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INDOLES XIV.[1] 4-PHENYLPYRIDO[4,3-*b*]INDOLES AND 5-PHENYLAZEPINO[4,5-*b*]INDOLES BY CYCLISATION OF *N*-INDOLYLALKYLEPHEDRINE DERIVATIVES – SCOPE AND STEREOSELECTIVITY

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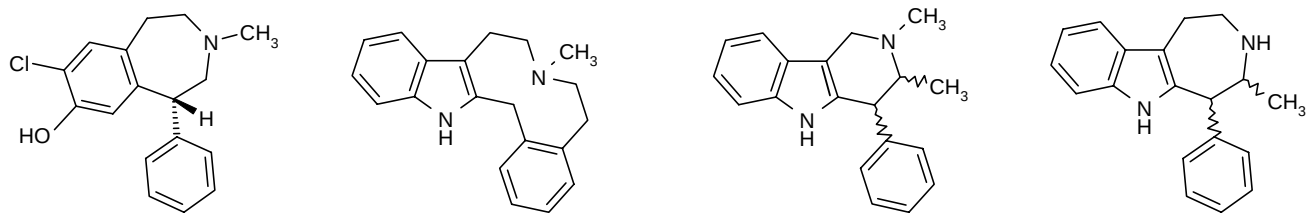
Abstract- 4-Phenyltetrahydropyrido[4,3-*b*]indoles (**1**) and 5-phenylhexahydro-azepino[4,5-*b*]indoles (**2**) were obtained by cyclisation reactions starting from *N*-3-indolylmethylephedrines and *N*-3-indolylethylnorephedrines respectively, using conc. sulfuric acid (for **1**) and PPA (for **2**), the latter cyclisation yielding to the racemised azepinoindoles (**2**), whereas the previous one reacts to **1** in a remarkably stereoselective manner with double inversion = retention of its configuration, obviously going through a spirocyclic intermediate.

Compounds with selectivity to dopamine receptor subtypes can be achieved through rigidification of indolyl- and phenylalkylamines. E.g. the well-known **SCH-23390**[2] and the recently presented **LE 300**[3] are molecular combinations of tryptamine and 2-phenylethylamine in a constrained conformation and they proved to be potent and selective D_1/D_5-antagonist. Having in mind these structures we focussed our efforts on the synthesis of other partially rigidified indolyl-phenyl-alkylamines such as **1** and **2**. Because of the stereogenic centres being of crucial importance for the receptor affinities (see **SCH-23390**) we decided to use the ephedrine enantiomers, as well as the pseudoephedrine enantiomers as synthons for the phenylethylamine part.

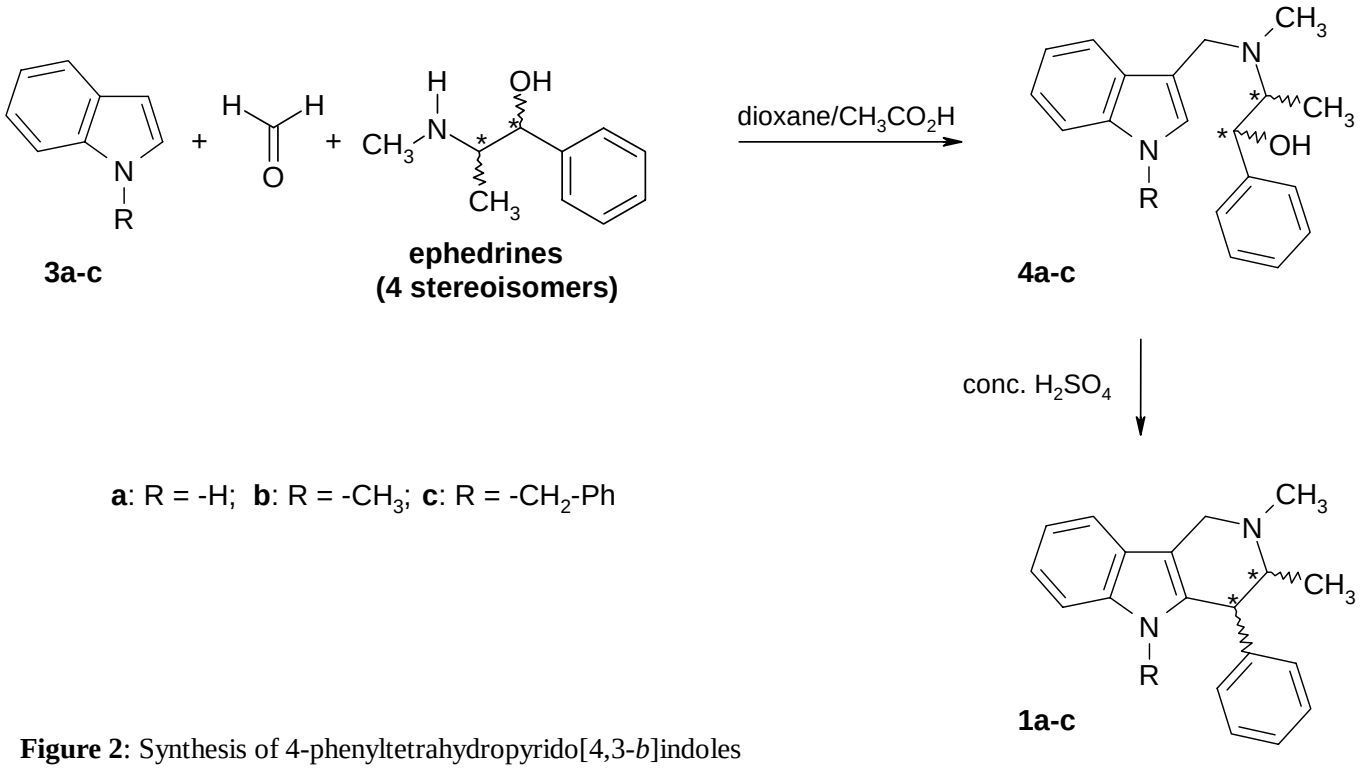


SCH-23390 **LE 300** **1** **2**

Figure 1: Potential dopamine D_1/D_5 receptor antagonists

RESULTS AND DISCUSSION

Twelve (3 x 4) 4-phenyltetrahydropyrido[4,3-*b*]indoles (**1**) were synthesised by a Mannich reaction using all four stereoisomers of ephedrine, including the pseudoephedrines, methanal and the three indoles (**3a-c**), followed by the cyclisation step with concentrated sulfuric acid at room temperature (**Figure 2**). The substituted indoles (**3b**,**c**) were prepared by direct alkylation with methyl iodide and benzyl chloride after deprotonation with potassium hydroxide in DMSO.[4] Other methods of cyclisation than treatment with cold conc. sulfuric acid have turned out to be unsuccessful, either because of total decomposition or because of the re-isolation of the starting materials being possible. These methods include cyclisation agents such as hydrochloric acid in different concentrations, a mixture of trifluoroacetic acid and concentrated sulfuric acid as well as trifluoromethanesulfonic acid anhydride.



