cdot}$], 10%), 191 (89%), 112 (10%), 96 (100%), 58 (19%); **20a**, **b**: $m/z = 197$ ([$M^{+\cdot}$], 22%), 138 (100%), 136 (40%), 108 (12%), 97 (9%), 55 (15%)).

Catalytic hydrogenation

As follows from the study of catalytic hydrogenation of di-, tri-, and tetracyclic enaminoketones, regio- and stereoselectivity of these reactions depends mainly on the kind of catalyst and the reaction medium used. The highest stereoselectivity of catalytic hydrogenation was observed on palladium for **1** in which 99% (Pd/C), 97% ($Pd/CaCO_3$), and 93% ($Pd/BaSO_4$) of the equatorial alcohol was formed. This reaction proceeded at a relatively slow rate *via* the intermediate **6** (Table 1, entries 6

Table 3. ^{1}H NMR chemical shifts and coupling constants of 4β-hydroxysparteine (**4a**) and 4α-hydroxysparteine (**4b**) in $CDCl_3$ (ppm from *TMS*)

Proton	**4a**		**4b**	
	δ_H/ppm	*J*/Hz	δ_H/ppm	*J*/Hz
2β/*ax*	2.78 (dd?)	11.3, 10.9	2.00 (dd?)	11.6, 11.0
2α/*eq*	2.39 (ddd?)	11.3, 5.7, 3.5	2.72 (dd?)	11.6, 3.0
3α/*ax*	1.87 (ddd?)	13.7, 10.9, 2.9	1.85 (m)	
3β/*eq*	1.76 (ddd?)	13.7, 3.7, 2.9	1.51 (m)	11.0
4	4.13 (dddd)	2.9, 2.9, 2.9, 2.9 ($\Sigma J = 11.6$)	3.57 (dddd)	11.0, 11.0, 4.6, 4.6 ($\Sigma J = 31.2$)
5α/*eq*	1.37 (ddd)	13.8, 2.9, 2.9	1.59 (m)	
5β/*ax*	1.64 (ddd)	13.8, 11.8, 2.9	1.47 (ddd)	11.1, 11.6, 11.0
6	2.26 (d??)	11.8	1.82 (ddd)	11.6, 2.3, 2.2
7	1.84 (dd)	9.8, 2.8	1.87 (m)	4.6, 2.5
8α/*eq*[a]	2.09 (m)	12.1	2.05 (dddd)	12.1, 4.0, 4.0, 1.95
8β/*ax*[b]	1.14 (ddd)	12.1, 2.8, 2.8	1.03 (dt)	12.1, 2.5, 2.5
9	1.52 (m)		1.49 (m)	
10α/*eq*	2.59 (d?)	10.8	2.59 (dd?)	10.9, 4.9
10β/*ax*	2.13 (dd?)	10.8, 2.6	1.99 (dd)	10.9, 2.6
11	2.14 (m)		1.96 (m)	10.1
12β/*ax*	1.52 (m)		1.36 (m)	11.1
12α/*eq*	1.39 (m)		1.50 (m)	11.1
13α/*ax*	1.29 (m)		1.31 (m)	
13β/*eq*	1.66 (m)		1.70 (m)	10.3, 2.2
14β/*ax*	1.58 (m)		1.56 (m)	
14α/*eq*	1.58 (m)		1.58 (m)	
15α/*ax*	2.14 (m)	12.4	2.01 (m)	11.0
15β/*eq*	2.819 (ddd?)	12.1, 4.1, 3.8	2.79 (ddd?)	11.0, 4.6, 1.34
17α	2.50 (dd?)	11.5, 5.2, 2.2	2.27 (dd)	11.3, 3.5
17β	2.41 (dd)	11.5, 9.8	2.78 (d?)	10.8

[a] Equatorial in ring B; [b] axial in ring B

and 8). The results indicate that the β-amino-vinyl-ketone is first reduced at the carbon-carbon double bond on palladium, desorbed from the catalyst (it was possible to separate 4-oxo-sparteine on a preparative scale), reabsorbed, and then reduced at the carbonyl group. Analysis of molecular models of **6** showed that the A/B fragment of the molecule should be able to be adsorbed on the surface of the catalyst on the β-side of the carbonyl group because of the diaxial interactions of the hydrogen atoms on C-3 and C-5. Therefore, attachment of a hydrogen atom on C-4 is favoured on the axial side, and the alcohol with the hydroxyl group in the equatorial position is formed predominantly.

