Woodinine and its Stereomers - Absolute Configuration

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Received August 6, 1992

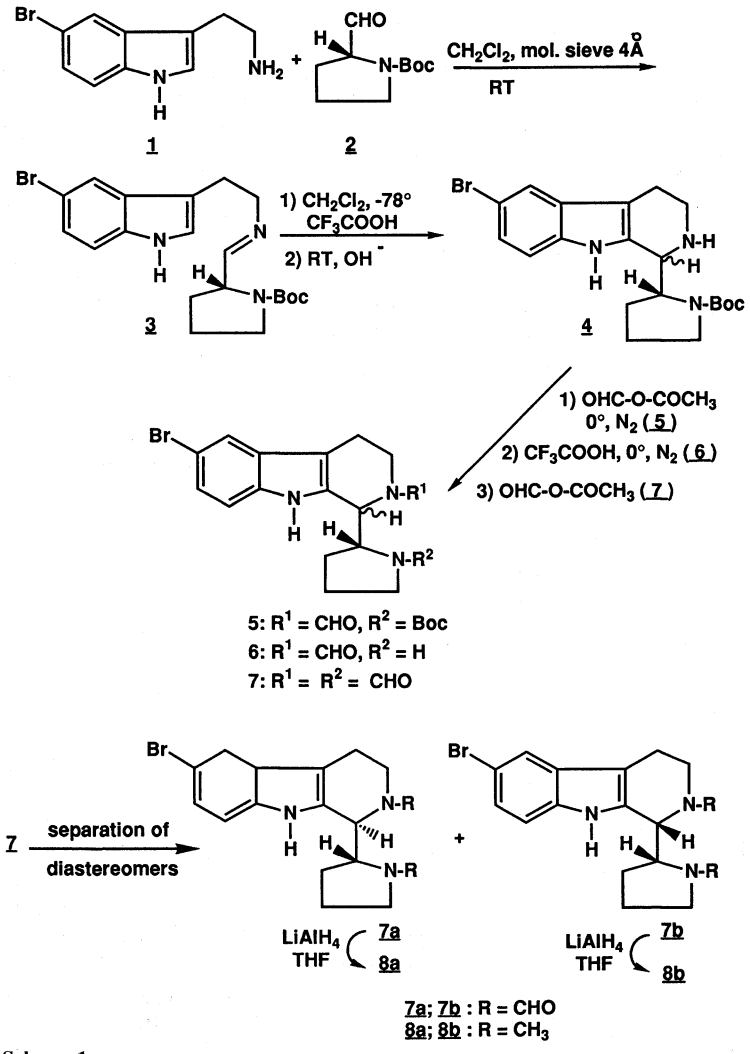
The synthesis of all the four stereomers of the alkaloid woodinine (**12a**)[1] is described and the stereochemical conclusions of *Païs*[3] and *Still*[6] are discussed. The absol. configurations of woodinine (**12a**) and its diastereomer **8b** are unequivocally deduced from the pertinent piperazinediones **16** and **17**.

Woodinin und seine Stereomeren - Absolute Konfiguration

Die Synthese aller vier Stereomerer des Alkaloids Woodinin (**12a**)[1] wird beschrieben, die stereochemischen Rückschlüsse von *Païs*[3] bzw. *Still*[6] werden diskutiert. Anhand der Piperazindione **16** und **17** wird die absol. Konfiguration von Woodinin (**12a**) und des Diastereomers **8b** bewiesen.

Recently we have described the synthesis of the alkaloid woodinine (**12a**, Scheme 2)[1]. The key step was the condensation of 5-bromotryptamine (**1**) with (*S*)-(-)-*N*-Boc-pyrrolidine-2-carboxaldehyde[1].

When we condensed 5-bromotryptamine (**1**) with *R*-(+)-*N*-Boc-pyrrolidine-2-carboxaldehyde (**2**) (Scheme 1), prepared from D-proline as described for the *S*-enantiomer[1], we



Scheme 1

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have obtained the *Schiff*-base **3** which was cyclized under the condi-tions cited[1] affording the diastereomers of compound **4**. These *sec.* amines were *N*-formylated to compounds **5**. - Deviating from our earlier procedure[1] **5** was hydrolyzed by CF_3COOH to amine **6** (this hydrolysis did not work with compound **4**; here a useless mixture of compounds arose). After a second formylation (cpd. **7**) the diastereomers were separated by flash-chromatography, whilst all our efforts to separate cpds. **5** and **9** (see below, Scheme 2) failed.