a: R = -H; **b**: R = -CH_3; **c**: R = -CH_2-Ph

Figure 2: Synthesis of 4-phenyltetrahydropyrido[4,3-*b*]indoles

In order to expand of the ring system we synthesised the 5-phenylhexahydroazepino[4,5-*b*]indoles (**2**) starting from indole-3-acetic acid, which was coupled to the two enantiomeric norephedrines using *N*,*N*´-carbonyldiimidazole (CDI), subsequent reduction with lithium aluminum hydride and finally cyclisation. **5a,b** were prepared by Fischer indole reactions.[5] Unfortunately the cyclisation step proved to be unsuccessful with concentrated sulfuric acid and the other agents mentioned above, even using modified temperatures and reaction times. Finally polyphosphoric acid (PPA) turned out to be an appropriate agent as previously described for similar indoloazepines[6] (**Figure 3**). Surprisingly, none of the *N*-methyl derivatives (**2b**) could be formed in our hands because of decomposition during the cyclisation step.

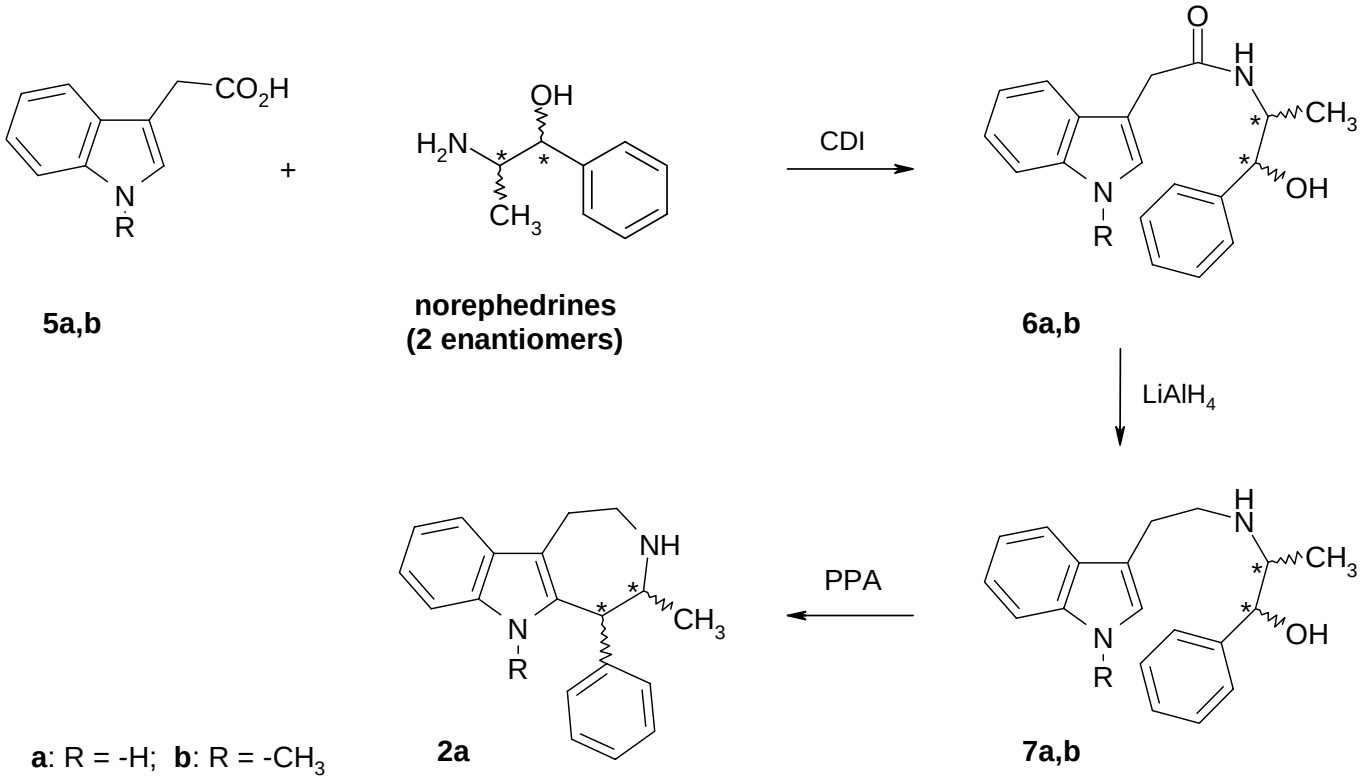


Figure 3: Synthesis of 5-phenylhexahydroazepino[4,5-*b*]indoles

Stereochemistry

Stereochemistry of the open chain precursors (**4**) of the pyrido[4,3-*b*]indoles (**1**) is given by the corresponding ephedrine stereoisomer. In the course of cyclisation, configuration at position 3 in **1** will remain unchanged but regarding position 4 one could expect racemisation yielding mixtures of two diastereomers of **1**. On the other hand a stereoselective cyclisation would give diastereo- and enantiopure

compounds by inversion or retention of the configuration. Unfortunately, NMR data (both ^{1}H- and ^{13}C-) were almost identical for all cyclisation products (with the same substituent at the indole-*N*-atom of course) so that such an analysis of the diastereomeres or the diastereomeric mixtures was impossible. In fact, not only the intermediates (**4**) but also all of the resulting derivatives (**1**) were optically active with absolute optical rotations in the same range for each pair of enantiomers (see **Table 1**) and showed only one peak in GC investigations. Thus a highly stereoselective cyclisation was obviously observed. Luckily we managed to crystallise the cyclisation product of (1*S*,2*S*)-**4a** from water/DMSO, so that we were able to determine the absolute configuration of the diastereomer (**1a**) by X-Ray analysis, making the plausible assumption, that the configuration of the carbon atom fixed to the methyl group is not affected during the course of the cyclisation. Due to the fact that the heterocycle takes the position of the hydroxy group in the CIP-sequence, the resulting compound (**1a**) (**Figure 4**) has the (3*S*,4*S*)-configuration, which means that the course of the **cyclisation is stereoselective with retention of configuration** at C1 of the starting material and C4 of the product, respectively.