The catalytic hydrogenation of **1**, **2**, and **3** on platinum in ethanolic and aqueous solutions drastically differs from that described in literature for **1** [8–11] and 1,10-didehydro-2-quinolizidone [19, 20]. *Rader et al.* [20] have reported that the catalytic hydrogenation of 1,10-didehydro-2-quinolizidone in ethanol gave a mixture of epimeric alcohols (29% *ax*, 67% *eq*) as well as a hydrogenolysis product (4%), but

Table 4. a) ^{13}C NMR chemical shifts of 4-oxosparteine (**6**) and sparteine (**5**) in $CDCl_3$ and C_6D_6; b) ^1H NMR chemical shifts and coupling constants of 4-oxosparteine (**6**) in C_6D_6 and $CDCl_3$ (ppm from *TMS*)

a)

Carbon	**5** ($CDCl_3$)	**6** ($CDCl_3$)	**6** (C_6D_6)
2	56.2	54.95	55.04
3	25.9	41.59	41.62
4	24.9	209.58	206.74
5	29.4	44.7	44.63
6	66.5	65.13	65.06
7	33.0[a]	32.49	32.84
8	27.6	26.35	26.51
9	36.2[a]	35.65	36.39
10	62.0	60.52	60.59
11	64.4	64.27	64.13
12	34.7	34.37	34.96
13	24.7	24.81	25.4
14	25.9	25.66	26.38
15	55.4	55.49	55.69
17	53.6	52.74	53.04

[a] Interchangeable

b)

	6 ($CDCl_3$)		**6** (C_6D_6)	
Proton	δ_H/ppm	*J*/Hz	δ_H/ppm	*J*/Hz
$2\beta/ax$	2.31	14.0	1.88	11.1
$2\alpha/eq$	3.01	14.0, 4.7	2.49	6.6, 2.2
$3\alpha/ax$	2.64	17.0	2.08	13.8, 2.2
$3\beta/eq$	2.29	17.0, 4.7	2.25	13.8, 6.6; 1.0
$5\beta/ax$	2.45	13.4	1.84	14.1, 12.2
$5\alpha/eq$	2.034	13.4, 3.0	2.13	14.1, 2.4
6	2.18	3.0	1.73	12.2, 2.1; 3.3
7	1.90	4.1, 2.2	1.45	
$8\beta/ax$[b]	1.05	9.6, 2.2	0.73	11.8, 2.7
$8\alpha/eq$[a]	2.12	9.6, 4.1	2.13	11.8, 2.0
9	1.56		1.28	5.0, 4.9, 2.7, 1.7
$10\beta/ax$	2.11	10.8	1.70	10.9, 2.7
$10\alpha/eq$	2.71	10.8, 2.6	2.36	10.9, 4.9, 2.0
11	2.07	2.2	1.96	13.5, 3.1
$12\beta/ax$	1.37	7.9, 3.1, 2.0	1.29	13.5, 9.5
$12\alpha/eq$	1.54		1.37	13.5, 1.5
$13\alpha/ax$	1.73	2.6	1.18	
$13\beta/eq$	1.30	2.7	1.58	11.9, 4.0, 3.9
$14\beta/ax$	1.58		1.47	15.1, 2.6
$14\alpha/eq$	1.62		1.62	4.0
$15\alpha/ax$	2.029	11.5	1.92	11.2
$15\beta/eq$	2.82	11.5, 1.3	2.72	11.2, 4.0, 2.6
17α	2.37	11.0	2.23	11.0, 3.5
17β	2.75	11.0, 10.7	2.46	11.0, 10.6

[a] Equatorial in ring B; [b] axial in ring B

Table 5. ^{13}C and ^{1}H NMR chemical shifts of 5,6-didehydromultiflorine (**7**) in $CDCl_3$ (ppm from *TMS*)

Carbon	δ_c/ppm	Proton	δ_H/ppm	*J*/Hz
2	139.76	2	7.20	7.57
3	118.05	3	6.35	7.57, 2.78
4	179.04	–	–	–
5	116.23	5	6.18	2.78
6	153.54	–	–	–
7	34.99	7	2.91	2.8
8	21.19	$8\alpha/eq$[a]	2.02	13.8, 1.3
		$8\beta/ax$[b]	1.75	13.8, 1.8
9	32.79	9	2.06	2.2, 1.68
10	57.57	$10\alpha/eq$	3.92	12.7, 2.2, 1.05
		$10\beta/ax$	4.13	12.7, 6.09
11	63.17	11	2.93	12.1, 2.2
12	22.34	$12\alpha/eq$	1.89	9.2
		$12\beta/ax$	1.12	9.2
13	25.59	$13\alpha/ax$	1.49	13.0, 3.5
		$13\beta/eq$	1.90	13.0
14	18.95	$14\alpha/ex$	1.16	12.1
		$14\beta/ax$	1.61	12.1, 3.5
15	54.45	$15\alpha/ax$	2.75	14.0, 12.1, 3.0
		$15\beta/eq$	2.68	14.0, 1.9
17	52.21	17α	2.49	10.9, 1.7
		17β	3.36	10.9, 2.8

