Monatshefte für Chemie 130, 1159–1166 (1999)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

New Dimethylaminoalkyl Substituted Auxin Derivatives

Sophie-Isabelle Bascop, Jean-Yves Laronze, and **Janos Sapi***

Laboratoire de Chimie Thérapeutique, UPRES A CNRS 6013 'Isolement, Structure, Transformations et Synthése de Produits Naturels', IFR 53 Biomolécules, Faculté de Pharmacie, Université de Reims Champagne-Ardenne, F-51096 Reims Cedex, France

Summary. 2-Dimethylaminoalkyl substituted indole-3-acetic acid derivatives were prepared and characterized.

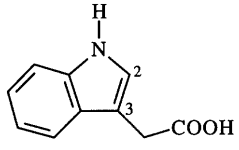
Keywords. Auxine; Cyclic gramines; Dimethylaminoalkyl-indole-3-acetic acids.

Neue dimethylaminoalkylsubstituierte Auxinderivate

Zusammenfassung. 2-Dimethylaminoalkylsubstituierte Derivate der Indol-3-essigsäure wurden hergestellt und charakterisiert.

Introduction

Indole-3-acetic acid (auxin, **1**) has been known for a long time as one of the most common vegetal growth and development factors acting at the cellular, tissue, and plant level [1]. Structure-activity relationship studies performed on natural substances (**1** and related compounds) or synthetic analogs (naphthalenes, phenylacetic acids) have led to the description of different models of auxin-binding sites [2]. It has been well established that **1** could bind to plant proteins [3], and for the first time a phytophoric conformation of the auxin-binding protein 1 of maize has been proposed [4].



1

Although a great number of derivatives of **1**, including 2-substituted ones [5], have been prepared and biologically evaluated, to the best of our knowledge the influence of a basic nitrogen linked to C-2 of **1** on intracellular diffusion, transport, and distribution

* Corresponding author

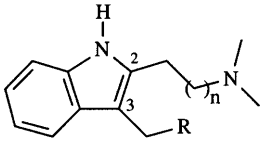
has not yet been examined. Herein we describe the preparation of some dimethylaminoalkyl substituted derivatives of **1** based on gramine chemistry [6].

Results and Discussion

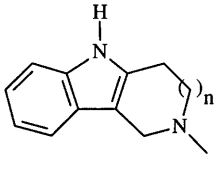
2-(Dimethylaminoethyl)-indole-3-acetic acid (**2**) was prepared by a two step procedure from nitrile **3** obtained by cyanide cleavage of cyclic gramine **9** [7] *via* **10**. Methanolysis of nitrile **3** led to ester **4** which was then subjected to alkaline hydrolysis to afford **2**.

In order to prepare the homolog **5** we envisaged the use of azepino[4,3-*b*]indole **11** following *Hester*'s procedure [8]. Since direct *Fischer* indolization of 1,3-cyclohexandione failed, we adopted the two step procedure of *Felton* [9]: isolation of phenylhydrazone **13** and sulfuric acid catalyzed cyclization led to tetrahydrocarbazolone **14** in 50% yield. The relatively poor yield can be explained by the instability of **13** in acidic medium and the hydrosolubility of the enol form **14b**. Indeed, the lack of a CO band in its IR spectrum and a keto carbon signal in its ^{13}C NMR spectrum confirmed the almost complete enolization of **13** and **14**. Oxime **15** obtained nearly quantitatively was subjected to *Hester*'s conditions [8] to give lactam **16** in poor yield (38%).

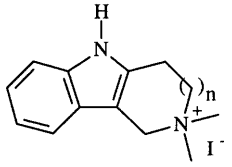
Optimization of the *Beckmann* rearrangement revealed that the yield depended on the reaction conditions. Finally, oxime **15** was transformed almost quantitatively