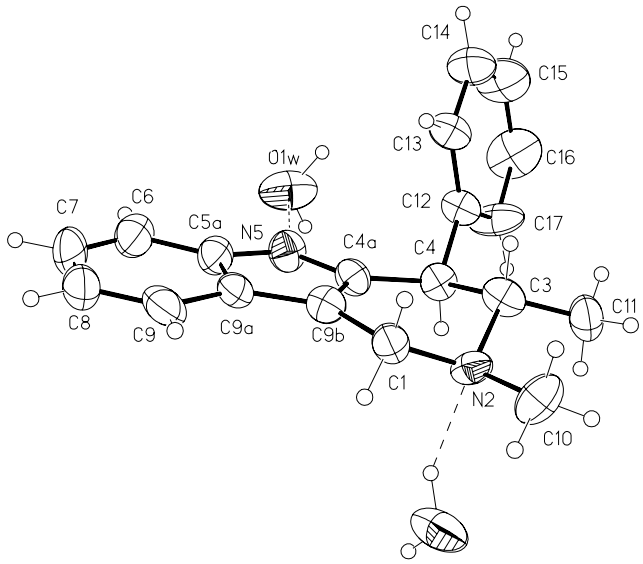


Figure 4:

ORTEP drawing of (3*S*,4*S*)-**1a** (crystals with water), obtained from (1*S*,2*S*)-**4a** by cyclisation with retention of configuration

This result is surprising, because due to the assumption, that the course of the reaction is according to an S_N1-mechanism, two diastereomeres should be formed; and according to an S_N2-mechanism inversion of configuration should take place. A clue for the solution of this problem was given by the characterisation of a by-product of the cyclisation. A small amount of compound (**8c**) was isolated, when **4c** was used as a starting material. Taking also into account the ^{13}C-labelling results of the Lewis-acid catalysed cyclisation of 4-(3-indolyl)butanol to 1,2,3,4-tetrahydrocarbazole by Smith *et al.*[7] and Curness`and Dyke`s investigations into the formation of tetrahydro-β-carbolines out of 3-indolylmethylaminoacetals with diluted hydrochloric acid,[8] the mechanism outlined in **Figure 5**, through a spirocyclic transition state with

two inversions seems to be fairly probable.

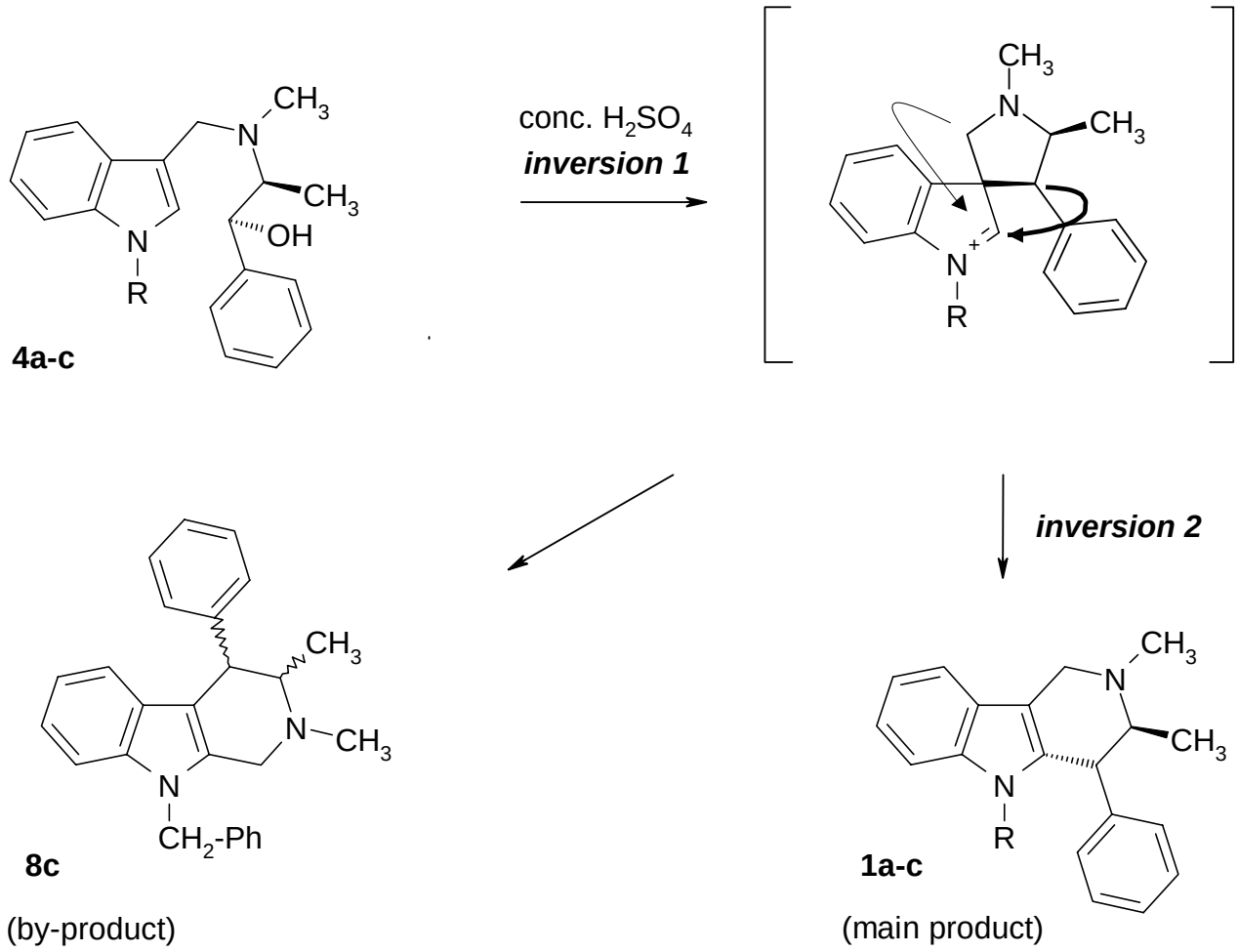


Figure 5: A possible mechanism for the retention of configuration through a spirocyclic compound