[a] Equatorial in ring B; [b] axial in ring B

Table 6. Catalytic hydrogenation and complex hydride reduction of *seco*-(11,12)-12,13-didehydromultiflorine (**2**; yield in %)

Entry	Condition	Medium	*t*/h	**12**	**13**	**14**	**15**	**16a**	**16b**
1	PtO_2	H_2O	68	48	3	49	–	–	–
2	PtO_2	EtOH (anhydrous)	24	44	2	54	–	–	–
3	PtO_2	1 *M* HCl	24		8	40	52	–	–
4	Pd/C	EtOH (anhydrous)	3		5	95	–	–	–
5	$NaBH_4$	MeOH	24		–	–	–	6	94
6	$LiAlH_4$	*THF*	8		–	6	–	16	78

only a mixture of epimeric alcohols (2% *ax* and 98% *eq*) in aqueous solution. *Comin* and *Deloufeu* [9] and *Wolińska-Mocydlarz* [11] have obtained only 4-hydroxysparteine of undetermined configuration from **1** under the same conditions.

According to our observations, catalytic hydrogenation of **1**, **6**, and **7** on platinum, irrespectively of the reaction medium used (EtOH, H_2O, AcOH, HCl), proceeds *via* the formation of two intermediates including a system of γ-piperidone

Table 7. Catalytic hydrogenation and complex hydride reduction of 3,4-didehydroquinolizidone-2 (**3**; yields in %)

Condition	Medium	*t*/h	**17**	**18**	**20a**	**20b**
PtO_2	H_2O	56	–	58	6	36
PtO_2	EtOH (anhydrous)	58	–	5	20	75
PtO_2	1 *M* HCl	24	50	–	3	47
$NaBH_4$	MeOH	19	–	–	18	82

(oxo derivative) or γ-pyridone (dehydro derivative) (Tables 1, 6, 7). The intermediates are formed simultaneously. Their presence was revealed by TLC already after 15 min of reduction, apart from a mixture of the epimeric alcohols. The dehydro product containing the γ-pyridone system does not undergo further reaction in media as EtOH or H_2O, whereas the γ-piperidone system of the oxo derivative experiences a reduction to a mixture of epimeric alcohols. The amount of the dehydro product formed from **1**, **2**, and **3** is different. In H_2O, the amount of the dehydro product reaches 78%, in EtOH 27%. The reduction of **6** in H_2O leads to 48% of the dehydro product (EtOH: 44%) whereas the reduction of **7** in H_2O gives 58% (EtOH: only 5%) of dehydro product. It is difficult to explain these differences. In all these three compounds the N–C=C–C=O group is part of the rigid *trans*-quinolizidine system. Repetition of the hydrogenation of **1**, **2**, and **3** for several times always gave the same results. Most probably, the differences should be interpreted as related to the molecule skeleton.

A chromatographic study of the hydrogenation of **1**, **2**, and **3** on platinum in HCl and AcOH showed that in these media the intermediate containing the γ-pyridone system reacts to **5** if **1** is used, to **15** with **2**, and to **17** in the case of **3**. The intermediate containing the γ-piperidone moiety undergoes reduction and hydrogenolysis to a mixture of epimeric alcohols and products including a methylene group (**5**, **15**, **17**). Therefore, the formation of **5**, **15**, and **17** obviously proceed *via* different pathways, *i.e*. through the intermediate with the γ-pyridone system or that with the γ-piperidone system, in these two cases. The observations are consistent with the suggestions of *Wolińskiej-Mocydlarz* [11].

The hydrogenolysis of the ketonic product **6** (from **1**) and, consequently, **13** and **19** from **2** and **3**, takes place probably according to the same mechanism as is the case with the isomers 13-oxo-sparteine (**11**) and 13-oxo-α-iso-sparteine [21]. An attempt to obtain **7** on Pt and Pd from **1** without hydrogen in ethanolic or aqueous solution failed. Dehydrogenation of **1** by other classical dehydrogenating agents gave very poor results.