	R	*n*
2	COOH	1
3	CN	1
4	COOMe	1
5	COOH	2
6	CN	2
7	COOMe	2
8	$CONH_2$	2

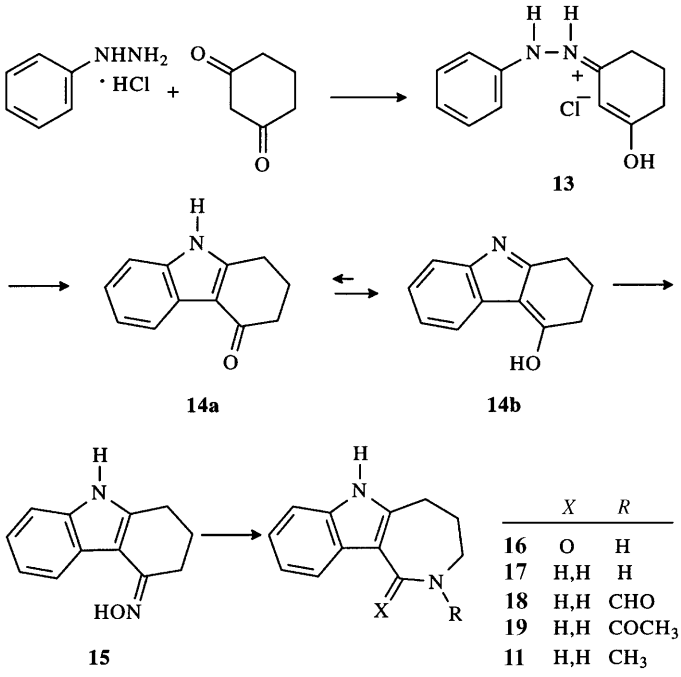


	n
9	1
11	2



	n
10	1
12	2

Scheme 1



Scheme 2

(97%) into the lactam **16** by heating (30 min) in polyphosphoric acid. Transformation of **16** into the tertiary amine **11** involved a hydride reduction – formylation – hydride reduction sequence (**16**→**17**→**18**→**11**) as described in Ref. [8]. It is interesting to note that the mixed formic-acetic anhydride mediated *N*-formylation of **17** was accompanied by some acetylation (**19** in 26% yield). Some technical modifications on *Hester*'s seven-step procedure [8] allowed an improvement of the total yield from 4 to 18% and full characterization of the intermediates.

Conversion of **11** into the indole-3-acetonitrile derivative **6** was performed by quaternization followed by cyanide ring opening of the corresponding gramine methoiodide **12** in 83% yield. Since direct hydrolysis of nitrile **6** to carboxylic acid **5** gave low yield, we applied a stepwise procedure: heating of **6** in saturated HCl-methanol led to methyl ester **7**, which was then saponified by means of $Ba(OH)_2$ to give **5** in 82% overall yield. In some cases, besides ester **7** amide **8** was also isolated as a side product (8%).

In conclusion, some derivatives of **1** could be prepared by means of common chemical reactions; the evaluation of their phytoactivity is in progress.

Experimental

Melting point were determined on a Reichert Thermovar hot-stage apparatus and are uncorrected. UV spectra were recorded in MeOH solution on a UNICAM 8700 UV/Vis spectrophotometer. IR (film) spectra were measured with a Bomem FTIR instrument. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were acquired on a Bruker AC 300 spectrometer using *TMS* as internal standard.

Mass spectra were recorded with a VG Autospec apparatus. Reactions were monitored using Merck TLC aluminium sheets (Kieselgel 60 F_{254}). Elemental analyses were found to be in satisfactory agreement with the calculated values.

2-(2-N,N-Dimethylaminoethyl)-indole-3-acetic acid (**2**; $C_{14}H_{18}N_2O_2$)

A mixture of 0.47 g **4** (1.80 mmol), 1.43 g $Ba(OH)_2 \cdot 8H_2O$ (4.53 mmol) in 8 cm^3 methanol, and 8 cm^3 water was stirred at room temperature for 4 h. After evaporation of the methanol, the solution was acidified ($pH = 5$–6) with 10% H_2SO_4. The precipitate was filtered off, and the filtrate was evaporated to dryness to obtain 0.38 g (86%) **2** as a white powder.

M.p.: 107–109°C; UV (CH_3OH): $\lambda_{max} = 222$, 285, 292 nm; IR (KBr): $\nu = 3247$, 1586, 1486 cm^{-1}; ^1H NMR ($CDCl_3$+*DMSO*-d_6, 300 MHz): $\delta = 2.33$ (6H, s), 2.81–2.98 (4H, m), 3.51 (2H, s), 5.12 (1H, br), 6.91 (1H, t, $J = 7$ Hz), 6.99 (1H, t, $J = 7$ Hz), 7.22 (1H, d, $J = 7$ Hz), 7.48 (1H, d, $J = 7$ Hz), 10.60 (1H, br) ppm; ^{13}C NMR ($CDCl_3$+*DMSO*-d_6, 75 MHz): $\delta = 22.5$, 32.5, 43.6, 43.6, 57.7, 107.1, 110.7, 118.3, 118.5, 120.8, 128.1, 133.1, 135.4, 175.8 ppm; MS: *m/z* (%) = 246 (M^+, 48), 202 (8), 156 (100); HREIMS: calcd. 246.136417, found 246.136359.