That means that the more nucleophilic position 3 of the indole could react first with an inversion to a spirocyclic compound, then stabilisation occurs through another stereoselective reaction with position 2. A decisive support for this mechanism would be the isolation of a β-carboline among all these γ-carbolines, since a spirocyclic intermediate must not be opened necessarily at the C-phenyl unit exclusively but also at the C-N unit, which would lead to compound (**8**). This is indeed the case, since we could isolate the β-carboline (**8c**) by column chromatography from the crude cyclisation product, obtained from one stereoisomer of **4c**. All enantiomerically and diastereomerically pure derivatives (**1**) could be synthesised with concentrated sufuric acid at room temperature from the corresponding ephedrine and pseudoephedrine derivatives (**4**). Transformations are summarized in **Table 1**.

Table. 1: Stereoselective conversion of ephedrines *via* **4a-c** into **1a-c** – Optical rotations ($[\alpha]^{24°}_{D}$) and other properties of intermediates and target compounds arranged in pairs of enantiomeres.

Educt ($[\alpha]^{24°}_{D}$)	→	**4** ($[\alpha]^{24°}_{D}$)	Properties/mp of **4** C;H;N, Calcd C;H;N, Found	→	**1** ($[\alpha]^{24°}_{D}$)	*) C;H;N, Calcd C;H;N, Found*)
1*S*,2*R*-ephedrine **+ 6.3**		1*S*,2*R*-**4a** **+ 31.4°**	Colorless crystals, 137°C 77.5; 7.5; 9.5 77.2; 7.5; 9.5		4*S*,3*R*-**1a** **+ 33.3°**	81.2; 7.5; 9.5 80.9; 7.3; 9.8 (contains 0.3 mol acetone)
1*R*,2*S*-ephedrine **- 6.3**		1*R*,2*S*-**4a** **- 31.3°**	Colorless crystals, 137°C 77.5; 7.5; 9.5 77.3; 7.5; 9.5		4*R*,3*S*-**1a** **- 32.5°**	80.6; 7.6; 9.2 80.2; 7.4; 9.2 (contains 0.5 mol acetone)
1*S*,2*S*-ephedrine **+ 51**		1*S*,2*S*-**4a** **+151.2°**	Colorless crystals, 185°C 77.5; 7.5; 9.5 77.2; 7.5; 9.5		4*S*,3*S*-**1a** **- 28.5°**	77.9; 7.8; 9.1 78.4; 7.5; 9.5 (contains 1 mol MeOH)
1*R*,2*R*-ephedrine **- 51**		1*R*,2*R*-**4a** **- 155.4°**	Colorless crystals, 185°C 77.5; 7.5; 9.5 77.4; 7.5; 9.5		4*R*,3*R*-**1a** **+ 24.9°**	81.2; 7.3; 9.3 80.8; 7.3; 9.7 (contains 0.3 mol ether)
1*S*,2*R*-ephedrine **+ 6.3**		1*S*,2*R*-**4b** **+ 25.8°**	Pale yellow oil 79.1; 7.9; 8.3 79.3; 8.3; 8.3 (contains 0.3 mol toluene)		4*S*,3*R*-**1b** **+ 96.3°**	82.7; 7.6; 9.6 82.6; 7.6; 9.6
1*R*,2*S*-ephedrine **- 6.3**		1*R*,2*S*-**4b** **- 27.4°**	Pale yellow oil 77.9; 7.8; 9.1 78.4; 8.1; 8.9		4*R*,3*S*-**1b** **- 94.2°**	82.7; 7.6; 9.6 81.9; 7.7; 9.4
1*S*,2*S*-ephedrine **+ 51**		1*S*,2*S*-**4b** **+ 137.7°**	Colorless crystals, 139°C 77.9; 7.8; 9.1 77.8; 7.8; 9.1		4*S*,3*S*-**1b** **- 59.0°**	82.7; 7.6; 9.6 82.2; 7.6; 9.5
1*R*,2*R*-ephedrine **- 51**		1*R*,2*R*-**4b** **- 140.7°**	Colorless crystals, 139°C 77.9; 7.8; 9.1 77.8; 7.8; 9.1		4*R*,3*R*-**1b** **+ 55.0°**	82.7; 7.6; 9.6 82.6; 7.6; 9.5
1*S*,2*R*-ephedrine **+ 6.3**		1*S*,2*R*-**4c** **+ 19.6°**	Pale yellow oil 81.2; 7.3; 7.3 81.1; 7.4; 7.2		4*S*,3*R*-**1c** **+ 44.8°**	83.9; 7.6; 7.2 84.0; 7.2; 7.4 (contains 0.3 mol ether)
1*R*,2*S*-ephedrine **- 6.3**		1*R*,2*S*-**4c** **- 16.6°**	Pale yellow oil 81.2; 7.3; 7.3 81.2; 7.6; 7.1		4*R*,3*S*-**1c** **- 47.1°**	85.2; 7.2; 7.6 84.7; 7.2; 7.5
1*S*,2*S*-ephedrine **+ 51**		1*S*,2*S*-**4c** **+108.4°**	Colorless crystals, 88°C 81.2; 7.3; 7.3 81.4; 7.3; 7.2		4*S*,3*S*-**1c** **- 12.9°**	81.2; 7.3; 7.3 80.8; 6.8; 7.2 (contains 1 mol water)
1*R*,2*R*-ephedrine **- 51**		1*R*,2*R*-**4c** **- 107.3°**	Colorless crystals, 88°C 81.2; 7.3; 7.3 80.5; 7.1; 7.1		4*R*,3*R*-**1c** **+ 12.9°**	85.2; 7.2; 7.6 85.0; 7.1; 7.3

*)All compounds (**1**) are yellow to pale yellow oils, some of them crystallise within days or weeks.

