Nicht-Identität von Nazlinin und 6-Azacyclodeca[5,4-b]indol-1-amin

Siavosh Mahboobi\*, Wolfgang Wagner, Thomas Burgemeister, and Wolfgang Wiegrebe

Faculty of Chemistry and Pharmacy, University, D-93040 Regensburg/Germany

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In 1991 Üstünes and coworkers have published isolation and structure elucidation of a new alkaloid from *Nitraria Schoberi* (Zygophyllaceae), which was named nazlinin<sup>1)</sup>. Its spectroscopic data led to the conclusion that nazlinin is 6-azacyclodeca[5,4-b]indol-1-amine (1) (the authors do not report upon measurements of optical activity). - Whilst the NMR-data of nazlinin can be attributed to structure 1, the base peak in its EI-MS at m/z = 171, in accordance with a *N*-protonated 3,4-dihydro- $\beta$ -carbolinium-ion, cannot be explained straightforwardly by structure 1 (Scheme 1).

Koomen et al.<sup>2)</sup> did not exclude the alternative structure of  $(+/-)-1-(\omega-amino-n-butyl)-1,2,3,4-tetrahydro-\beta-carboline (2) which was synthesized by this group. The authors found the published NMR-data of nazlinin to be in complete agreement with those obtained for 2 in CD<sub>3</sub>OD containing more than two equivalents of F<sub>3</sub>C-COOD.$ 



Scheme 1

Moreover,  $2^{++}$  is expected to give rise to a fragment ion at m/z 171 by benzylic/ $\beta$ -cleavage<sup>3)</sup> of high intensity, which is actually reported to be the base peak in the ms of nazlinin<sup>1)</sup>.

It remained open why the NMR-data published for nazlinin strongly deviate from those obtained for 2 in  $CD_3OD$ whilst those of (at least) diprotonated 2 and those of nazlinin are identic<sup>2)</sup>. In order to shed some additional light onto this problem we have synthesized compound 1 (Scheme 2).

The 1,2,3,4,6,7-hexahydro-12H-indolo[2,3-a]quinolizine  $3^{4}$  was converted by benzyl chloroformate in MeOH/Na<sub>2</sub>CO<sub>3</sub> to the ten-membered ring urethan 4 (mixture of rotamers)<sup>5)</sup> which was readily oxidized to ketone 5 by *tert*-butyl hypochlorite, according to lit.<sup>6)</sup>. Reaction of **5** with O-methylhydroxylamine HCl in pyridine afforded the oxime ether 6 which was reduced specifically by NaBH<sub>4</sub> and almost equimolar amounts of F<sub>3</sub>C-COOH in THF<sup>7</sup>) leading to the amine-urethan 7 besides some 5. Surprisingly, hydrogenation of the oxime ether 6 on Pd/C led to the tetracyclic starting material 3: this can be explained by hydrogenolysis of the urethan, transannular addition of the sec. amin at the C=N-OMe group and subsequent hydrogenolysis of the benzylic C-NH-OCH<sub>3</sub> increment. - Hydrogenolysis of the carbamate group of 7 afforded the title component 1. The chromatographic data of 1 are very similar



