Non-Identity of Nazlinin and 6-Azacyclodeca[5,4-*b*]indol-1-amine

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

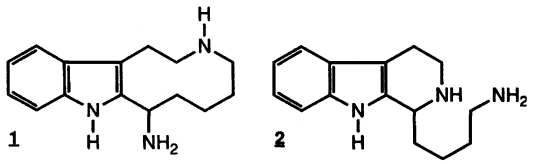
Siavosh Mahboobi*, Wolfgang Wagner, Thomas Burgemeister, and Wolfgang Wiegrebe

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

Received February 17, 1994

In 1991 Üstünes and coworkers have published isolation and structure elucidation of a new alkaloid from *Nitraria Schoberi* (Zygophyllaceae), which was named nazlinin[1]. 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-β-carbolinium-ion, cannot be explained straightforwardly by structure **1** (Scheme 1).

Koomen et al.[2] did not exclude the alternative structure of (+/-)-1-(ω-amino-*n*-butyl)-1,2,3,4-tetrahydro-β-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_3OD containing more than two equivalents of F_3C-COOD.

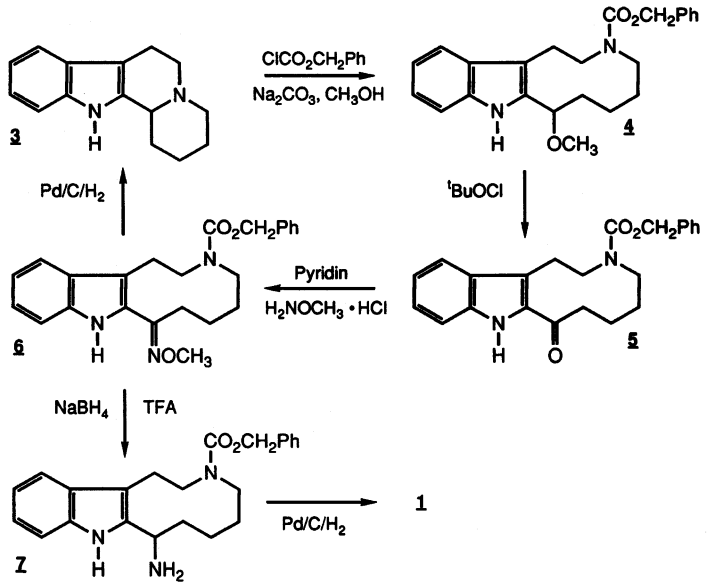


Scheme 1

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

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[2]. 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-12*H*-indolo[2,3-*a*]quinolizine **3**[4] was converted by benzyl chloroformate in $MeOH/Na_2CO_3$ to the ten-membered ring urethan **4** (mixture of rotamers)[5] which was readily oxidized to ketone **5** by *tert*-butyl hypochlorite, according to lit.[6]. Reaction of **5** with *O*-methylhydroxylamine·HCl in pyridine afforded the oxime ether **6** which was reduced specifically by $NaBH_4$ and almost equimolar amounts of F_3C-COOH in THF[7] 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_3 increment. - Hydrogenolysis of the carbamate group of **7** afforded the title component **1**. The chromatographic data of **1** are very similar



Scheme 2

  0365-6233/94/0707-0463 $ 5.00 + .25/0

Table: NMR-spectra in CD_3OD

*-H	1	1 + [D]TFA	natural alkaloid [lit[1]] or 2 + [D]TFA [lit[2]]	2 [lit[2]]
3	0.79-0.95 (1H, m) 1.46-1.56 (1H, m)	1.03-1.16 (1H, m)	1.70 (2H, m)	1.5 (4H, m)
4	1.57-1.70 (2H, m)	1.67-1.89 (3H, m, + one 3-H)	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	2.55-2.63 (1H, m)	3.06-3.16 (1H, m)	3.00 (2H, m)	2.67 (4H, m)
7/8	2.81-2.90 (1H, m) 2.90-3.02 (2H, m, + one 5-H) 3.05-3.15 (1H, m) 3.17-3.29 (1H, m)	3.26-3.59 (5H, m, + one 5-H)	3.10 (2H, m) 3.45 (1H, m) 3.72 (1H, m)	2.95 (1H, dxdxd, J=12.3,8.9,5.2Hz) 3.31 (1H, m)
1	**4.44 (1H, dd, J^1=8.4, J^2=7.2Hz)**	**5.07 (1H, dd, J^1=6.0, J^2=5.5Hz)**	**4.72 (1H, m)**	**4.02 (1H, m, J=8.4,3.5, 1.8Hz)**
10/11	6.99-7.03 (1H, m) 7.09-7.11 (1H, m)	7.13-7.17 (1H, m) 7.24-7.28 (1H, m)	7.05 (1H, dt, J=7.5, 1.5Hz) 7.15 (1H, dt, J=7.5, 1.5Hz)	6.98 (2H, m)
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)

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

By $^1H/^1H$- and $^1H/^{13}C$-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_3C-COOD shifts this signal to 5.07 ppm without changing its shape, indicating that this dd results from a neighbouring CH_2-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 NMR-conditions 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.