Methyl-2-(2-(2-N,N-dimethylaminoethyl)-indol-3-yl)-ethanoate (**4**; $C_{15}H_{20}N_2O_2$)

A solution of 1.00 g **3** [7] (4.40 mmol) in 10 cm^3 methanol was heated under reflux in the presence of 25 cm^3 saturated HCl-methanol for 7 h. After evaporation of the solvent, the residue was rendered alkaline with 10% Na_2CO_3 to $pH = 9$, extracted with 3×30 cm^3 $CHCl_3$, dried (Na_2SO_4), filtered, and evaporated to obtain 0.82 g (72%) **4** as a yellowish oil which was partially cristallized from ether-hexan.

M.p.: 63–64°C; UV (CH_3OH): $\lambda_{max} = 222$, 281, 293 nm; IR (KBr): $\nu = 3420$, 1732, 1462 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 2.82$ (6H, s), 3.27 (2H, t, $J = 8$ Hz), 3.38 (2H, t, $J = 8$ Hz), 3.63 (3H, s), 3.82 (2H, s), 6.99 (1H, t, $J = 7.5$ Hz), 7.01 (1H, t, $J = 7.5$ Hz), 7.33 (1H, d, $J = 7.5$ Hz), 7.42 (1H, d, $J = 7.5$ Hz), 11.36 (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 21.0$, 29.5, 42.2, 42.2, 51.9, 55.9, 104.8, 111.1, 118.1, 118.9, 121.2, 127.9, 132.4, 135.6, 172.3 ppm; MS: *m/z* (%) = 260 (M^+, 65), 201 (19), 156 (36), 143 (100); HREIMS: calcd. 260.152478, found 260.150406.

2-(3-N,N-Dimethylaminopropyl)-indole-3-acetic acid (**5**; $C_{15}H_{20}N_2O_2$)

A mixture of 0.74 g **7** (2.70 mmol), 2.46 g $Ba(OH)_2 \cdot 8H_2O$ (7.80 mmol) in 8 cm^3 methanol, and 8 cm^3 water was stirred at room temperature for 3 h. After evaporation of the methanol, CO_2 was bubbled through the solution, the precipitate was filtered off, and the filtrate was extracted with 3×15 cm^3 $CHCl_3$. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness to obtain 0.68 (97%) **5** as a white-grey powder.

M.p.: 198–202°C; UV (CH_3OH): $\lambda_{max} = 224$, 282, 291 nm; IR (KBr): $\nu = 3215$, 1572, 1446 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 1.83$ (2H, quint, $J = 7$ Hz), 2.23 (6H, s), 2.35 (2H, t, $J = 7$ Hz), 2.74 (2H, t, $J = 7$ Hz), 3.56 (2H, s), 5.72 (1H, br), 6.94 (1H, t, $J = 8$ Hz), 7.01 (1H, t, $J = 8$ Hz), 7.28 (1H, d, $J = 8$ Hz), 7.44 (1H, d, $J = 8$ Hz), 10.73 (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 23.4$, 26.7, 30.6, 44.6, 44.6, 58.2, 104.6, 110.5, 117.9, 118.2, 120.1, 128.5, 135.4, 136.8, 173.8 ppm; MS: *m/z* (%) = 260 (M^+, 6), 216 (34), 170 (32); HREIMS: calcd.: 260.152478, found 260.150406.

3-(3-Cyanomethylindol-2-yl)-N,N-dimethylpropylamine (**6**; $C_{15}H_{19}N_3$)

A solution of 4.12 g **12** (12.04 mmol) in 50 cm^3 ethanol was refluxed with a solution of 2.20 g KCN (33.8 mmol) in 10 cm^3 water for 3 h. After evaporation of the solvent, the residue was dissolved in

50 cm^3 water, rendered alkaline under cooling with 10% aq NaOH, and extracted with 3×50 cm^3 ether. The combined organic layers were washed with 30 cm^3 water, dried (Na_2SO_4), filtered, and evaporated to afford 2.49 g (86%) **6** as a crystalline product.

