Stereoselective synthesis of 4-substituted 1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indoles

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4-Substituted 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles were synthesized from 2-cyanoindole. (*R*)-4-Methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole was obtained by the Mitsunobu reaction. Stereoselective reduction of 4-substituted 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles gave 4-substituted 1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indoles. (4*R*,10a*R*)-4-Methyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indole was synthesized.

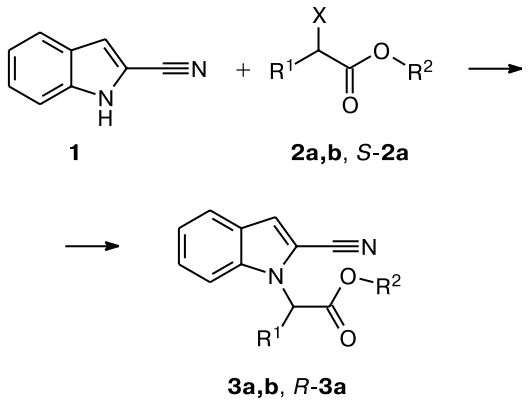
Key words: 1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indoles; 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles; *N*-substituted indoles; reduction of nitriles; 2-cyanoindole; Mitsunobu reaction.

Derivatives of 1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indole and 1,2,3,4-tetrahydropyrazino[1,2-*a*]indole exhibit a broad spectrum of biological activity.[1,2] In this study, 4-substituted 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles were obtained and stereoselectively reduced into the corresponding 1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indoles. The starting 2-cyanoindole for the synthesis of 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles was prepared according to a known procedure.[3] Having an increased acidity of the NH proton, 2-cyanoindole (**1**) reacts with alkylating agents and K_2CO_3 under mild conditions to give *N*-substituted indoles **3a,b** in high yields (Scheme 1). Non-racemic indole derivatives with a chiral substituent at the N atom are most expediently obtained by the Mitsunobu reaction with secondary alcohols as alkylating agents and a redox PPh_3—dialkyl azodicarboxylate (*e.g.*, diisopropyl azodicarboxylate, DIAD) system as a condensing agent. The use of optically active secondary alcohol *S*-**2a** made it possible to obtain derivative *R*-**3a** containing a chiral substituent at the N atom (Mitsunobu reaction proceeds stereospecifically and inverts the configuration of the asymmetric atom of the starting alcohol[4]).

Note that the reported syntheses of similar individual indole stereoisomers are few;[5—8] a chiral substituent was directly introduced at the N atom of indole by the Mitsunobu reaction only in two documented cases.[7,8]

Catalytic reduction of the cyano group in compound **3** with $NaBH_4$ at nickel boride[9] prepared *in situ* from $NiCl_2 \cdot 6H_2O$ and $NaBH_4$ is accompanied by intramolecular acylation to give cyclic amides **4** in 60 to 65% yields (Scheme 2). The analogous reduction of compound **3a** in the presence of Boc_2O[10] affords a *N*-Boc derivative **5** in 74% yield and, on elimination of the protective group with CF_3COOH, amide **4a** in total 68% yield.

