Woodinine and its Stereomers - Absolute Configuration

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The synthesis of all the four stereomers of the alkaloid woodinine (12a) is described and the stereochemical conclusions of Pais' and Still' are discussed. The absol. configurations of woodinine (12a) and its diastereomer 8b are unequivocally deduced from the pertinent piperazinediones 16 and 17.

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

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, we...
have obtained the Schiff-base 3 which was cyclized under the condi-
tions cited\(^1\) affording the diastereomers of com-
 pound 4. These sec. amines were N-formylated to com-
 pounds 5. - Deviating from our earlier procedure\(^1\) 5 was
hydrolyzed by CF\(_3\)COOH to amine 6 (this hydrolysis did not work with compound 4; here a useless mixture of com-
 pounds arose). After a second formylation (cpd. 7) the dia-
 stereomers 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\(_4\) with-
in 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). - 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 affor-
ded woodinine (12a) and the enantiomer 12b of diastereo-
mer 8b. By this route cpd. 12b (C-1-epimer of natural woo-
dinine 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 natu-
re.

Stereochemistry

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

Mme Pais et al.\(^3\) present a formula of woodinine (cpd. 2 in their publica-
tion\(^3\)) indicating \(\alpha\)-configuration for H-1 of the tetrahydro-\(\beta\)-carboline
ring. On the other side, however, they point out: "...la courbe de de, qui
présente un effet Cotton positif à 243 nm, permet de préciser que l’hydro-
gène en 1 est en position \(\beta\)". - Pais quotes Rinehart Jr. et al.\(^4\) who
describe structure elucidations of eudistomines and their O-acetyl derivati-
ves, 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 \(\alpha\)-configuration for H-1." So Rinehart’s statement is contradictory to
Pais’ text but corroborates her formula shown\(^3\).

Pais\(^3\) cites Bläha et al.\(^5\) who deal with 5,16-cyclocorynane alkaloids.
Bläha and coworkers represent the CD-spectrum of "(+)-1-methyl-
1,2,3,4-tetrahydro-\(\beta\)-carboline with \(\alpha\)-configuration for H-1 (called "3\(\alpha\)H"
by Bläha because H-1 of tetrahydro-\(\beta\)-carbines 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 Bläha’s publication\(^5\) "3\(\beta\)H" configu-
ration is attributed to "(+)-1,2,3,4-tetrahydroharmane (= 1-methyl-1,2,3,4-
tetrahydro-\(\beta\)-carbine). This is a contradiction in terms. So, only the
cyclocorynanes with \(\alpha\)-configuration for H-3 can be used for correlation.

![Scheme 2](image-url)
“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 eudistomines6).

In 1991 Still et al.6) have reported on the synthesis of woodinine (12a) and of its epimer, starting from L-prolinol. Still6) 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...α-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’ data5) - and 7% of the C-1-α-epimer were isolated.

The analysis of the NMR-data, 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 strategy9) 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 piperazinedione 16 14b-H resonates at δ = 5.03 ppm as a doublet with 3.60 Hz, as a doublet with 3.60 Hz. - In the epimer 17 14b-H shows a doublet at δ = 5.46 ppm with 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

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Irradiation into the NH-frequency of 17 at $\delta = 10.98$ ppm only increases the intensity of the 13-H doublet at $\delta = 7.38$ 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 $\delta = 5.03$ ppm simplifies the multiplet of 14c-H at $\delta = 3.69$ 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 $^{6b}$.

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**Experimental Part**

General remarks: lit.$^{1,3}$.- [a] values at D-line and 20°C, if not otherwise stated.

5-Bromotryptamine (1): lit.$^{1}$ and cit. there.

(RS)-(+)-N-(tert-Butyoxycarbonyl)-pyrrolidine-2-carboxaldehyde (2)

was prepared as described for its enantiomer$^{1}$ starting from D-proline.

Data: lit.$^{1}$ and cit. there.

(R)-β-(5-Bromoindol-3-yl)-N-[N-(tert-butyloxycarbonyl)-pyrrolidin-2-yl-methylene]-ethylamine (3) and

1-[(R)-N-(tert-Butyloxycarbonyl)pyrrolidin-2-yl]-6-bromo-1,2,3,4-tetrahydro-β-caroline (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 absolv. CHCl$_3$ was stirred with molecular sieve 4 Å under N$_2$ for 1 h at room temp. After filtration and washing with absolv. CHCl$_3$, the solution of imine 3 was cooled to -78°C. 1.3 ml (10.5 mmol) F$_2$CCOOH 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$_2$CO$_3$ at 0°C, washed with water (2 x 20 ml), dried (Na$_2$SO$_4$), 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.$^{13}$.

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

This mixture of cpds. 5 was prepared as described for the diastereomers with S-configuration at pyrrolidine-C-2$^{13}$.- Analytical data: lit.$^{13}$.

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

To the solution of 940 mg (2.09 mmol) 5 in 10 ml of absolv. CHCl$_3$ 10 ml of F$_2$CCOOH 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$_2$CO$_3$. The org. layer was separated, the aqueous phase was extracted with CHCl$_3$ (2 x 15 ml). The combined org. phases were dried (Na$_2$SO$_4$) and evaporated to dryness in vacuo: yellow powder which was dried at room temp. and 0.05 mm Hg.: 710 mg (97%) which were directly convered to cpds. 7.- IR of 6-mixture (KBr): $\nu$: 3436 (br., NH); 1678 cm$^{-1}$ (CO).