M.p.: 95–97°C (ether); UV (CH_3OH): λ_{max} = 221, 274, 279, 290 nm; IR (KBr): ν = 3138, 2243, 1462 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 300 MHz): δ = 1.82 (2H, t, J = 7 Hz), 2.19 (6H, s), 2.26 (2H, t, J = 7 Hz), 2.81 (2H, t, J = 7 Hz), 3.99 (2H, s), 7.05 (1H, t, J = 8 Hz), 7.12 (1H, t, J = 8 Hz), 7.36 (1H, d, J = 8 Hz), 7.47 (1H, d, J = 8 Hz), 11.09 (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): δ = 12.1, 23.1, 27.2, 45.3, 45.3, 58.4, 99.5, 111.0, 117.4, 118.9, 119.6, 121.0, 127.2, 135.4, 137.7 ppm; MS: *m/z* (%) = 241 (M^+, 69), 196(3), 181 (2), 169(3), 156 (2).

Methyl-(2-(3-N,N-dimethylaminopropyl)-indol-3-yl)-ethanoate (**7**; $C_{16}H_{22}N_2O_2$)

A cold (−15°C) solution of 2.60 g **6** (10.77 mmol) in 180 cm^3 saturated HCl-methanol was allowed to stand for 72 h. After warming to room temperature, 120 cm^3 methanol and 5 cm^3 water were added, and the reaction mixture was heated under reflux for 3 h. After evaporation to dryness, the residue was dissolved in 20 cm^3 water, rendered alkaline with 30% NaOH under cooling, and extracted with 3×40 cm^3 $CHCl_3$. The organic layers were dried (Na_2SO_4), filtered, evaporated, and purified by flash chromatography (eluant: $CHCl_3$:MeOH:NH_4OH = 98:2:0.1 → 70:30:2) to afford 2.50 g (85%) **7** and 0.23 g (8%) **8**.

7: M.p.: 77–77.5°C (ether); UV (CH_3OH): λ_{max} = 223, 282, 290 nm; IR (KBr): ν = 3395, 1734, 1464 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 300 MHz): δ = 1.80 (2H, quint, J = 7.5 Hz), 2.20 (6H, s), 2.26 (2H, t, J = 7.5 Hz), 2.73 (2H, t, J = 7.5 Hz), 3.59 (3H, s), 3.71 (2H, s), 6.97 (1H, t, J = 8 Hz). 7.04 (1H, t, J = 8 Hz), 7.30 (1H, d, J = 8 Hz), 7.42 (1H, d, J = 8 Hz), 11.90 (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): δ = 23.4, 27.3, 29.7, 45.2, 45.2, 51.6, 58.6, 103.3, 110.7, 117.8, 118.5, 120.4, 128.3, 135.5, 137.6, 172.2 ppm; MS; *m/z* (%) = 274 (M^+, 64), 229 (11), 215 (17), 203 (44), 170 (57).

(2-(3-N,N-dimethylaminopropyl)-indol-3-yl)-methyl-carboxamide (**8**; $C_{15}H_{21}N_3O$)

Amorphous; UV (CH_3OH): λ_{max} = 222, 282, 290 nm; IR (KBr): ν = 3455, 3271, 1668, 1464 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 300 MHz): δ = 1.74 (2H, t, J = 7 Hz), 2.24 (6H, s), 2.33 (2H, t, J = 7 Hz), 2.78 (2H, t, J = 7 Hz), 3.50 (2H, s), 6.83 (2H, br), 6.95 (1H, t, J = 8 Hz), 7.02 (1H, t, J = 8 Hz), 7.29 (1H, d, J = 8 Hz), 7.50 (1H, d, J = 8 Hz), 10.80 (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz); δ = 23.5, 27.2, 31.5, 45.1, 45.1, 58.6, 105.1, 110.6, 118.1, 118.3, 120.3, 128.5, 135.5, 137.3, 173.5 ppm; MS: *m/z* (%) = 259 (M^+, 73), 215 (10), 201 (15), 186 (34), 170 (73).