Financial support by Fonds der Chemischen Industrie is gratefully acknowledged.

Experimental Part

General remarks: m.p.: Büchi 512.- IR: FT Nicolet 510.- ^1H-NMR: Varian EM 390 (90 MHz), Bruker ARX 400 (400 MHz).- ^{13}C-NMR: Bruker ARX 400 (100.61 MHz); all NMR-spectra in $CDCl_3$, if not otherwise stated.- MS: Varian MAT 112 S/SS, 70 eV.- Column chromatography (cc): SiO_2/flash, if not otherwise stated.- All reactions have been performed under N_2.

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

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

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_2CO_3 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_2Cl_2 and 50 ml of ice water and stirred vigorously for 10 min. The org. phase was washed with a satd. aq. solution of $NaHCO_3$, then with water and dried (Na_2SO_4): 1.95 g (77%) yellowish oil. After cc (column: 2.5 x 40 cm^2; CH_2Cl_2/ethyl acetate = 95/5) 1.82 g (71%) **4**: colourless oil.- $C_{24}H_{28}N_2O_3$ (392.5).- IR (Film): $\tilde{\nu}$ = 3315 (NH); 2933; 1684 (CO); 1464; 1422; 1337; 1258; 1094; 743 cm^{-1}.- ^1H-NMR (90 MHz): δ (ppm) = 0.70-2.36 (6H; m), 2.50-4.22 (6H; m), 3.27 (3H; s, OCH_3), 4.23-4.57 (1H; m), 4.87 (2/3H; d, J = 13 Hz, AB-system, CH_2Ph, rotamer), 5.26 (2/3H; d, J = 13 Hz, AB-system, CH_2Ph, rotamer), 5.26 (2/3H; br s, CH_2Ph, rotamer), 7.02-7.68 (9H; m), 8.87 (1H, br s, NH-indole, exchangeable).- MS (70 eV): m/z = 392 (92) [$M^{+\cdot}$], 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 $NaHCO_3$ were added, and the mixture was poured into a mixture of 10 ml of CH_2Cl_2 and 10 g of ice immediately. The aqueous phase was thoroughly extracted with CH_2Cl_2, the org. phase was washed with satd. $NaHCO_3$-solution and water. Evaporation of the solvent yielded 1.71 g (98%) brownish oil. After cc (column: 2.5 x 40 cm^2; CH_2Cl_2/ethyl acetate = 95/5): 1.06 g **5** (61%), colourless oil.- $C_{23}H_{24}N_2O_3$ (376.5).- IR (Film): $\tilde{\nu}$ = 3327 (NH); 2935; 1694 (CO); 1636 (CO); 1472; 1420; 1339; 1270; 1240; 1216; 1120; 741 cm^{-1}.- ^{1}H-NMR (90 MHz): δ (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_2Ph, rotamer), 5.14 (1H; br s, CH_2Ph, rotamer), 6.91-7.82 (9H; m), 9.33 (1H; br s, NH-indole, exchangeable).- MS (70 eV): m/z = 376 (31) [$M^{+\cdot}$], 241 (12), 91 (100) $[C_7H_7]^+$.

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_2Cl_2 were added. The org. phase was 3 x extracted with 2N HCl and washed with half satd. $NaHCO_3$-solution. After evaporation of solvent: 1.12 g (94%) **6**, dark brown oil. Purification by cc (column: 2.5 x 40 cm^2; CH_2Cl_2/ethyl acetate = 98/2): 1.03 g (87%) colorless oil.- $C_{24}H_{27}N_3O_3$ (405).- IR (Film): $\tilde{\nu}$ = 3327 (NH), 2937; 1690 (CO); 1472; 1420; 1335; 1272; 1243; 1212; 1054; 745 cm^{-1}.- ^{1}H-NMR (400 MHz): δ (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, $NOCH_3$, rotamers), 5.01 (1H; s, CH_2Ph, rotamer), 5.15 (1H; s, CH_2Ph, 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) [$M^{+\cdot}$], 374 (33), 225 (11), 91 (100) $[C_7H_7]^+$.