Reductions employing complex hydrides

The reduction of **1** and **2** by $LiAlH_4$ and $NaBH_4$ resulted in the formation of a mixture of epimeric alcohols with a predominance of the epimer with an equatorial hydroxy group (Tables 1 and 6). The process of reduction by $LiAlH_4$ proceeds rather slowly, so we were able to separate from **1** the intermediate product of **6**. This

fact indicates that the initial hydride delivery to **1** (and, consequently, to **2** and **3**) occurs at C-4, resulting in an enolate form. This observation is in agreement with the work of *Goldberg et al*. [10]. The predominating formation of the equatorial alcohol is a consequence of the fact that steric approach control and product development control would be expected to direct this reaction.

In order to perform conformational assignments for **4a**, **b**, the NMR spectra of these compounds were examined; the data are summarized in Tables 2 and 3.

NMR spectroscopy

Table 2 lists the ^{13}C NMR chemical shifts of 4β- and 4α-hydroxysparteine (**4a**, **b**). The signals were assigned by comparison with the spectra of compounds of similar structure (13α-hydroxysparteine (**9**), 13α- (**10a**) and 13β-hydroxylupanine (**10b**) [18]) and by comparing the spectra of **4a** and **4b**. The correctness of these assignments was verified by molecular model considerations of **4a**, **b** and on the basis of chemical the shifts of C-6 and C-2. The ^{13}C NMR spectrum of the isomer with the hydroxyl group in the axial position (**4a**) reveals upfield shifts of 1.23 (C-2), 4.68 (C-4), and 4.61 (C-6) ppm relative to the positions of these signals in the spectrum of **4b** (Table 2). The upfield shift of C-2 and C-6 is a result of a γ-*gauche* substituent effect [22–24]; in the case of C-4, the upfield shift is similar as observed in some related compounds [18].

A complete assignment of the ^{1}H NMR spectra of **4a**, **b** as well as the determination of coupling constants was achieved by the analysis of HMQC and DQF-COSY spectra (Table 3). Large coupling constants of H-4 (twice 11.0 Hz) and a large value of the coupling constant sum $\Sigma J = 31.2$ Hz (Table 3) and the coupling of H-4 with axial protons at C-3 and C-5 prove the axial position of atom H-4 and are in agreement with the equatorial position of the hydroxyl group on C-4 in **4b** [25]. On the other hand, low values of the vicinal coupling constants (four times 2.9 Hz) and a low coupling constants sum of $\Sigma J = 11.7$ Hz (Table 3) of the relatively narrow signal of H-4 in **4a** prove the axial position of the hydroxy group at C-4. A similar relationship has been noted in the case of 14α-acetoxymatrine and 14β-acetoxymatrine [25].

The chemical shifts (^{1}H, ^{13}C) of **6** were assigned employing one- and two-dimensional techniques in $CDCl_3$ as well as by comparison with spectra of sparteine (Table 4a). The coupling constants were obtained directly from the ^{1}H NMR spectrum of **6** in $CDCl_3$ and C_6D_6 (Table 4b). The ^{1}H and ^{13}C chemical shifts of **7** (Table 5) and the corresponding coupling constants are in agreement with those published previously [3, 26, 27].

Experimental

IR spectra were recorded with Perkin Elmer 580 and Bruker FTIR 113v spectrometers. ^{1}H and ^{13}C NMR spectra (including DEPT, DQF-COSY, HMQC, *J*-resolved spectroscopy) were recorded in $CDCl_3$ and in C_6D_6 on a Varian Unity 300 NMR spectrometer; chemical shifts are quoted relative to internal *TMS*. GC-MS spectra were recorded on a JEOL IMSD-100 instrument connected with a Varian Series 3300 gas chromatograph. Chromatography conditions: column: DB1 (0.25 mm×20 m); carrier gas: He; split: 1:20; injector temperature: 260°C; temperature program: 200°C/1 min, 5 to

300°C/10 min. Systems for TLC: (a) EtOH:$CHCl_3$ = 3:2, (b) Acetone:MeOH:NH_3/MeOH = 4:1:1, (c) MeOH:ethyl acetate = 1:4.

Plant material: The alkaloids **1** and **2** were isolated from *Lupinus albus* cv. BAC seeds [28] and separated by short column chromatography with Kieselgel (Merck 70–230 mesh) and system (a) according to a method described previously [17].

Catalytic hydrogenations were performed in a glass apparatus under slightly elevated pressure and intense stirring with a magnetic stirrer. The processes were observed by TLC on silica gel; for their development, system (b) was used. The final products of hydrogenations and reduction reactions were analyzed by GC-MS.