For the synthesis of the azepinoindoles, norephedrines which lack the methyl group connected to the nitrogen atom were used, because different substituents should be connected to the ring nitrogen later. As mentioned above, cyclisation was only successful with PPA. All of the resulting azepinoindoles (**2**) did not show any significant optical activity, which can be taken as an indication for a predominantly non-stereoselective course of the cyclisation. On the other hand they produced single peaks in GC investigations. For this reason capillary electrophoretic investigations were performed.

Capillary electrophoresis

In order to optimize the CE methods, the following parameters were varied one after the other whilst keeping the others constant: the concentration of the background electrolyte (50 and 100 mM KH_2PO_4 buffer), the pH values (3.0, 4.5, 6.0, 7.5), and the chiral additives to the BGE (α-cyclodextrin, ß-cyclodextrin, γ-cyclodextrin, sulfated ß-cyclodextrin (Sulf), sulfobutyl ether ß-cyclodextrin (SBE), and *heptakis*(2,3-di-*O*-acetyl-6-sulfato)-ß-cyclodextrin (HDAS) and the concentration of the additive in a range of 1 and 18 mM. More details and results on CE experiments are in press elsewhere.[9]

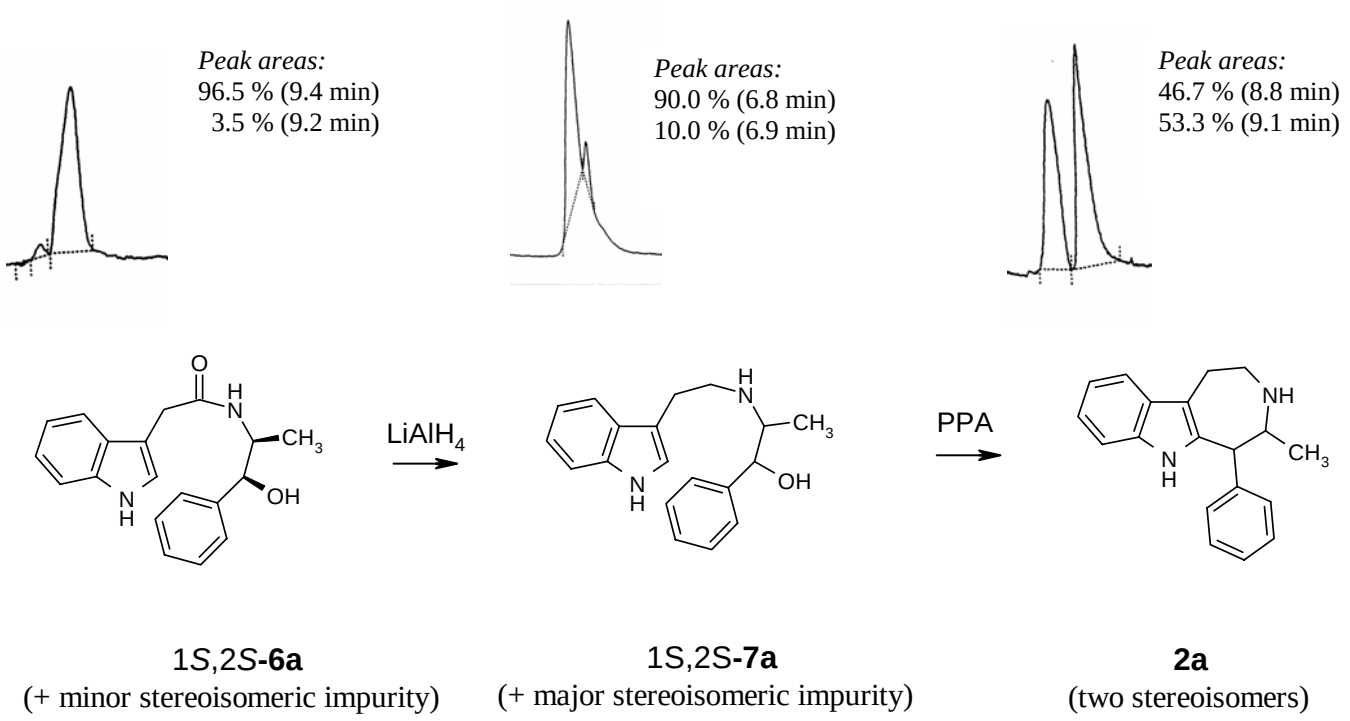


Figure 6: Stereochemical course of the reduction of 1*S*,2*S*-**6a** and the cyclisation of **7a**, monitored by electropherogramms (**6a**: 3 mM sulfated ß-cyclodextrin, pH 6.0, 100 mM KH_2PO_4 buffer; **7a**: 3 mM *heptakis*(2,3-di-*O*-acetyl-6-sulfato)-ß-cyclodextrin, pH 7.5, 50 mM KH_2PO_4 buffer; **2a**: 1 mM sulfobutylether β-cyclodextrine, pH 7.5, 50 mM KH_2PO_4 buffer).

The fundamental result to this study is that all of the cyclisation products (**2a**) do not appear as single stereoisomers but as stereoisomeric mixtures. This is demonstrated in **Figure 6** for the cyclisation product resulting from 1*S*,2*R*-**7a.** The reduction of the amide (**6**), which containes a minor stereoisomeric impurity, goes along with an epimerisation reaction to some extend (~ 10%). Subsequently the formation of a second stereoisomer is dramatically increased in the cyclisation reaction (~ 50%), indicating that even the use of a single stereoisomer of **7** would not have produced a single stereoisomer of **2**.

In conclusion, we found that for a stereoselective formation of 4-phenyltetrahydropyrido[4,5-*b*]indoles the chiral pool of ephedrines and pseudoephedrines can be used with retention of configuration, since the cyclisation of *N*-(3-indolylmethyl)ephedrines catalysed with concentrated H_2SO_4 proceeds stereoselectively. In addition we could obtain the homologeous 5-phenylhexahydroazepino[4,5-*b*]indoles, but not as single stereoisomers, since the PPA-catalysed cyclisation of *N*-(3-indolylethyl)norephedrines does not proceed stereoselectively.