Diastereomers **7a** and **7b** were reduced with $LiAlH_4$ within 1 h producing the enantiomer **8a** of natural woodinine (**12a**) and its 1-(*R*)-2'-(*R*)-diastereomer **8b**. - Woodinine (**12a**) and its stereomers will be tested by microbiologists for antibacterial activity in comparison with woodinine (**12a**) which is effective against *Mycobacterium tuberculosis*[2].

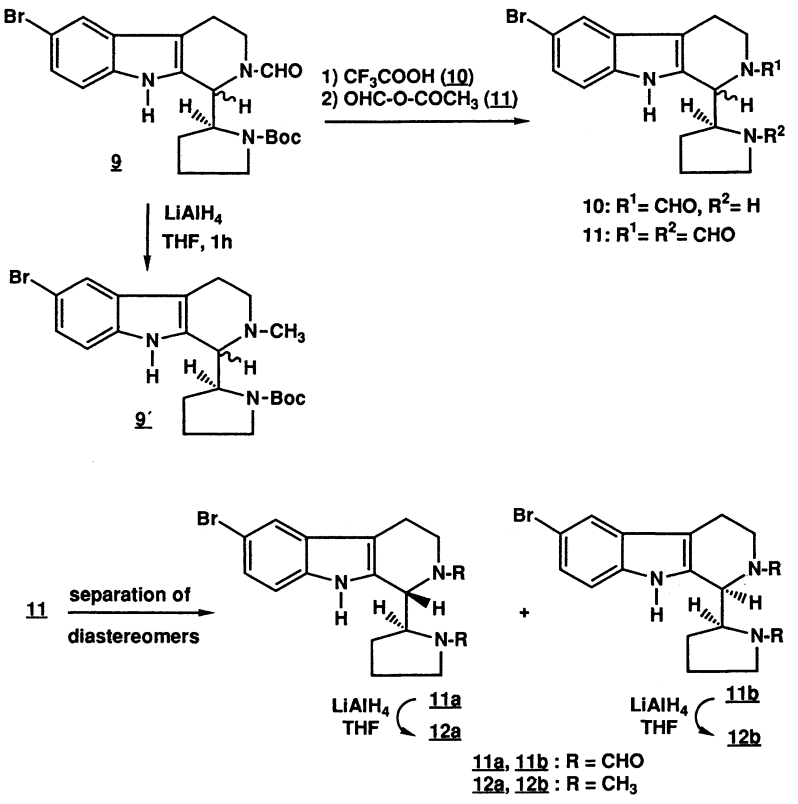
Hydrolytic removal of the *N*-Boc-protecting group with subsequent formylation to **7**, e.g. (Scheme 1) followed by reduction is superior to direct reduction of *N*-formyl-*N*'-Boc-compounds (**5**, e.g.) with $LiAlH_4$[1]) (mild reduction of a pyrrolidine-*N*-Boc/piperidine-N-CHO-derivative (**9**[1], e.g.) with $LiAlH_4$ in refluxing tetrahydrofurane for 1 h reduces the *N*-CHO-increment leaving the *N*-Boc-protecting group unaffected, so yielding **9'**). Therefore, we used the route *via* the bis-formyl compounds also for the preparation of natu-ral woodinine (**12a**). - Separation of the *N,N'*-bis-formyl compounds **11** (mixture of diastereomers with *S*-configuration in the pyrrolidine increment, obtained from cpd. **9** *via* amine **10**) and subsequent $LiAlH_4$-reduction afforded woodinine (**12a**) and the enantiomer **12b** of diastereomer **8b**. By this route cpd. **12b** (C-1-epimer of natural woodinine **12a**) which was available in trace quantities only according to our earlier procedure[1] (cpd. 9a in lit.[1]) can be obtained in 95% yield. - To our knowledge epiwoodinine (**8b**) or its enantiomer **12b** have not yet been found in nature.