Scheme 2

*-H	1	1 + [D]TFA	natural alkaloid [lit <sup>1)</sup> ] or 2 + [D]TFA [lit <sup>2)</sup> ]	2 [lit <sup>2)</sup> ]
3	0.79-0.95 (1H, m)	1.03-1.16 (1H, m)	1.70 (2H, m)	1.5 (4H, m)
4	1.46-1.56 (1H, m) 1.57-1.70 (2H, m)	1.67-1.89 (3H, m,	1.83 (2H, m)	1.71 (1H, m)
2	1.95-2.07 (2H, m)	2.15-2.28 (1H, m) 2 32-2 43 (1H m)	2.03 (1H, m) 2 30 (1H m)	1.99 (1H, m)
5 7/8	2.55-2.63 (1H, m) 2.81-2.90 (1H, m)	3.06-3.16 (1H, m) 3.26-3.59 (5H, m)	3.00 (2H, m) 3.10 (2H, m)	2.67 (4H, m) 2.95 (1H, dxdxd,
170	2.90-3.02 (2H, m, + one 5-H)	+ one 5-H)	3.45 (1H, m) 3.72 (1H, m)	J=12.3,8.9,5.2Hz) 3.31 (1H, m)
	3.05-3.15 (1H, m) 3.17-3.29 (1H, m)			,.,
1	4.44 (1H, dd, J <sup>1</sup> =8.4,	5.07 (1H, dd, J <sup>1</sup> =6.0,	4.72 (1H, m)	4.02 (1H, m, J=8.4,3.5,
10/11	J <sup>2</sup> =7.2Hz) 6.99-7.03 (1H, m) 7.09-7.11 (1H, m)	J <sup>2</sup> =5.5Hz) 7.13-7.17 (1H, m) 7.24-7.28 (1H, m)	7.05 (1H, dt, J=7.5, 1.5Hz)	6.98 (2H, m)
			7.15 (1H, dt, J=7.5, 1.5Hz)	
9/12	7.33-7.35 (1H, m) 7.48-7.51 (1H, m)	7.48-7.50 (1H, m) 7.67-7.69 (1H, m)	7.38 (1H, d, J=7.5Hz) 7.48 (1H, d, J=7.5Hz)	7.27 (1H, m) 7.36 (1H, dxd, J=7.1,1.3Hz)

Table: NMR-spectra in CD<sub>3</sub>OD

with those reported for nazlinin, the spectroscopic data of 1, however, are absolutely different from those of nazlinin.

By <sup>1</sup>H/<sup>1</sup>H- and <sup>1</sup>H/<sup>13</sup>C-correlation spectra all the signals can be attributed to atoms of compound **1**. The resonance frequency of 1-H is of special importance: in **1** (base) it resonates as a dd at 4.44 ppm, whilst addition of F<sub>3</sub>C-COOD shifts this signal to 5.07 ppm without changing its shape, indicating that this dd results from a neighbouring CH<sub>2</sub>-group which is part of a cyclic system. In β-carboline **2** 1-H resonates as a m, probably because the mobility of the side chain at C-1 is not restricted. Under these NMRconditions bis-amine **1** is stable, whilst it is partially degraded by prolonged warming (8 d at 30-40°C) or by treatment with 0.1 N HCl (slow reaction at room temp., fast reaction at about 40°C), leading to more polar unknown compounds. In conclusion compound **1** is not identic with nazlinin,

neither as a base nor as its dication.

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# **Experimental Part**

General remarks: m.p.: Büchi 512.- IR: FT Nicolet 510.- <sup>1</sup>H-NMR: Varian EM 390 (90 MHz), Bruker ARX 400 (400 MHz).- <sup>13</sup>C-NMR: Bruker ARX 400 (100.61 MHz); all NMR-spectra in CDCl<sub>3</sub>, if not otherwise stated.- MS: Varian MAT 112 S/SS, 70 eV.- Column chromatography (cc): SiO<sub>2</sub>/flash, if not otherwise stated.- All reactions have been performed under N<sub>2</sub>.

#### 1,2,3,4,6,7-Hexahydro-12H-indolo[2,3-a]chinolizine (3)

**3** was prepared according to *Costerousse et al.*<sup>4a)</sup> (1. step), *Costerousse*<sup>4a)</sup> and *Tamelen*<sup>4b)</sup> (2. step), and *Rapoport*<sup>4c)</sup> (3. step): colourless crystals, m.p. 147-149°C (lit.<sup>4c)</sup>: 147-149°C). For <sup>1</sup>H-NMR data see lit.<sup>4c)</sup>-