EXPERIMENTAL

Melting points are uncorrected and were measured in open capillary tubes, using a Gallenkamp melting point apparatus. ^{1}H-NMR spectral data were obtained on a Varian XL300 (300 MHz). Elemental analyses were performed on a Hereus apparatus. IR spectral data were measured with a 1420 apparatus of Perkin Elmer. For experimental details on capillary electrophoresis, see ref.[9]

X-Ray analysis

$C_{19}H_{20}N_2PH_2O$, orthorombic, space group $P2_12_12_1$ (No. 19), dimensions 0.35 x 0.45 x 0.70 mm^3, a = 10,345(3) Å, b = 10,877(4) Å, c = 14,893(5) Å, V = 1675,8(1) Å^3, D_c = 1.17 Mg m^{-3}, Z = 4, μ (MoKα) = 0,073 mm^{-1}, T = 293(2) K, F(000) = 632; 2606 reflections were collected on a Nicolet R3m-diffractometer ($2\theta_{max.}$ = 50°), of which 2292 symmetry independent reflections were used for the structure solution (direct methods; SHELXS-90) and refinement (full-matrix least-squares on F^2, 208 parameters, 2 restraints; SHELXS-93), non-hydrogen atoms were refined anisotropically, H atoms localised by difference electron density and refined using a `riding`model. wR2 = 0.401 {R_1 = 0.094 [I>2 σ(I)]}. The absolute configuration could not be determined reliably by Flack`s x-refinement.[10] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-147447 (**1a**). Copies of Cambridge CB2 1EZ, UK (Fax: int. Code *(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).

N-(2-Hydroxy-1-methyl-2-phenylethyl)-2-(*H*-indol-3-yl)acetamides (**6a**,**b**) – general procedure

0.05 Mol of the free acid are dissolved in *ca.* 50 mL of dried THF, then 8.1 g (0.05 mol) of *N*,*N´*-carbonyldiimidazole are added. After ~15 min the formation of carbon dioxide ends, the solution is then allowed to stand for 3 h. The activated acid is slowly added dropwise (in order to avoid the formation of ester) to a solution of 0.05 mol of the corresponding norephedrine under vigorous stirring. The solution is stirred over night at rt. Then the solution is washed once with 25 mL of 1N H_2SO_4, and twice with water. During the course of the second washing with water often separation of phases does not take place, so that more water (~100 mL) has to be added for separation (this time the organic phase is below). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The products were purified by column chromatography on silica (500 g, CH_2Cl_2/MeOH/conc. NH_3 = 85/14/1).

N-(2-Hydroxy-1-methyl-2-phenylethyl)-2-(1*H*-indol-3-yl)acetamide (**6a**): 89 %; white powder; mp 122 °C (purification by column chromatography was sufficient, recrystallisation was not performed); ^{1}H-NMR (DMSO-d_6) 0.95 (d, J = 7 Hz, 3H), 3.5 (d, J = 0.5 Hz, 2H), 3.95 (dq, J = 7 and 2 Hz, 1H), 4.6 (dd, J = 5 and 2 Hz, 1H), 5.3 (d, J = 5 Hz, 1H), 6.9 – 7.8 (m, 10 H), 10.9 (br s, 1H); Anal. Calcd for $C_{19}H_{22}N_2O$ x ½ H_2O: C; 69.9 , H; 6.8, N; 8.6. Found: C; 69.1, H; 6.7, N; 8.5; IR (KBr, cm^{-1}): 3360, 3292, 2361, 1631, 1546, 1458, 1264, 1023, 746.

N-(2-Hydroxy-1-methyl-2-phenylethyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (**6b**): 82 %; white powder; mp 51 °C (purification by column chromatography was sufficient, recrystallisation was not performed); ^{1}H-NMR (DMSO-d_6) 0.95 (d, J = 7 Hz, 3H), 3.5 (d, J = 0.5 Hz, 2H), 3.8 (s, 3H), 3.95 (dq, J = 7 and 2 Hz, 1H), 4.6 (t, J = 5 and 2 Hz, 1H), 5.3 (d, J = 5 Hz, 1H), 6.9 – 7.8 (m, 10 H); Anal. Calcd for $C_{20}H_{22}N_2O_2$ x ¼ H_2O:C; 73.5, H; 6.9, N; 8.6. Found: C; 73.8, H; 6.9, N; 8.6; IR (KBr, cm^{-1}): 3285, 2361, 1654, 1543, 1253, 736.

2-[2-(1*H*-Indole-3-yl)ethylamino]-1-phenylpropan-1-oles (**7a**,**b**) – general procedure

0.05 Mol of the corresponding amide (**6a**,**b**) is dissolved in 80 mL of dried ether. This solution is slowly added to an ice-cold suspension of 75.9 g (2 mol) of lithium aluminum hydride in 300 mL of dried ether. Then the suspension is stirred and boiled under reflux for 18 h. After cooling the excess $LiAlH_4$ is destroyed with 0.5 N NaOH, which is added dropwise under ice-cooling till the formation of hydrogen is finished. The inorganics are filtered, washed twice with ether and the filtrate is dried with $MgSO_4$ and evaporated in vacuo. **7a** could be obtained from recrystallisation with CH_3CN as a pale-cream powder (6.6 g, 45%), and **7b** (5.6 g, 36 %) was purified by column chromatography on silica (500 g, CH_2Cl_2/MeOH/conc. NH_3 = 85/14/1).

2-[2-(1*H*-Indol-3-yl)ethylamino]-1-phenylpropan-1-ol (**7a**): mp 120 °C (purification by column chromatography was sufficient, recrystallisation was not performed); ^{1}H-NMR (DMSO-d_6) 0.9 (d, J = 7 Hz, 3H), 2.8 –2.9 (m, 5H) , 4.7 (d, J = 4 Hz, 1H), 6.9 – 7.5 (m, 10H), 10.8 (s, 1H); Anal. Calcd for $C_{19}H_{22}N_2O$ x ½ H_2O: C; 75.2, H; 7.3, N; 9.2. Found: C; 75.2, H; 7.7, N; 8.4; IR (KBr, cm^{-1}): 3401, 2361, 1457, 1426, 1092, 738, 702.