Stereochemistry

Concerning the stereochemistry of woodinine (**12a**) some questions arise from the published data:

Mme *Païs* et al.[3] present a formula of woodinine (cpd. 2 in their publication[3]) indicating α-configuration for H-1 of the tetrahydro-β-carboline ring. On the other side, however, they point out: "...la courbe de dc, qui présente un effet Cotton positif à 243 nm, permet de préciser que l'hydrogene en 1 est en position β"[3]. - *Païs* quotes *Rinehart Jr.* et al.[4] who describe structure elucidations of eudistomines and their O-acetyl derivatives, respectively (see cpds. 3 and 4 in lit.[4]): "...The CD spectra (MeOH) of 3 and 4 show a positive Cotton effect in the 240-300 nm region, indicating an α-configuration for H-1." So *Rinehart's* statement is contradictory to *Païs'* text but corroborates her formula shown[3].

Païs[3] cites *Bláha* et al.[5] who deal with 5,16-cyclocorynane alkaloids. *Bláha* and coworkers represent the CD-spectrum of "(+)"-1-methyl-1,2,3,4-tetrahydro-β-carboline with α-configuration for H-1 (called "3αH" by *Bláha* because H-1 of tetrahydro-β-carbolines is numbered H-3 in 5,16-cyclocorynanes): this spectrum clearly indicates a positive Cotton effect at about 240 nm. Unfortunately these data cannot be used for comparison because in the Experimental Part of *Bláha's* publication[5] "3βH" configuration is attributed to "(+)"-1,2,3,4-tetrahydroharmane (= 1-methyl-1,2,3,4-tetrahydro-β-carboline). This is a contradiction in terms. So, only the cyclocorynanes with α-configuration for H-3 can be used for correlation:



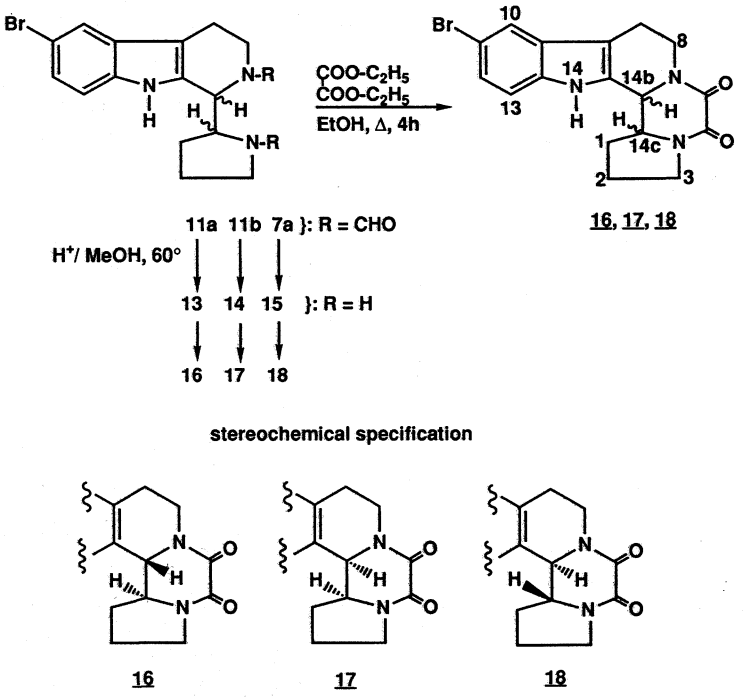
Scheme 2

"In the whole series, the absolute configuration on the $C_{(3)}$ atom is the same (S),"...[5]). - It should be realized, however, that these heterocycles contain the C-H-increment under consideration as part of an annelated ring system. This holds true also for the eudistomines[4]).