## 6-Benzyloxycarbonyl-1-methoxy-6-azacyclodeca[5,4-b]indole (4)

1.46 g (6.46 mmole) 3 were dissolved in 10 ml of absol. THF and 1 ml of absol. MeOH. 3 g of Na<sub>2</sub>CO<sub>3</sub> were added, this suspension was cooled to 0°C and 1.21 g (7.11 mmole) of benzyl chloroformate were added dropwise. The mixture was stirred for 2 h at room temp., poured into a mixture of 20 ml of CH<sub>2</sub>Cl<sub>2</sub> and 50 ml of ice water and stirred vigorously for 10 min. The org. phase was washed with a satd. aq. solution of NaHCO<sub>3</sub>, then with water and dried (Na<sub>2</sub>SO<sub>4</sub>): 1.95 g (77%) yellowish oil. After cc (column: 2.5 x 40 cm<sup>2</sup>; CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate = 95/5) 1.82 g (71%) 4: colourless oil.-  $C_{24}H_{28}N_2O_3$  (392.5).- IR (Film):  $\tilde{v} = 3315$  (NH); 2933; 1684 (CO); 1464; 1422; 1337; 1258; 1094; 743 cm<sup>-1</sup>.- <sup>1</sup>H-NMR (90 MHz):  $\delta$  (ppm) = 0.70-2.36 (6H; m), 2.50-4.22 (6H; m), 3.27 (3H; s, OCH<sub>3</sub>), 4.23-4.57 (1H; m), 4.87 (2/3H; d, J = 13 Hz, AB-system, CH<sub>2</sub>Ph, rotamer), 5.26 (2/3H; d, J = 13 Hz, AB-system, CH<sub>2</sub>Ph, rotamer), 5.26 (2/3H; br s, CH<sub>2</sub>Ph, rotamer), 7.02-7.68 (9H; m), 8.87 (1H, br s, NH-indole, exchangeable).- MS (70 eV): m/z = 392 (92) [M<sup>++</sup>], 226 (19), 225 (77), 91  $(100) [C_7H_7]^+$ .

#### 6-Benzyloxycarbonyl-6-azacyclodeca[5,4-b]indol-1-one (5)

To the solution of 1.82 g (4.64 mmole) 4 in 10 ml of absol.  $CH_2Cl_2$  were added at 0°C 453 mg (4.87 mmole) of tert-butyl hypochlorite drop by drop under stirring (the solution became red but the colour faded away by the time). Stirring was continued for 10 min after the addition, then 2 g of

solid NaHCO<sub>3</sub> were added, and the mixture was poured into a mixture of 10 ml of CH<sub>2</sub>Cl<sub>2</sub> and 10 g of ice immediately. The aqueous phase was thoroughly extracted with CH<sub>2</sub>Cl<sub>2</sub>, the org. phase was washed with satd. NaHCO<sub>3</sub>-solution and water. Evaporation of the solvent yielded 1.71 g (98%) brownish oil. After cc (column: 2.5 x 40 cm<sup>2</sup>; CH<sub>2</sub>Cl<sub>2</sub>cHtyl acetate = 95/5): 1.06 g 5 (61%), colourless oil.- C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub> (376.5).- IR (Film):  $\vec{v} = 3327$  (NH); 2935; 1694 (CO); 1636 (CO); 1472; 1420; 1339; 1270; 1240; 1216; 1120; 741 cm<sup>-1.-1</sup>H-NMR (90 MHz):  $\delta$  (ppm) = 1.12-2.13 (5H; m), 2.76-3.04 (2H; m), 3.25-3.57 (3H; m), 3.58-3.83 (1H; m), 3.84-4.40 (1H; m), 4.99 (1H; br s, CH<sub>2</sub>Ph, rotamer), 5.14 (1H; br s, CH<sub>2</sub>Ph, rotamer), 6.91-7.82 (9H; m), 9.33 (1H; br s, NH-indole, exchangeable).-MS (70 eV): m/z = 376 (31) [M<sup>++</sup>], 241 (12), 91 (100) [C<sub>7</sub>H<sub>7</sub>]<sup>+</sup>.