2-Methyl-1,2,3,4,5,6-hexahydroazepino[4,3-b]indole (**11**; $C_{13}H_{16}N_2$)

To a stirred solution of 1.41 g **18** (6.58 mmol) in 120 cm^3 *THF*, 1.36 g $LiAlH_4$ (35.8 mmol) was added in portions, and the reaction mixture was heated under reflux for 45 min. The excess of $LiAlH_4$ was destroyed with sat. aq Na_2SO_4, filtered, and washed with 4×20 cm^3 *THF*. The filtrate was concentrated to 10–20 cm^3, diluted with 60 cm^3 water, and extracted with 3×30 cm^3 $CHCl_3$. The combined organic layers were dried (Na_2SO_4), filtered, evaporated to dryness, and the residue was crystallized from cold ethylacetate to yield 1.13 g (86%) **11** as a white powder.

M.p.: 165–170°C (EtOAc) (Ref. [8]: m.p.: 168.5–170°C); UV (CH_3OH): λ_{max} = 221, 281, 289 nm; IR (KBr): ν = 3136, 1448 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 300 MHz): δ = 1.80 (2H, m), 2.32 (3H, s), 2.87 (4H, m), 3.74 (2H, s), 6.93 (1H, t, J = 8 Hz), 6.99 (1H, t, J = 8 Hz), 7.25 (1H, d, J = 8 Hz), 7.39 (1H, d, J = 8 Hz), 10.80 (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): δ = 25.5, 27.6, 44.9, 52.7, 60.6, 109.6, 110.7, 117.0, 118.3, 119.8, 128.5, 134.4, 138.2 ppm; MS: *m/z* (%) = 200 (M^+, 65), 199 (47), 157 (100), 156 (52).

2,2-Dimethyl-1,2,3,4,5,6-hexahydroazepino[4,3-b]indol-2-ium-iodide (**12**; $C_{14}H_{19}N_2I$)

To a solution of 2.63 g **11** (13.13 mmol) in 25 cm^3 methanol, 5.7 cm^3 methyl iodide (91.2 mmol) were added, and the solution was stirred at room temperature for 30 min. After evaporation of the solvent the residue was crystallized from a mixture of methanol-ether to obtain 4.35 g (97%) quaternary iodide **12** as a white crystals.

M.p.: 186.5–189°C (MeOH-ether); UV (CH_3OH): $\lambda_{max} = 218$, 280, 288 nm; IR (KBr): $\nu = 3212$, 1470 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 2.11$ (2H, m), 3.04 (2H, m), 3.11 (6H, s), 3.81 (2H, m), 4.89 (2H, s), 7.04 (1H, t, $J = 8$ Hz), 7.07 (1H, t, $J = 8$ Hz), 7.37 (1H, d, $J = 8$ Hz), 7.72 (1H, d, $J = 8$ Hz), 11.42 (1H, br) ppm: ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 20.3$, 23.8, 48.8, 48.8, 57.7, 65.9, 98.3, 109.5, 115.5, 117.8, 119.1, 126.6, 132.7, 139.2 ppm; MS: *m/z* (%) = 214 (M-HI, 55), 202 (5), 199 (4), 170 (42), 157 (19), 144 (31).

3-Phenylhydrazonocyclohexan-1-one (**13**; $C_{12}H_{14}N_2O$)

A mixture of 6.0 g 1,3-cyclohexanedione (53.5 mmol) and 7.74 g phenylhydrazine hydrochloride (53.5 mmol) in 16 cm^3 50% aqueous acetic acid was heated under stirring at 40°C for 5 min. The reaction mixture was allowed to crystallize at room temperature for 2 h, filtered, washed with acetonitrile, and dried to give 11.9 g (93%) **13** as a hydrochloride salt.

M.p.: 166–169°C (CH_3CN); UV (CH_3OH): $\lambda_{max} = 204$, 230, 283 nm; IR (KBr): $\nu = 3166$, 1570, 1534 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 1.97$ (2H, quint, $J = 6.5$ Hz), 2.57 (2H, t, $J = 6.5$ Hz), 2.82 (2H, t, $J = 6.5$ Hz), 6.09 (1H, s), 6.83 (1H, d, $J = 8$ Hz), 6.93 (1H, t, $J = 8$ Hz), 7.06 (1H, d, $J = 8$ Hz), 7.24 (1H, t, $J = 8$ Hz), 7.27 (1H, t, $J = 8$ Hz), 10.43 (1H, br), 12.21 (1H, br), ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 20.7$, 26.3, 30.6, 93.5, 113.5, 114.8, 120.7, 129.1, 129.3, 146.1, 176.9, 190.4 ppm; MS: *m/z* (%) = 202 (M^+, 100), 175 (14), 163 (10), 145 (13), 130 (12).