Catalytic hydrogenation: To a mixture of a proper amount of reduced PtO_2 (0.01 g, 0.044 mmol), 5%Pd/$BaSO_4$ (0.03 g), 5%Pd/$CaCO_3$ (0.03 g), or 10% Pd/C (0.04 g), 0.02 g (0.08 mmol) substrate dissolved in 2 cm^3 of an adequate solvent were added. The reactions were performed until reduction of the substrate and intermediate products was complete. After filtering off the catalyst, the solvent was evaporated; the resulting mixture was dissolved in H_2O and alkalized with KOH. The alkaloids were extracted with diethyl ether and then with CH_2Cl_2. The products were analyzed by TLC using system (b) and by GC-MS.

Hydride reduction: To the alkaloid dissolved in a proper amount of solvent the hydride was added in 5-fold gravimetric excess relative to the substance. The reaction mixture was stirred at room temperature until reduction of the substrate was complete. The excess of hydride was destroyed with H_2O or 1 *N* HCl, and the solvent was evaporated under reduced pressure. The residue was alkalized with 25% KOH, extracted with diethyl ether and CH_2Cl_2, dried over $MgSO_4$, and evaporated.

The hydroxylic products were converted to the O-acetyl derivatives by mixing **4** with acetic anhydride and keeping it overnight. Then the mixture of **8a** and **8b** was analyzed by TLC (system (c)) and by GC-MS. Preparative separation of the 4-O-acetyl derivatives **8a**, **b** was achieved by short column chromatography [17] on Al_2O_3 or TLC (ICN Germany) with system (c). Alkaline hydrolysis of acetylated compounds was achieved by heating overnight with 25% KOH.

5,6-Didehydromultiflorine (**7**; $C_{15}H_{20}N_2O$)

Crystallized from CH_2Cl_2/hexane; white needles; m.p.: 175–176°C; $[\alpha]_D^{20} = -90°$ (EtOH); MS: m/z = 244 ([$M^{+\cdot}$], 100%), 163 (21%), 162 (59%), 146 (19%), 96 (46%); IR (KBr): ν = 1636, 1556, 1560, 2800–2600 (CH_{trans}) cm^{-1}, NMR: Table 5.

4α-Acetoxysparteine (**8b**; $C_{17}H_{28}N_2O_2$)

M.p.: 97–101°C; $[\alpha]_D^{20} = -5.9°$ (EtOH); MS: m/z = 292 ([$M^{+\cdot}$], 46%), 251 (27%), 233 (28%), 195 (100%), 136 (38%), 135 (88%), 98 (42%), 96 (47%); IR (KBr): ν = 1736 (C=O), 979 (C–O), 2800–2700 (CH_{trans}) cm^{-1}.

4β-Acetoxysparteine (**8a**; $C_{17}H_{28}N_2O_2$)

Oil; $[\alpha]_D^{20} = -4.6°$ (EtOH); MS: m/z = 292 ([$M^{+\cdot}$], 62%), 251 (49%), 233 (33%), 195 (94%), 136 (60%), 135 (100%), 98 (68%), 96 (47%); IR (film): ν = 1734 (C=O), 958 (C–O), (CH_{trans}) 2850–2700 cm^{-1}.

4α-Hydroxysparteine (**4b**, $C_{15}H_{26}N_2O$)

M.p.: 74–75°C (Ref. [10]: 67–72°C); $[\alpha]_D^{20} = -20.8°$ (EtOH); MS: m/z = 250 ([$M^{+\cdot}$], 29%), 209 (19%), 153 (100%), 136 (41%), 114 (46%), 98 (25%), 55 (20%); IR (KBr): ν = 3265–3427 (OH), 975.3 (C–O), 2880–2700 (CH_{trans}) cm^{-1}.

4β-Hydroxysparteine (**4a**; $C_{15}H_{26}N_2O$)

Oil; $[\alpha]_D^{20} = -7.9°$ (EtOH); MS: $m/z = 250$ ([$M^{+\cdot}$], 29%), 209 (48%), 153 (100%), 136 (38%), 114 (58%), 98 (33%), 55 (6%); IR (film): $\nu = 3285$–3470 (OH), 2880–2700 (CH_{trans}), 953.7 (C–O) cm^{-1}.

4-Oxosparteine (**6**; $C_{15}H_{24}N_2O$)

Light yellow oil; $[\alpha]_D^{20} = -27°$ (EtOH); MS: $m/z = 248$ ([$M^{+\cdot}$] 73%), 207 (14%), 151 (100%), 136 (76%), 112 (33%), 97 (60%), 55 (41%); IR (film): $\nu = 1724$ (C=O), 2850–2700 (CH_{trans}) cm^{-1}; NMR: Tables 4a, b.

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