In 1991 *Still* et al.[6]) have reported on the synthesis of woodinine (**12a**) and of its epimer, starting from L-prolinal. *Still*[6]) expected to get woodinine (**12a**) as the main diastereomer: "Based upon several known diastereoselective *Pictet-Spengler* reactions with chiral α-amino aldehydes it appears that...D-amino aldehydes give the major product having the C-1 hydrogen in the α-position while the L-aldehydes...give the major product having the C-1 hydrogen β,...". - This assumption proved to be correct: 55% of woodinine (**12a**) - identified by comparison of NMR-data and optical rotation with *Païs'* data[3]) - and 7% of the C-1-α-epimer were isolated[6]). *Still's* synthesis[6]) clearly indicates that the absol. configuration at C-2' (pyrrolidine increment) must be *S*, the absol. configuration at C-1 (tetrahydro-β-carboline ring) remained to be established. Because *Still*[6]) had both diastereomers at hand he was able to correlate both stereomers of woodinine with the diastereomers of the (twofold primary) amines 1-(piperidin-2-yl)-1,2,3,4-tetrahydro-β-carboline[7]). *Still* et al. "feel that compounds (woodinine and its diastereomer) probably exist in solution as hydrogen-bonded structures,"[6]) (H-bond between NH of the indole part and the *tert.* amine of the pyrrolidine group).

We have some concerns about a H-bridge because neither protonation of the pyrrolidine- and the piperidine-N-atom nor deuteriation of the indole-NH-group (yielding indole-ND) influenced the shape of the 1-H-signal: the configuration of woodinine (**12a**) may be independent of a H-bridge. - Based on *Dreiding* models *Still* et al.[6]) correlate the coupling constants for H-1 of woodinine (**12a**) ("singlet at δ = 3.52 for the C-1 H"[6]); "3,60 (1H, s large)"[3]) (French word, meaning broad s)) and that of woodinine epimer ("doublet at δ = 3.17 (J = 10.0 Hz)"[6]) with the coupling constants of the piperidin-2-yl-tetrahydro-β-carbolines[7]) (see above) and deduced 1-(*R*)-2'-(*S*)-configuration for woodinine (**12a**) and 1-(*S*)-2'-(*S*)-configuration for its diastereomer **12b**. The broad singlet in **12a** observed by *Païs*[3]), *Still*[6]), and one of us[1]) may hide a coupling constant of 4-6 Hz, especially because 1-H may couple with the N-CH_3-group: this line broadening, caused by the quadrupol relaxation of the ^{14}N-nucleus attached to the C-H-proton does not allow exact determination of a ^3J-coupling[8]). Determination of the absol. configuration at a center of chirality in the neighbourhood of a chiral center of known absol. configuration by ^1H-NMR-correlation, however, requires exact determination of the pertinent coupling constant.

This situation prompted us to check the stereochemical aspects of woodinine (**12a**) and its epimer. - We inhibited free rotation around the C-1 - C-2'-bond by cyclization adopting *Dreiding's* strategy[9]) by twofold reaction of the secondary amines **13**, **14**, and **15** (obtained by hydrolysis of **11a**, **11b**, and **7a**) (Scheme 3) with diethyl oxalate, leading to the piperazinediones **16**, **17** and **18**. Because the piperazin-**di**-on-substructure comprises two sp^2-hybridized C-atoms, we had not to bother about conformations as described by *Misztal*[7]). In the piperazinedione **16** 14b-H resonates at δ = 5.03 ppm as a doublet with ^3J = 10.7 Hz. - In the epimer **17** 14b-H shows a doublet at δ = 5.46 ppm with ^3J = 4.9 Hz. According to the *Karplus-Conroy*-curve 10.7 Hz correspond to either 0° or 180°; 4.87 Hz to 40° or 130°. - We discriminated between the two possibilities by NOE-experiments: irradiation into the doublet at δ = 5.03 ppm (14b-H) of **16** increases the intensity of the indole NH-singlet at δ = 10.96 ppm. The multiplet of 14c-H was not influenced indicating that 14b-H and 14c-H are nearly perpendicular to each other. - Similar NOE-measurements with the epimer **17** show that irradiation into the doublet of 14b-H at δ = 5.46 ppm increased the intensity of the 14c-H-multiplet, indicating *cis*-standing protons at C-14b and C-14c.



Scheme 3

Irradiation into the NH-frequency of **17** at δ = 10.98 ppm only increases the intensity of the 13-H doublet at δ = 7.38 ppm.

Homo-decoupling of 14c-H of **16** converts the doublet of 14b-H to a singlet (besides decoupling of the signal at 3.5 ppm). Irradiation into the doublet of 14b-H at δ = 5.03 ppm simplifies the multiplet of 14c-H at δ = 3.69 ppm.