1,2,3,4-Tetrahydrocarbazol-4-one (**14**; $C_{12}H_{11}NO$)

A degassed solution of 4.0 g **13** (15.2 mmol) in 37 cm^3 water and 15 cm^3 sulfuric acid was heated at 100°C under argon for 1 h. After cooling, the reaction mixture was diluted with 120 cm^3 water and extracted with 6×60 cm^3 CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, evaporated to dryness, and the residue was crystallized from cold ethanol to afford 1.52 g (54%) **14** as a white-grey powder.

M.p.: 221–222°C (EtOH) (Ref. [9]: m.p.: 223°C); UV (CH_3OH): $\lambda_{max} = 216$, 242, 265, 297 nm; IR (KBr): $\nu = 3160$, 1609, 1578, 1462 cm^{-1}; ^1H NMR ($CDCl_3$+*DMSO*-d_6, 300 MHz): $\delta = 2.15$ (2H, quint, $J = 7$ Hz), 2.44 (2H, t, $J = 7$ Hz), 2.97 (2H, t, $J = 7$ Hz), 7.06 (2H, m), 7.38 (1H, m), 8.00 (1H, m), 11.75 (1H, br) ppm; ^{13}C NMR ($CDCl_3$+*DMSO*-d_6, 75 MHz): $\delta = 22.9$, 23.5, 37.9, 111.5, 111.9, 120.3, 121.4, 122.4, 124.6, 136.0, 152.1, 192.9 ppm; MS: *m/z* (%) = 185 (M^+, 82), 157 (100), 146 (28), 134 (27).

1,2,3,4-Tetrahydrocarbazol-4-one-oxime (**15**; $C_{12}H_{12}N_2O$)

A mixture of 2.98 g **14** (16.09 mmol), 1.68 g hydroxylamine hydrochloride (24.18 mmol), 3.28 g sodium acetate trihydrate (24.1 mmol) in 33 cm^3 ethanol, and 15 cm^3 water was heated under reflux for 10 h. After evaporation of the ethanol the remaining crystalline product was filtered, washed with 3×15 cm^3 water, and dried to give 3.11 g (97%) of **15** as white crystals.

M.p.: 205–207°C (dec.) (Ref. [8]: m.p.: 208.5–210°C; UV (CH_3OH): $\lambda_{max} = 226$, 261, 283 nm; IR (KBr): $\nu = 3418$, 3373, 1627, 1565, 1490 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 1.94$ (2H, quint, $J = 6.5$ Hz), 2.70 (2H, t, $J = 6.5$ Hz), 2.82 (2H, t, $J = 6.5$ Hz), 7.03 (1H, t, $J = 8$ Hz), 7.10 (1H, t, $J = 8$ Hz), 7.34 (1H, d, $J = 8$ Hz), 7.92 (1H, d, $J = 8$ Hz), 10.26 (1H, s), 11.22 (1H, br) ppm;

^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 22.1$, 22.6, 22.8, 106.7, 111.1, 119.7, 121.2, 121.4, 124.3, 136.2, 141.6, 152.7 ppm; MS: *m/z* (%) = 200 (M^+, 100), 183 (18), 168 (10).

1,2,3,4,5,6-Hexahydroazepino[4,3-b]indol-1-one (**16**; $C_{12}H_{12}N_2O$)

2.60 g of **15** (12.98 mmol) were added under vigorous stirring to 97 g preheated (110°C) polyphosphoric acid, and the reaction mixture was kept at this temperature for 30 min. Then the viscous mixture was poured into 200 g ice-water and triturated to complete the dissolution of the polyphosphoric acid. After 1 h stirring at room temperature, the suspension was filtered, the solid was washed with $10\times10\,cm^3$ water and subsequently with $7\,cm^3$ aqueous NH_4OH, dried, and recrystallized from ethyl acetate to yield 2.51 g (97%) **16**.