2-[2-(1-Methyl-1*H*-indol-3-yl)ethylamino]-1-phenylpropan-1-ol (**7b**): mp oil; ^{1}H-NMR (DMSO-d_6) 0.9 (d, J = 7 Hz, 3H), 2.8 –2.9 (m, 5H),3.8 (s, 3H), 4.7 (d, J = 4 Hz, 1H), 6.9 – 7.5 (m, 10H); Anal. Calcd for $C_{20}H_{24}N_2O$: C; 77.9, H; 7.8, N; 9.1. Found: C; 77.3, H; 7.7, N; 8.8; IR (KBr, cm^{-1}): 3446, 2361, 1654, 1474, 736, 698, 668.

4-Methyl-5-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (**2a**)

7.36 g (0.025 mol) of **7a** are added to a mixture of 500 mL of $CHCl_3$ and 200 mL of PPA, then stirred and boiled under reflux. After 1 h, the mixture is cooled, the chloroform decanted and the PPA is dissolved under ice-cooling (!) and vigorous stirring in ~1 L of water. Subsequently, the solution is made basic (pH = 8) with 6N NaOH again at 0°C. The product is extracted twice with 500 mL of ethyl acetate. The combined organic extracts are washed with water, dried with $MgSO_4$ and the solvent removed under reduced pressure. Chromatography on silica (500 g, CH_2Cl_2/MeOH/conc. NH_3 = 85/14/1) gave **2a** (830 mg, 12 %); mp 76 °C; pale-cream powder; ^{1}H-NMR (DMSO-d_6) 1.1 (d, J=7 Hz, 3H), 2.8 – 3.3 (m, 5H), 4.0 (d, J= 6 Hz, 1H), 6.9– 7.4 (m, 9H), 10.2 (s, 1H); Anal. Calcd for $C_{19}H_{20}N_2$ x ½ H_2O: C; 80.0, H; 7.4, N; 9.8. Found: C; 80.0, H; 7.2, N; 9.9; IR (KBr, cm^{-1}): 3421, 2361, 1458, 668.

2-[*N*-(1*H*-Indol-3-ylmethyl)-*N*-methyl]amino-1-phenylpropan-1-ols (**4a,b,c**) – general procedure

0.1 Mol of the corresponding ephedrine stereoisomer are dissolved in 60 mL of a 1:1 mixture of dioxane and glacial acetic acid, cooled to 0°C and 0.1 mol of methanal (40% in water) are added. Without cooling the solution is stirred for 5 min, and then again under ice-cooling 0.1 mol of the corresponding indole (**6a,b,c**) are added. The cooling is finally removed and the mixture is stirred for at least 2 days at rt. The reaction is ended through the addition of 100 mL of saturated $NaHCO_3$-solution under ice-cooling. The solution is basified with conc. NH_3 till pH = 10 is reached. The organic phase is extracted twice with ether, dried over $MgSO_4$ and evaporated in vacuo. Chromatography on silica [500 g, 500 mL ether/toluene (1:2), 300 mL ether/toluene (2:1)] gives 78 % of **4c** (70 % **4a**, 75 % **b**).

2-[*N*-(1*H*-Indol-3-ylmethyl)-*N*-methyl]amino-1-phenylpropan-1-ol (**4a**): mp 137 °C (from ephedrines) and 185 °C (from pseudoephedrines); colorless crystals; the following entries are for the (1*R*,2*S*)-compound: ^{1}H-NMR ($CDCl_3$) 1.0 (d, J = 7 Hz, 3H), 2.2 (s, 3H), 3.0 (dq, J = 9 and 7 Hz, 1H), 3.8 (d, J =

13 Hz, 1H), 3.9 (d, J = 13 Hz, 1H), 4.95 (d, J = 5 Hz, 1H), 7.05 – 7.4 (m, 9H), 7.6 (m, 1H), 8.05 (s, 1H); Anal. Calcd for $C_{19}H_{22}N_2O$: C; 77.5, H; 7.5, N; 9.5. Found: C; 77.3, H; 7.5, N; 9.5 ; IR (KBr, cm^{-1}): 3540, 2840, 1600, 1540, 1450, 1380, 1255, 1110, 990, 790, 700, 650.

2-[*N*-(1-Methyl-1*H*-indol-3-ylmethyl)-*N*-methyl]amino-1-phenylpropan-1-ol (**4b**): mp 139 °C (from pseudoephedrines) as colorless crystals; yellow oil (from ephedrines); the following entries are for the (1*R*,2*S*) compound: ^{1}H-NMR ($CDCl_3$) 0.95 (d, J = 7 Hz, 3H), 2.2 (s, 3H), 3.0 (dq, J = 7 and 5 Hz, 1H), 3.75 (s, 3H), 3.8 (d, J = 14 Hz, 1H), 3.9 (d, J = 14 Hz, 1H), 4.95 (d, J = 5 Hz, 1H), 6.9 (s, 1H), 7.1 (ddd, J = 7, 7 and 2 Hz, 1H), 7.15 – 7.4 (m, 7H), 7.6 (ddd, J = 8, 1 and 1 Hz, 1H); Anal. Calcd for $C_{20}H_{24}N_2O$: C; 77.9, H; 7.8, N; 9.1. Found: C; 78.4, H; 8.1, N; 8.9; (KBr, cm^{-1}): 3240, 2960, 1470, 1420, 1245, 1030, 930, 795, 740, 700.