Because the bis-formamides **11a** and **11b** are unequivocally correlated as well with the bis-amines **13** and **14** as with woodinine (**12a**) and the enantiomer **12b** of **8b** (no attacks at the centers of chirality) the stereochemistry of **12a** and **12b** is definitely established. Our results secure the conclusions of *Still* and coworkers[6].

Financial support of this project by Fonds der chemischen Industrie is gratefully acknowledged.

Experimental Part

General remarks: lit.[1].- [α]-values at D-line and 20°C, if not otherwise stated.

5-Bromotryptamine (**1**): lit.[1] and lit. cited there.

(R)-(+)-N-(tert-Butoxycarbonyl)-pyrrolidine-2-carboxaldehyde (**2**)

2 was prepared as described for its enantiomer[1] starting from D-proline. Data: lit.[1] and lit. cited there.

(R)-β-(5-Bromoindol-3-yl)-N-[N-(tert-butoxycarbonyl)-pyrrolidin-2-yl-methylidene]-ethylamine (**3**) *and 1-[(R)-(N-tert-Butoxycarbonyl)pyrrolidin-2-yl]-6-bromo-1,2,3,4-tetrahydro-β-carboline* (**4**), *mixture of diastereomers*

Cf. lit.[1].- Formation of the imine group by molecular sieve improves the yield: The solution of 1.25 g (5.22 mmol) **1** and 1.04 g (5.22 mmol) **2** in 40 ml of absol. CH_2Cl_2 was stirred with molecular sieve 4 Å under N_2 for 1 h at room temp. After filtration and washing with absol. CH_2Cl_2, the solution of imine **3** was cooled to -78°C. 1.3 ml (10.5 mmol) F_3CCOOH were added dropwise during 2.5 h at -78°C, the solution was allowed to warm to +20°C during 4 h under stirring, poured into ice water, alkalized with 2N Na_2CO_3 at 0°C, washed with water (2 x 20 ml), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was dried at room temp. and 0.05 mm Hg: yellowish amorphous powder of β-carbolines **4**. 2.18 g (99%).- M.p. (crude product) 68-70°C.- Analytical data: lit.[1].

1-[(R)-(N-tert-Butoxycarbonyl)pyrrolidin-2-yl]-6-bromo-2-formyl-1,2,3,4-tetrahydro-β-carboline (**5**), *mixture of diastereomers*

This mixture of cpds. **5** was prepared as described for the diastereomers with *S*-configuration at pyrrolidine-C-2[1].- Analytical data: lit.[1].

1-[(R)-Pyrrolidin-2-yl]-6-bromo-2-formyl-1,2,3,4-tetrahydro-β-carboline (**6**), *mixture of diastereomers*

To the solution of 940 mg (2.09 mmol) **5** in 10 ml of absol. $CHCl_3$ 10 ml of F_3CCOOH were added drop by drop at 0°C under N_2 and stirring. After 9 h at 0°C the solution was diluted with ice water and basified with 2N Na_2CO_3. The org. layer was separated, the aqueous phase was extracted with $CHCl_3$ (2 x 15 ml). The combined org. phases were dried (Na_2SO_4) and evaporated to dryness *in vacuo*: yellow powder which was dried at room temp. and 0.05 mg Hg.: 710 mg (97%) which were directly converted to cpds. **7**.- IR of **6**-mixture (KBr): $\tilde{\nu}$ = 3436 (br., NH); 1678 cm^{-1} (CO).

1-[(R)-N-Formylpyrrolidin-2-yl]-6-bromo-2-formyl-1,2,3,4-tetrahydro-β-carbolines (**7**), *mixture of diastereomers, and separation of 7-diastereomers*

To the solution of 697 mg (2 mmol) crude **6** (see above) in 15 ml of absol. CH_2Cl_2 were added under N_2 2.5 ml acetic-formic anhydride[1] drop by drop at 0°C under stirring. After further 30 min at 0°C the mixture was alkalized by Na_2CO_3-solution to pH = 9, and the org. phase was separated, dried (Na_2SO_4), and evaporated: 736 mg white amorphous solid (98%).