M.p.: 209–210°C (EtOAc) (Ref. [10]: m.p.: 210°C); UV (CH_3OH): $\lambda_{max} = 215$, 228, 251, 281, 288 nm; IR (KBr); $\nu = 3302$, 1626, 1591, 1480 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 300 MHz): $\delta = 2.01$ (2H, m), 3.14 (2H, t, $J = 7$ Hz), 3.24 (2H, q, $J = 7$ Hz), 7.04 (1H, t, $J = 8$ Hz), 7.11 (1H, t, $J = 8$ Hz), 7.32 (1H, d, $J = 8$ Hz), 7.43 (1H, t, $J = 7$ Hz), 8.23 (1H, d, $J = 8$ Hz), 11.45 (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 26.4$, 28.3, 41.1, 106.8, 110.5, 120.1, 121.7, 121.8, 128.9, 135.7, 142.3, 167.9 ppm; MS: *m/z* (%) = 200 (M^+, 100), 183 (5), 170 (82), 158 (23).

1,2,3,4,5,6-Hexahydroazepino[4,3-b]indole (**17**; $C_{12}H_{14}N_2$)

To a stirred suspension of 1.01 g **16** (5.04 mmol) in $400\,cm^3$ dioxane, 2.12 $LiAlH_4$ (55.8 mmol) were added in portions, and the reaction mixture was heated under reflux for 15 h. The excess of $LiAlH_4$ was destroyed with sat. aq Na_2SO_4, filtered, and washed with $8\times50\,cm^3$ dioxane. The filtrate was concentrated to 20–30 cm^3, diluted with 80 cm^3 water, and extracted with $3\times30\,cm^3$ $CHCl_3$. The combined organic layers were dried (Na_2SO_4), filtered, evaporated to dryness, and the residue was crystallized from cold ethanol to yield 0.55 g (59%) **17**. Melting point measurements on an analytically pure sample revealed polymorphism.

M.p.: 168–169°C and 179.5–181°C (EtOH) (Ref. [8]: m.p.: 200–202.5°C); UV (CH_3OH): $\lambda_{max} = 215$, 282, 289 nm; IR (KBr): $\nu = 3416$, 3276, 1621, 1448 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 300 MHz): $\delta = 1.76$ (2H, m). 2.90 (2H, dd, $J_1 = 6$, $J_2 = 7$ Hz), 3.03 (1H, br), 3.06 (2H, dd, $J_1 = 6$, $J_2 = 7.5$ Hz), 3.88 (2H, s), 6.92 (1H, t, $J = 8$ Hz), 6.97 (1H, t, $J = 8$ Hz), 7.24 (1H, d, $J = 8$ Hz), 7.36 (1H, d, $J = 8$ Hz), 10.74 (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = 27.9$, 29.6, 44.5, 52.3, 110.6, 114.1, 117.0, 118.2, 119.8, 127.7, 134.3, 138.0 ppm; MS: *m/z* (%) = 186 (M^+, 82), 168 (8), 158 (85), 157 (100).

1,2,3,4,5,6-Hexahydroazepino[4,3-b]indol-2-carbaldehyde (**18**; $C_{13}H_{14}N_2O$)

To a cold mixture of $1.4\,cm^3$ acetic anhydride (14.84 mmol) and $0.6\,cm^3$ 99% formic acid (15.9 mmol), 0.87 g **17** (4.67 mmol) were added in small portions. The reaction mixture was stirred at room temperature for 14 h. After dilution with $5\,cm^3$ water, the precipitate was extracted with $3\times10\,cm^3$ $CHCl_3$, and the organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by circular chromatography (eluant: CH_2Cl_2:MeOH = 99:1) to obtain 0.73 g (73%) **18** and 0.29 g (26%) **19**.

18. M.p.: 155–157°C (ether) (Ref. [8]: m.p.: 160–161°C); UV (CH_3OH): $\lambda_{max} = 205$, 222, 279, 289 nm; IR (KBr): $\nu = 3260$, 1651, 1472, 1448 cm^{-1}; ^{1}H NMR (*DMSO*-d_6, 300 MHz); $\delta = 1.91$ (2H, m), 2.97 (2H, m), 3.73 (2H, m), (4.64) 4.65 (2H, s), 7.01 (2H, m), 7.28 (1H, d, $J = 8$ Hz), 7.47 (7.52) (1H, d, $J = 8$ Hz), 8.05 (8.20) (1H, s), 10.90 (10.93) (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta =$ (26.0) 26.4, (26.9) 28.5, 37.2 (43.5), (44.8) 50.2, 109.3 (109.7), 110.8, 117.1 (117.2), 118.7, 120.3 (120.5), (126.8) 127.4, 134.3 (134.4), (137.4) 137.7, 161.7 (162.1) ppm (signals in parentheses belong to the minor (20%) rotamer); MS: *m/z* (%) = 214 (M^+, 100), 213 (26), 185 (18), 169 (21), 158 (32), 157 (27).