1-[(R)-N-Formylpyrrolidin-2-yl]-6-bromo-2-formyl-1,2,3,4-tetrahydro-β-caroline (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 absolv. CHCl$_3$ 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$_2$CO$_3$-solution to pH = 9, and the org. phase was separated, dried (Na$_2$SO$_4$), and evaporated: 736 mg white amorphous solid (98%).

7-Diastereomers were separated by flash-chromatography (SiO$_2$; CH$_2$Cl$_2$;hexane:MeOH = 82:15:3 - v/v).

7a: 582 mg, colourless crystals, m.p. 215-220°C (dec.) (EtOH, Et$_2$O, hexane).- [a] = +126.5° (CHC$_2$H$_2$, c = 0.6).- C$_{17}$H$_{20}$BrN$_3$O$_4$ (376.3) Calc. C 17.0 H 0.6 Found C 17.0 H 0.6.- IR (film): $\nu$ = 3417; 2931; 2790 cm$^{-1}$; 1665 cm$^{-1}$ (CO).- MS (70 eV): m/z = 377/375 (10%, M$^+$; 1665 cm$^{-1}$ (CO).- MS (70 eV): m/z = 377/375 (10%, M$^+$; 1665 cm$^{-1}$ (CO).

7b: 103 mg, m.p. 201-206°C (dec.) (EtOH, Et$_2$O, hexane).- [a] = +80.2° (MeOH, c = 0.6).- C$_{17}$H$_{18}$BrN$_3$O$_4$ (376.3) Calc. C 54.3 H 4.82 N 11.2.- IR (KBr): $\nu$: 3268 (NH); 1655 cm$^{-1}$ (CO).

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

The solution of 400 mg 7a in 6 ml of absolv. tetrahydrofurane (THF) was added drop by drop at 0°C to the suspension of 300 mg LiAlH$_4$ in 6 ml of absolv. THF under N$_2$. After reflux for 1.5 h the mixture was hydrolyzed by Et$_2$O/water at 0°C, the org. phase was dried (Na$_2$SO$_4$) and evaporated in vacuo: oily material (homogeneous according to tic; SiO$_2$; CH$_2$Cl$_2$;MeOH = 94:6), which crystallized whilst standing at room temp.: 390 mg (100%).

Purification by column chromatography (cc) (SiO$_2$; CH$_2$Cl$_2$;MeOH = 94:6), crystallization from MeOH: colourless crystals, m.p. 112-113°C (enantioner of woodinine). [a] = +80.2° (MeOH, c = 0.6).- C$_{17}$H$_{18}$BrN$_3$O$_4$ (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 1H-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-caroline (8b)

40 mg (0.106 mmol) 7b in 2 ml of absolv. 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$_2$Cl$_2$;MeOH = 40:57:3 - v/v); wax like solid, 32 mg (86%).- [a] = +18.3° (MeOH, c = 0.6).- IR (film): $\nu$: 3417; 2931; 2790 cm$^{-1}$.- 1H-NMR (250 MHz, CDCl$_3$): $\delta$ (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-Benzoxycarbonyl)pyrrolidin-2-yl]-6-bromo-2-formyl-1,2,3,4-tetrahydro-β-caroline (9), mixture of diastereomers: see 8a + 8b in lit.1)

1-[(S)-N-(tert-Benzoxycarbonyl)pyrrolidin-2-yl]-6-bromo-2-methyl-1,2,3,4-tetrahydro-β-caroline (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,

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1-{[S]-Pyrrrolidin-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 (KBr): ν = 3407 (NH); 1671 cm⁻¹ (CO). - *H-NMR (250 MHz, DMSO): δ (ppm) = 7.38 (d; J = 8.5 Hz, 1H, 10-H), 7.62 (d; J = 2 Hz, 1H, 12-H), 7.37 (d; J = 8.5 Hz, 1H, 13-H), 7.68 (d; J = 10 Hz, 1H, 10-H), 7.23 (dd; J₉ = 8.5, J₈ = 2 Hz, 1H, 12-H), 7.37 (d; J = 8.5 Hz, 1H, 13-H), 7.68 (d; J = 2 Hz, 1H, 10-H), 10.98 (sharp s; 1H, NH). - MS (70 eV): m/z = 375/373 (8%; M⁺), 347/345 (1: M - CO)⁺, 250/248 (21; 6-bromo-3,4-dihydro-β-carboline), 70 (100; C₇H₇N⁺). * This nomenclature was deduced from that of a similar heterocycle: S. Misztal et al. ⁷⁹).

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, CHCl₃). - [α] = +75° (CHCl₃, c = 0.4). - IR (KBr): ν = 3284 (NH); 1671 cm⁻¹ (CO). - ¹H-NMR (250 MHz, DMSO): δ (ppm) = 7.38-8.08 (9H), 4.30-4.75 (1H, 14c-H), 5.46 (d; J = 4.9 Hz, 1H, 14b-H), 7.23 (dd; J₉ = 8.5, J₈ = 2 Hz, 1H, 12-H), 7.37 (d; J = 8.5 Hz, 1H, 13-H), 7.68 (d; J = 10 Hz, 1H, 10-H), 7.23 (dd; J₉ = 8.5, J₈ = 2 Hz, 1H, 12-H), 7.37 (d; J = 8.5 Hz, 1H, 13-H), 7.68 (d; J = 2 Hz, 1H, 10-H), 10.98 (sharp s; 1H, NH). - MS (70 eV): m/z = 375/373 (8%; M⁺), 347/345 (1: M - CO)⁺, 250/248 (21; 6-bromo-3,4-dihydro-β-carboline), 70 (100; C₇H₇N⁺).

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