7-Diastereomers were separated by flash-chromatography (SiO_2; CH_2Cl_2:hexane:MeOH = 82:15:3 - v/v).

7a: 582 mg, colourless crystals, m.p. 215-220°C (dcp.) (EtOH, Et_2O, hexane).- [α] = +126.5° ($CHCl_3$, c = 0.6).- $C_{17}H_{18}BrN_3O_2$ (376.3) Calc. C 54.3 H 4.82 N 11.2 Found C 54.0 H 4.86 N 11.0.- IR (KBr): $\tilde{\nu}$ = 3278 (NH); 1665 cm^{-1} (CO).- MS (70 eV): m/z = 377/375 (10%, $M^{+\bullet}$), 279/277 (9; M - $C_5H_8NO)^+$, 251/249 (279/277 - CO)$^+$, 98 (100; $C_5H_8NO)^+$, 70 $(C_4H_8N)^{+\bullet}$.- (^{1}H-NMR-spectra could not be interpreted, probably on account of ring chain tautomers or rotamers).

7b: 103 mg, m.p. 201-206°C (dcp.) (EtOH, Et_2O, hexane).- [α] = -76.5° ($CHCl_3$, c = 0.6).- $C_{17}H_{18}BrN_3O_2$ (376.3) Calc. C 54.3 H 4.82 N 11.2 Found C 54.9 H 4.82 N 11.2.- IR (KBr): $\tilde{\nu}$ = 3268 (NH); 1655 cm^{-1} (CO).

(S)-1-[(R)-N-Methylpyrrolidin-2-yl]-6-bromo-2-methyl-1,2,3,4-tetrahydro-β-carboline (***8a***)

The solution of 400 mg **7a** in 6 ml of absol. tetrahydrofurane (THF) was added drop by drop at 0°C to the suspension of 300 mg $LiAlH_4$ in 6 ml of absol. THF under N_2. After reflux for 1.5 h the mixture was hydrolyzed by Et_2O/water at 0°C, the org. phase was dried (Na_2SO_4) and evaporated *in vacuo*: oily material (homogenous according to tlc; SiO_2; CH_2Cl_2:MeOH = 94:6), which crystallized whilst standing at room temp.: 390 mg (100%). Purification by column chromatography (cc) (SiO_2; CH_2Cl_2:MeOH = 94:6), crystallization from MeOH: colourless crystals, m.p. 112-113°C (enantiomer of woodinine). [α] = +80.2° (MeOH, c = 0.6).- $C_{17}H_{22}BrN_3$ (348.1) Calc. C 58.6 H 6.37 N 12.1 Found C 58.6 H 6.27 N 12.0.- IR-, mass-, and ^{1}H-NMR-spectra: identical with those of woodinine (**12a**).

(R)-1-[(R)-N-Methylpyrrolidin-2-yl]-6-bromo-2-methyl-1,2,3,4-tetrahydro-β-carboline (**8b**)

40 mg (0.106 mmol) **7b** in 2 ml of absol. THF were reduced with 40 mg $LiAlH_4$ in 1 ml THF as described for **7a**.- Work-up (see **8a**) led to 38 mg of a yellowish oil which was purified by cc (SiO_2; EtOAc:CH_2Cl_2:MeOH = 40:57:3 - v/v): wax like solid, 32 mg (86%).- [α] = -18.3° (MeOH, c = 0.6).- IR (film): $\tilde{\nu}$ = 3417; 2931; 2790 cm^{-1}.- ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.81-3.20 (m; 12 H), 1.98 (s; 3H, NCH_3), 2.46 (s; 3H, NCH_3), 7.206 (s; 1H aromat.), 7.21 (s; 1H aromat.), 7.62 (br. s; 1H aromat.), 8.9 (br. s; 1H, NH, exchangeable).

Woodinine diastereomer ***12b*** *and improved preparation of woodinine* (**12a**)

1-[(S)-(N-tert-Butoxycarbonyl)pyrrolidin-2-yl]-6-bromo-2-formyl-1,2,3,4-tetrahydro-β-carboline (**9**), mixture of diastereomers: see 8a + 8b in lit.1).