2-[*N*-(1-Benzyl-1*H*-indol-3-ylmethyl)-*N*-methyl]amino-1-phenylpropan-1-ol (**4c**): mp 88°C (from pseudoephedrines) as colorless needles; pale yellow oil (from ephedrines); the following entries are for the (1*R*,2*S*) compound: ^{1}H-NMR ($CDCl_3$) 1.0 (d, J =7 Hz, 3 H), 2.2 (s, 3H), 3.0 (dq, J = 7 and 5 Hz, 1H), 3.8 (d, J = 14 Hz, 1H), 3.9 (d, J = 14 Hz, 1H), 4.95 (d, J = 5 Hz, 1H), 5.3 (s, 2H), 7.0 (s, 1H), 7.1 – 7.4 (m, 13H), 7.6 –7.7 (m, 1H); Anal. Calcd for $C_{26}H_{28}N_2O$: C; 81.2, H; 7.3, N; 7.3. Found: C; 81.2, H; 7.3, N; 7.2; IR (KBr, cm^{-1}): 3420, 3040, 2940, 2825, 1550, 1460, 1330, 1195, 1025, 930, 790, 720, 640.

4-Phenyltetrahydropyrido[4,3-*b*]indoles (**1a,b,c**) – general procedure

3 Mmol of **4a,b** or **c** are given to 10 mL of conc. H_2SO_4 under ice-cooling. Then the cooling is removed and the solution is stirred for 6 h at rt. Finally the mixture is poured into 100 mL of ice-water and basified under vigorous stirring and further cooling with conc. NH_3. The aqueous phase is extracted twice with ether. The solvent is removed in vacuo and chromatographied on silica (200 g, PE/acetone = 7/3) to give 20 – 30 % yield of **1a,b,c**.

2,3-Dimethyl-4-phenyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**1a**): colorless crystals; the following entries are for the (1*R*,2*S*) compound: ^{1}H-NMR ($CDCl_3$) 1.1 (d, J = 6,4 Hz, 3H), 2.5 (s, 3H), 2.8 (dq, J = 8 and 6 Hz, 1H), 3.85 (ddd, J = 8, 2 and 1.5 Hz, 1H), 3.9 (dd, J = 15 and 2 Hz, 1H), 4.0 (dd, J = 15 and 2 Hz, 1H), 7.05 –7.75 (m, 9H), 7.4 (s, 1H); IR (KBr, cm^{-1}): 3380, 2780, 1620, 1590, 1445, 1290, 1230, 1020, 735, 695.

4-Phenyl-2,3,5-trimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**1b**): yellow oil; the following entries are for the (1*R*,2*S*)- compound: ^{1}H-NMR ($CDCl_3$) 1.2 (d, J = 6.4 Hz, 3H), 2.45 (s, 3H), 2.95 (dq, J = 6 and 5 Hz, 1H), 3.2 (s, 3H), 3.8 (dd, J = 14 and 1.2 Hz, 1H), 3.9 (ddd, J = 5, 1 and 1 Hz, 1H), 4.0 (dd, J = 14 and 1.2 Hz, 1H), 7.05 –7.35 (m, 8H), 7.5 (ddd, J = 8, 2 and 0.6 Hz, 1H); IR (KBr, cm^{-1}):3420, 2770, 1480, 1460, 1435, 1350, 1310, 1130, 755, 740, 730, 698.

5-Benzyl-2,3-dimethyl-4-phenyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole (**1c**): yellow oil; the following entries are for the (1*R*,2*S*) compound: ^{1}H-NMR ($CDCl_3$) 1.1 (d, J = 6.4 Hz, 3H), 2.45 (s, 3H), 2.8 (dq, J = 8 and 6.5 Hz, 1H), 3.75 (dd, J = 16 and 1.2 Hz, 1H), 3.9 (dd, J = 16 and 1.2 Hz, 1H), 3.95 (ddd, J = 8, 2 and 1.4 Hz, 1H), 5.3 (s, 2H), 6.8 (ddd, J = 8, 1.4 and 0.6 Hz, 1 H), 6.85 (ddd, J = 8, 8 and 1 Hz, 1H), 7.0 –7.1 (m, 3H), 7.2 –7.35 (m, 9H); IR (KBr, cm^{-1}): 2760, 1485, 1450, 1370, 1348, 1150, 790, 770, 740, 720, 695.

9-Benzyl-2,3-dimethyl-4-phenyl-2,3,4,5-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**8c**)

This compound can be isolated from the crude product of the previous reaction by two column chromatographic purifications (200g silica, PE/acetone = 8/2) in a yield of 8 %. Yellow powder; ^{1}H-NMR ($CDCl_3$) 0.8 (d, J = 7 Hz, 3H), 2.65 (s, 3 H), 3.1 (dq, J = 7 and 5 Hz, 1 H), 3.5 (dd, J = 15 and 1.4 Hz, 1H), 3.9 (dd, J = 15 and 1.4 Hz), 4.4 (ddd, J = 5, 2 and 1.4 Hz, 1H), 5.3 (s, 2H), 6.8 – 6.95 (m, 2H), 6.95 – 7.1 (m, 4 H), 7.2 – 7.35 (m, 8 H); Anal. Calcd for $C_{26}H_{26}N_2$: C; 83.2, H; 7.3, N; 7.5. Found: C; 83.4, H; 7.4, N; 7.4; IR (KBr, cm^{-1}): 2760, 1485, 1450, 1370, 1348, 1020, 740, 695.

REFERENCES

1. J. Lehmann, M. Nieger, and Th.Witt, *Heterocycles*, 1995, **41**, 119.
2. A.V. Christensen, J.Arnt, J. Hyttel, J.J. Larssen, and O. Svendson, *Life Sci*., 1984, **34**, 1529.
3. Th. Witt, S. Hock, and J. Lehmann, *J. Med. Chem*., 2000, **43**, 2079.
4. H. Heaney and S.V. Ley, *J. Chem. Soc., Perkin Trans. I*, 1973, **1**, 499.
5. P. Rosenmund, G. Meyer, and I. Hansal, *Chem. Ber.*, 1975, **108**, 3538.
6. A.J. Elliot, E.H. Gold, and H. Guzik, *J. Med. Chem.*, 1980, **23**, 1268.
7. A.H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron*, 1968, **24**, 6119.
8. K. Curness and S. Dyke, *Heterocycles*, 1979, **12**, 1133.
9. M. Wedig, M. Thunhorst, S. Laug, M. Decker, J. Lehmann, and U. Holzgrabe, *Fresenius J. Anal. Chem*., 2001, *in press.*
10. H.D. Flack, *Acta Crystallogr Sect. A*, 1983, **39**, 876.