2-Acetyl-1,2,3,4,5,6-hexahydroazepino[4,3-b]indole (**19**; $C_{14}H_{16}N_2O$)

M.p.: 171–172°C (ether); UV (CH_3OH): $\lambda_{max} = 206$, 223, 282, 290 nm; IR (KBr): $\nu = 3391$, 3251, 1621, 1464 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 1.82$ (2H, m), (1.96) 1.98 (3H, s), 2.94 (2H, m), 3.77 (2H, m), (4.64) 4.67 (2H, s), 7.01 (2H, m), 7.29 (1H, m), (7.44) 7.55 (1H, d, $J = 8$ Hz), (10.86) 10.98 (1H, br) ppm; ^{13}C NMR (*DMSO*-d_6, 75 MHz): $\delta = (21.6)$ 21.7, 25.8 (26.7), 26.8 (27.3), 44.2, 50.9, 110.1 (110.2), (110.7) 111.0, 116.7 (117.3), (118.5) 119.0, (120.1) 120.3, 127.1 (127.6), 134.1 (134.2), (137.3) 138.2, (169.0) 169.2 ppm (signals in parentheses belong to the minor (35%) rotamer); MS: *m/z* (%) = 228 (M^+, 100), 200 (10), 185 (50), 179 (53), 178 (26), 158 (47).

Acknowledgement

An *Europol Agro* doctoral fellowship for *S.-I. B.* is gratefully acknowledged.

References

[1] Parry RJ (1972) In: Houlihan WJ (ed) Indoles, Part 2. In: Weissberger A, Taylor EC (eds) The Chemistry of Heterocyclic Compounds, vol 25. Wiley, New York, pp 9–15; Schneider EA, Wightman F (1978) In: Letham DS, Higgins TJV, Goodwin PB (eds) Phytohormones and Related Compounds. Elsevier, North-Holland, Amsterdam; Takahashi N (1986) Chemistry of Plant Hormones. CRC, Boca Raton; Samizu K, Ogasawara K (1994) Synlett 499; Guan X, Borchardt RT (1994) Tetrahedron Lett **35**: 3013

[2] Kaethner TM (1977) Nature **267**: 19; Lehmann PA (1978) Chem Biol Interactions **20**: 239; Katekar GF (1979) Phytochemistry **18**: 223; Katekar GF, Geissler AE (1983) Phytochemistry **22**: 27; Ramek M, Tomic S, Kojic-Prodic B (1996) Int J Quantum Chem 60

[3] Napier RM, Venis MA (1990) J Plant Growth Regul **9**: 113; Hesse T, Palme K Biochemical Mechanisms Involved in Plant Growth Regulation. In: Smith CJ, Gallon J, Chiatante D, Zocchi G (eds) Proceedings of the Phytochemical Society of Europe, vol 36. Clarendon Press, Oxford, pp 103–122

[4] Edgerton MD, Tropsha A, Jones AM (1994) Phytochemistry **35**: 1111

[5] Hoffmann OL, Fox SW, Bullock MW (1952) J Biol Chem **196**: 437; Porter WL, Thimann KV (1965) Phytochemistry **4**: 229; Schlender KK, Bukovac MJ, Sell HM (1966) Phytochemistry **5**: 133

[6] Parry RJ (1972) In: Houlihan WJ (ed) Indoles, Part 2. In: Weissberger A, Taylor EC (eds) The Chemistry of Heterocyclic Compounds, vol 25. Wiley, New York, pp 200–203

[7] Sapi J, Grébille Y, Laronze J-Y, Lévy J (1992) Synthesis 383

[8] Hester JB (1967) J Org Chem **32**: 3804

[9] Clemo GR, Felton DGI (1951) J Chem Soc 700

[10] Teuber HJ, Cornelius D, Wölcke U (1966) Liebigs Ann Chem **696**: 116

Received March 12, 1999. Accepted (revised) April 7, 1999