1-[(S)-(N-tert-Butoxycarbonyl)pyrrolidin-2-yl]-6-bromo-2-methyl-1,2,3,4-tetrahydro-β-carboline (**9'**)

When the mixture of **9**-diastereomers was reduced with $LiAlH_4$ in THF for 1 h under reflux (tlc control, no more cpd. **9**) and worked up as usual,

*) This nomenclature was deduced from that of a similar heterocycle: *S. Misztal* et al.[7b].

cpd. **9'** was obtained.- M.p. 180-182° (hexane/diisopropyl ether).- IR (KBr): $\tilde{\nu}$ = 3316 (NH); 1667 cm^{-1} (CO).- ^{1}H-NMR (250 MHz, $C_2D_2Cl_4$): δ (ppm) = 1.2 (s; 9H, Boc), 1.69-4.15 (m; 12 H), 2.46 (s; 3H, NCH_3), 7.11 (d; J = 7.5 Hz, 1H, 8-H), 7.18 (dd; J_o = 7.5 Hz, J_m = 1.8 Hz, 1H, 7-H), 7.56 (d; J_m = 1.8 Hz, 1H, 5-H), 8.16 (br. s; 1H, NH).- MS (70 eV): m/z = 435/433 (1.3%, $M^{+\bullet}$), 362/360 (1), 265/263 (100, M - $C_9H_{16}NO_2$)$^+$, 70 (C_4H_8N)$^+$. - The pertinent diastereomer was not found by tlc systems and by ^{1}H-NMR-spectroscopy.

1-[(S)-Pyrrolidin-2-yl]-6-bromo-2-formyl-1,2,3,4-tetrahydro-β-carboline (**10**), *mixture of diastereomers*

For preparation of cpds. **10** from cpds. **9** cf. cpd. **6** - **10** (mixture) was obtained as a white amorphous powder which was directly converted to the bis-formamides **11**.- IR (**10**) (KBr): $\tilde{\nu}$ = 3407 (NH); 1659 cm^{-1} (CO).

1-[(S)-N-Formylpyrrolidin-2-yl]-6-bromo-2-formyl-1,2,3,4-tetrahydro-β-carboline (**11**), *mixture of diastereomers*

For preparation from amines **10** cf. cpd. **7**.- Separation of diastereomers by flash chromatography (cf. cpd. **7**).

(R)-1-[(S)-N-Formylpyrrolidin-2-yl]-6-bromo-2-formyl-1,2,3,4-tetrahydro-β-carboline (**11a**)

Colourless crystals, m. range 220-226°C (ring-chain-tautomers?) (EtOH, Et_2O, hexane).- [α] = -140.8° ($CHCl_3$, c = 0.6).- $C_{17}H_{18}BrN_3O_2$ (376.3) Calc. C 54.3 H 4.82 N 11.2 Found C 53.9 H 4.88 N 10.9.- IR- and mass-spectra: cf. enantiomer **7a**.

(S)-1-[(S)-N-Formylpyrrolidin-2-yl]-6-bromo-2-formyl-1,2,3,4-tetrahydro-β-carboline (**11b**)

Colourless crystals, m. range 203-208°C (dec.) (EtOH, Et_2O, hexane; ring-chain-tautomers?).- [α] = +72.8° ($CHCl_3$, c = 0.6).- Further data: enantiomer **7b**.

Woodinine (**12a**)

$LiAlH_4$-reduction of **11a** as described for **7a** and usual work-up led to woodinine (**12a**), m.p. 112-113°C, identical in all aspects with our reference sample[1].

(S)-1-[(S)-N-Methylpyrrolidin-2-yl]-6-bromo-2-formyl-1,2,3,4-tetrahydro-β-carboline (**12b**)

12b was obtained from **11b** (cf. conversion of **11a** to **12a**) as a yellowish wax-like material, m.p. 39-41°C.- [α] = +19.7° (MeOH, c = 0.6).- Further data: enantiomer **8b**.

1-(Pyrrolidin-2-yl]-6-bromo-1,2,3,4-tetrahydro-β-carbolines **13, 14, 15**

Cpds. **13**, **14**, and **15** were prepared from the pertinent bis-formamides **11a**, **11b**, and **7a** as described for **11a** (see below) (**7b** was not included on account of the small quantity available).