## 6-Benzyloxy-1-methoxyimino-6-azacyclodeca[5,4-b]indole (6)

1.10 g (2.93 mmole) **5** and 10 g *O*-methylhydroxylamine-HCl were suspended in 50 ml of freshly distilled absol. pyridine and heated to reflux for 14 h. After cooling 20 g ice and 100 ml of CH<sub>2</sub>Cl<sub>2</sub> were added. The org. phase was 3 x extracted with 2N HCl and washed with half satd. NaHCO<sub>3</sub>-solution. After evaporation of solvent: 1.12 g (94%) **6**, dark brown oil. Purification by cc (column: 2.5 x 40 cm<sup>2</sup>; CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate = 98/2): 1.03 g (87%) colorless oil.-  $C_{24}H_{27}N_3O_3$  (405).- IR (Film):  $\tilde{v}$  = 3327 (NH), 2937; 1690 (CO); 1472; 1420; 1335; 1272; 1243; 1212; 1054; 745 cm<sup>-1</sup>.-<sup>1</sup>H-NMR (400 MHz):  $\delta$  (ppm) = 1.33-1.43 (1H; m), 1.49-1.57 (1H; m), 1.74-1.84 (2H; m), 2.84-2.92 (2H; m), 3.20-3.41 (4H; m), 3.61-3.67 (2H; m), 3.963 and 3.965 (3H; 2 x s, NOCH<sub>3</sub>, rotamers), 5.01 (1H; s, CH<sub>2</sub>Ph, rotamer), 5.15 (1H; s, CH<sub>2</sub>Ph, rotamer), 7.06-7.19 (2H; m), 7.19-7.42 (6H; m), 7.49-7.57 (1H; m), 8.70 and 8.71 (1H; 2 x s, NH-indole, exchangeable, rotamers).- MS (70 eV): m/z = 405 (35) [M<sup>++</sup>], 374 (33), 225 (11), 91 (100) [C<sub>7</sub>H<sub>7</sub>]<sup>+</sup>.

#### 6-Benzyloxycarbonyl-6-azacyclodeca[5,4]indol-1-amine (7)

130 mg (3.45 mmole) of NaBH<sub>4</sub> were slowly added at 0°C to 57 ml of absol. THF, being 0.06 molar in F<sub>3</sub>C-COOH. When the reaction had ceased 230 mg (0.57 mmole) 6 in 5 ml of absol. THF were added drop by drop at 0°C, then the mixture was refluxed for 90 min. After cooling and dilution with 50 ml of Et<sub>2</sub>O, 0.5 g of solid NaHCO<sub>3</sub> were added followed by washing with water.- Drying (Na<sub>2</sub>SO<sub>4</sub>) and evaporation of the org. phase yielded 200 mg (93%) of yellowish oil which was purified by cc (column:  $1.5 \times 30 \text{ cm}^2$ ; CH<sub>2</sub>Cl<sub>2</sub>/EtOH (about 1% of NH<sub>3</sub> gas) = 98/2): 122 mg (57%) of 7 as a colourless oil besides 15 mg (7%) of 5.-  $C_{23}H_{27}N_3O_2$ (377.5).- IR (Film): v = 3340 (NH); 2933; 1679 (CO); 1463; 1424; 1333; 1260; 1218; 1121; 735 cm<sup>-1</sup>.- <sup>1</sup>H-NMR (400 MHz):  $\delta$  (ppm) = 0.67-1.00 (1H; m), 1.13-1.82 (5H; m), 1.57 (2H; br s, NH<sub>2</sub>, exchangeable), 2.53-3.63 (5H; m), 3.93-4.02 (2/3 H; m, rotamer), 4.17-4.30 (4/3 H; m, rotamer), 4.79 (2/3 H; d, J = 12.4 Hz, AB-system, CH<sub>2</sub>Ph, rotamer), 5.13 (2/3 H; d, J = 12.4 Hz, AB-system, CH<sub>2</sub>Ph, rotamer), 5.14 (2/3 H; s, CH<sub>2</sub>Ph, rotamer), 7.02-7.49 (9H; m), 8.58 (1H; br s, NH-indole, exchangeable).- MS (70 eV):  $m/z = 377 (100) [M^{++}]$ , 243 (14), 225 (51), 198 (30), 91 (92)  $[C_7H_7]^+$ .