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

130 mg (3.45 mmole) of $NaBH_4$ were slowly added at 0°C to 57 ml of absol. THF, being 0.06 molar in F_3C-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_2O, 0.5 g of solid $NaHCO_3$ were added followed by washing with water.- Drying (Na_2SO_4) and evaporation of the org. phase yielded 200 mg (93%) of yellowish oil which was purified by cc (column: 1.5 x 30 cm^2; CH_2Cl_2/EtOH (about 1% of NH_3 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): $\tilde{\nu}$ = 3340 (NH); 2933; 1679 (CO); 1463; 1424; 1333; 1260; 1218; 1121; 735 cm^{-1}.- ^{1}H-NMR (400 MHz): δ (ppm) = 0.67-1.00 (1H; m), 1.13-1.82 (5H; m), 1.57 (2H; br s, NH_2, 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_2Ph, rotamer), 5.13 (2/3 H; d, J = 12.4 Hz, AB-system, CH_2Ph, rotamer), 5.14 (2/3 H; s, CH_2Ph, rotamer), 7.02-7.49 (9H; m), 8.58 (1H; br s, NH-indole, exchangeable).- MS (70 eV): m/z = 377 (100) [$M^{+\cdot}$], 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_2 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^2; ethyl acetate/propan-2-ole/NH_3 (aq., 25%) = 55/30/15.- 2.column: CH_2Cl_2/EtOH (satd. with NH_3 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*.- $C_{15}H_{21}N_3$ (243.5).- Bis-picrate·2 MeOH: m.p. 231°C (decomp.): $C_{29}H_{35}N_9O_{16}$ (765.6) calcd. C 45.5 H 4.61 N 16.5 found C 45.3 H 4.35 N 16.2.- IR (KBr): $\tilde{\nu}$ = 3290 (NH); 2929; 1461; 1337; 1273; 1175; 1148; 1055; 747 cm^{-1}.- ^{1}H-NMR (400 MHz, CD_3OD): δ (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^1 = 8.4, J^2 = 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).- ^{13}C-NMR (CD_3OD): δ (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).- ^{13}C-DEPT (CD_3OD, rel.Int.): δ (ppm) = 21.03 (-84, CH_2), 21.88 (-92, CH_2), 28.81 (-82, CH_2), 38.46 (-56, CH_2), 44.19 (-89, CH_2), 45.59 (-91, CH_2), 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) [$M^{+\cdot}$], 226 (66), 225 (100), 197 (22).- FD-MS (MeOH): 243.0 [$M^{+\cdot}$].- To 4.0 mg (0.016 mmole) **1** dissolved in 1 ml of CD_3OD were added 4 µl (3.2 equiv) of [D]TFA: ^{1}H-NMR (400 MHz): δ (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_2CO_3 **1** was recovered unchanged so excluding a reaction of the skeleton.

References

1 L. Üstünes, A. Özer, G.M. Laekeman, J. Corthout, L.A.C. Pieters, W. Baeten, A.G. Herman, M. Claeys, A.J. Vlietinck, *J. Nat. Prod.* **1991**, *54*, 959-966.

2 M.J. Wanner, A.W. Velzel, G.J. Koomen, *J. Chem. Soc. Chem. Commun.* **1993**, 174-175.

3a M. Hesse, *Indolalkaloide,* Verlag Chemie, Weinheim, **1974**, p. 103-216.

3b S. Mahboobi, *Arch. Pharm. (Weinheim)* **1992**, *325*, 249-250.

3c J. Gynther, P. Peura, S. Salmi, *Acta. Chem. Scand.* **1985**, *B35*, 849-859.

4a G. Costerousse, J. Buendia, E. Toromanoff, J. Martel, *Bull. Soc. Chim. France II* **1978**, 355-360.

4b E.E. Tamelen, P.E. Aldrich, T.J. Katz, *Chem. Ind.* **1956**, 793.

4c J.E. Johansen, B.D. Christie, H. Rapoport, *J. Org. Chem.* **1981**, *46*, 4914-4920.

5a G. Schill, H. Löwer, C.U. Priester, U.F. Windhövel, H. Fritz, *Tetrahedron* **1987**, *43*, 3729-3745.

5b M.J. Calverley, J. Harley-Mason, S.A. Quarrie, P.D. Edwards, *Tetrahedron* **1981**, *37*, 1547-1556.

5c T. Koike, H. Takayama, S. Sakai, *Chem. Pharm. Bull.* **1991**, *39*, 1677-1681.

6 S. Sakai, E. Yamanaka, L.J. Dolby, *Heterocycles* **1976**, *4*, 981-984.

7 N. Umino, T. Iwakuma, M. Ikesaki, N. Itoh, *Chem. Pharm. Bull.* **1978**, *26*, 2897-2898.

[KPh615]