37.6 mg (1 mmol) **11a** in 3 ml MeOH was refluxed with 0.5 ml 3N HCl for 3.5 h under N_2 in the dark, poured onto ice, and the aqueous solution so obtained was basified by Na_2CO_3 and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated *in vacuo*: 30 mg (93%) of **13**; yellowish oil, which was cyclized to the pyrazinedione **16** without further purification.

13: MS (70 eV): m/z = 321/319 (0.03%; $M^{+\bullet}$), 251/249 (11; M - C_4H_8N)$^+$, 70 (100; C_4H_8N)$^+$.

Bis-amines **14** (from **11b**) and **15** (from **7a**) were prepared analogously and used for the next step without further purification.

1,2,8,9,14b,14c-Hexahydro-11-bromo-pyrrolo[1'',2'':1',2']pyrazino-[4',3':1,2]pyrido[3,4-b]indol-5,6-(3H)diones **16, 17, 18**[*)]

14b(*R*),14c(*S*)-Diastereomer **16**

Under N_2 24 mg (0.075 mmol) diamine **13** and 60 mg diethyl oxalate in 1.5 ml EtOH were refluxed in the dark for 3.5 h. During the reaction white crystals began to precipitate. After 3.5 h at room temp. the crystals were harvested, washed with ice cold EtOH and recrystallized from EtOH: 15.5 mg (55%), m.p. 338°C (EtOH) (dec.).- [α] = +251.6° (DMSO, c = 0.6).- $C_{17}H_{16}BrN_3O_2$ (374.2) Calc. C 54.5 H 4.31 N 11.2 Found C 55.0 H 4.40 N 11.2.- IR (KBr): $\tilde{\nu}$ = 3284 (NH); 1671 cm^{-1} (CO).- ^{1}H-NMR (250 MHz, [D_6]DMSO): δ (ppm) = 1.75-3.55 (m; 9H), 3.69 (m; 1H, 14c-H), 4.75 (m; 1H, 8-H eq.), 5.03 (d; J = 10.7 Hz, 1H, 14b-H), 7.23 (dd; J_o = 8.5, J_m = 2 Hz, 1H, 12-H), 7.37 (d; J = 8.5 Hz, 1H, 13-H), 7.68 (d; J = 2 Hz, 1H, 10-H), 10.96 (sharp s, 1H, NH).- MS (70 eV): m/z = 375/373 (8%; $M^{+\bullet}$), 347/345 (1; M - CO)$^{+\bullet}$, 250/248 (21; 6-bromo-3,4-dihydro-β-carboline), 70 (100; C_4H_8N)$^+$.

*) This nomenclature was deduced from that of a similar heterocycle: S. Misztal et al.[7b].

14b(*S*),14c(*S*)-Diastereomer **17**

The diastereomeric piperazinedione **17** was obtained from diamine **14** as described for the preparation of **16**.- Colourless crystals, m.p. 260-263°C (MeOH, $CHCl_3$).- [α] = -75° ($CHCl_3$, c = 0.4).- IR (KBr): $\tilde{\nu}$ = 3280 (NH); 1669 cm^{-1} (CO).- ^{1}H-NMR (250 MHz, [D_6]DMSO): δ (ppm) = 1.75-3.69 (m; 9H), 4.30 (m; 1H, 14c-H), 4.75 (m; 1H, 8-H eq.), 5.46 (d; J = 4.9 Hz, 1H, 14b-H), 7.22 (dd; J_o = 8.6; J_m = 2 Hz, 1H, 12-H), 7.38 (d; J = 8.6 Hz, 1H, 13-H), 7.62 (d; J = 2 Hz, 1H, 10-H), 10.98 (sharp s; 1H, NH).

The enantiomer of **17** has not been prepared on account of economic reasons.

14b(*S*),14c(*R*)-Diastereomer **18** (enantiomer of **16**)

Cyclization of **15** as described for **13** led to the piperazinedione **18**.- M.p. 336°C (EtOH).- [α] = -247.4° (DMSO, c = 0.6).- $C_{17}H_{16}BrN_3O_2$ (374.2) Calc. C 54.5 H 4.31 N 11.2 Found C 54.9 H 4.29 N 11.2.- Further data: enantiomer **16**.

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