## 6-Azacyclodeca[5,4-b]indol-1-amine (1)

Under normal pressure 150 mg (0.40 mmole) urethan 7, dissolved in 2 ml of absol. MeOH, were stirred with 150 mg Pd/C (5%) under H<sub>2</sub> at 30°C for 10 min. The catalyst was filtered off using celite and was washed several times with warm MeOH until the reaction with *Mayer's* reagent was negative. Evaporation of solvent afforded a yellow oil (80 mg, 82%) which was purified by twofold cc (1.column: 1.5 x 10 cm<sup>2</sup>; ethyl

acetate/propan-2-ole/NH<sub>3</sub> (aq., 25%) = 55/30/15.- 2.column: CH<sub>2</sub>Cl<sub>2</sub>/EtOH (satd. with NH<sub>3</sub> gas) = 8/2): 25 mg (26%) colourless oil, precipitating from ethyl acetate/hexane = 2/1 as a colourless powder after scratching.- Melting range: 83-90°C.- 1 decomposes partially when we tried to get rid of solvent by drying at 30-40°C in vacuo.- C15H21N3 (243.5).- Bis-picrate-2 MeOH: m.p. 231°C (decomp.): C29H35N9O16 (765.6) calcd. C 45.5 H 4.61 N 16.5 found C 45.3 H 4.35 N 16.2.- IR (KBr):  $\tilde{v} = 3290$  (NH); 2929; 1461; 1337; 1273; 1175; 1148; 1055; 747 cm<sup>-1</sup>.- <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  (ppm) = 0.79-0.95 (1H; m, 3-H), 1.46-1.56 (1H; m, 3-H), 1.57-1.70 (2H; m, 4-H), 1.95-2.07 (2H; m, 2-H), 2.55-2.63 (1H; m, 5-H), 2.81-2.90 (1H; m, 7-H or 8-H), 2.90-3.02 (2H; m, H-5, 7-H/8-H), 3.05-3.15 (1H; m, 7-H/8-H), 3.17-3.29 (1H; m, 7-H/8-H), 4.44 (1H; dd, J<sup>1</sup> = 8.4, J<sup>2</sup>)= 7.2 Hz, 1-H), 6.99-7.03 (1H; m, 10-H/11-H), 7.09-7.11 (1H; m, 10-H/11-H), 7.33-7.35 (1H; m, 9-H/12-H), 7.48-7.51 (1H; m, 9-H/12-H).-<sup>13</sup>C-NMR (CD<sub>3</sub>OD):  $\delta$  (ppm) = 21.08 (C-3), 22.11 (C-8), 28.07 (C-4), 38.68 (C-2), 44.20 (C-5), 45.67 (C-7), 47.98 (C-1), 108.12 (pyrrol), 112.04 (C-10/C-11), 119.28 (C-10/C-11), 120.04 (C-9/C-12), 122.90 (C-9/C-12), 128.37 (pyrrol), 138.28 (pyrrol), 144.22 (pyrrol).- <sup>13</sup>C-DEPT (CD<sub>3</sub>OD, rel.Int.):  $\delta$  (ppm) = 21.03 (-84, CH<sub>2</sub>), 21.88 (-92, CH<sub>2</sub>), 28.81 (-82, CH<sub>2</sub>), 38.46 (-56, CH2), 44.19 (-89, CH2), 45.59 (-91, CH2), 47.99 (+82, CH), 112.11 (+89, CH), 119.29 (+100, CH), 120.11 (+100, CH), 122.99 (+94, CH).- MS (70 eV): m/z = 243 (31) [M<sup>++</sup>], 226 (66), 225 (100), 197 (22).-FD-MS (MeOH): 243.0 [M<sup>++</sup>].- To 4.0 mg (0.016 mmole) 1 dissolved in 1 ml of CD<sub>3</sub>OD were added 4 µl (3.2 equiv) of [D]TFA: <sup>1</sup>H-NMR (400 MHz):  $\delta$  (ppm) = 1.03-1.16 (1H; m), 1.67-1.89 (3H; m), 2.15-2.28 (1H; m), 2.32-2.43 (1H; m), 3.06-3.16 (1H; m), 3.26-3.59 (5H; m), 5.07 (1H; dd,  $J^1 = 6.0$ ,  $J^2 = 5.5$  Hz, 1-H), 7.13-7.17 (1H; m), 7.24-7.28 (1H; m), 7.48-7.50 (1H; m), 7.67-7.69 (1H; m).- After alkalisation by Na<sub>2</sub>CO<sub>3</sub> 1 was recovered unchanged so excluding a reaction of the skeleton.

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