Scheme 1

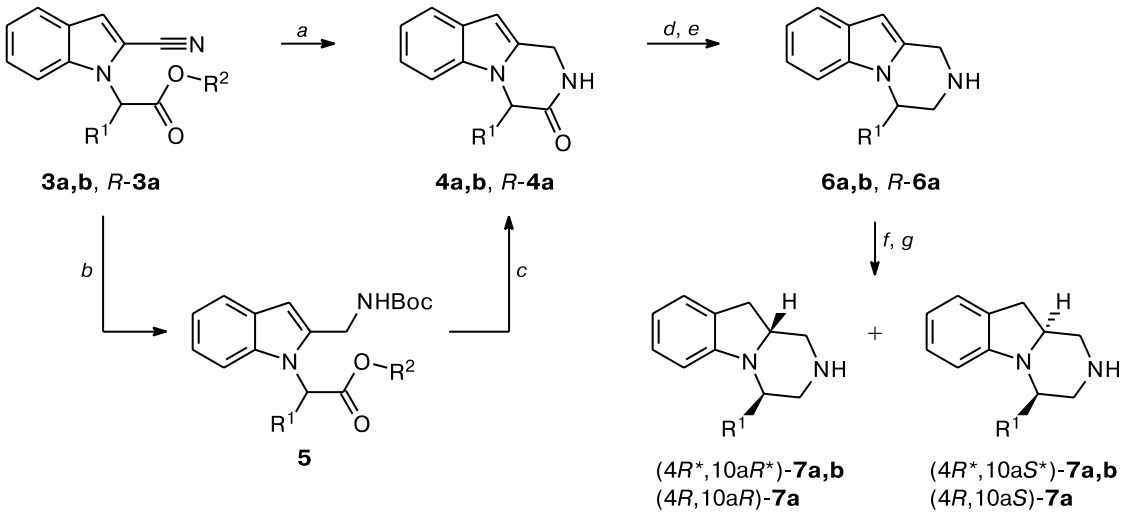


2a: R^1 = Me, R^2 = Et, X = Br;
S-**2a:** R^1 = Me, R^2 = Et, X = OH;
2b: R^1 = Ph, R^2 = Me, X = OMs;
3a: R^1 = Me, R^2 = Et;
3b: R^1 = Ph, R^2 = Me

Reagents and conditions: (*a*) DIAD, PPh_3, THF or (*b*) K_2CO_3, DMF.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 221—225, January, 2005.

Scheme 2



3a: R^1 = Me, R^2 = Et; **5:** R^1 = Me, R^2 = Et; **3b:** R^1 = Ph, R^2 = Me;
4a: R^1 = Me; **4b:** R^1 = Ph; **6a, 7a:** R^1 = Me; **6b, 7b:** R^1 = Ph

Reagents and conditions: *a*. $NaBH_4$, MeOH, $NiCl_2$; *b*. $NaBH_4$, MeOH, $NiCl_2$, Boc_2O; *c*. TFA, CH_2Cl_2; *d*. $LiAlH_4$, THF; *e*. BH_3, THF; *f*. BH_3 (excess), THF; *g*. $NaBH_3CN$.

Amides **4a,b** were reduced with $LiAlH_4$ in THF into the corresponding 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **6a,b** in 72 and 87% yields, respectively (see Scheme 2). The optically active amide *R*-**4a** was reduced with a BH_3—THF complex. The reduction of amide **4a** with a large excess of the borane complex unexpectedly gave the corresponding 4-methyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indole (**7a**), although these reagents were reported[11] to reduce indoles into indolines only in acidic media. For instance, the reaction of amide **4a** with 5 equiv. of $BH_3 \cdot Me_2S$ in boiling THF for 12 h yielded a mixture of compounds **6a** (25%) and **7a** (75%, 1 : 2 mixture of diastereomers) (^{1}H NMR and GC-MS data).

1,2,3,4-Tetrahydropyrazino[1,2-*a*]indoles **6a,b** and *R*-**6a** were reduced into the corresponding indolines **7a,b** and (4*R*,10a*R*)-**7a** with $NaBH_3CN$ (see Scheme 2) used earlier[5] for asymmetric reduction of indoles into indolines.

The reduction was carried out under different conditions (temperature, solvent, and the amount of the reducing agent); the results obtained are summarized in Table 1. The ratio of the diastereomers and the degree of conversion were determined from ^{1}H NMR data.

In all cases, one of the diastereomers was obtained in a large excess. A virtually complete conversion of 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **6a,b** into the corresponding indolines **7a,b** was achieved by the room-temperature reaction in AcOH; for compound **6a**, the content of the minor diastereomer was ~9%, while for compound **6b** containing the Ph group in position 4, its content was 14%. In the reduction of compound **6a** at −70 °C, the content of the minor diastereomer was no higher than 3%; however, the total yield was poor. Nevertheless, the yield was increased by elevating the reaction temperature to −10 °C, *dr* remaining virtually the same. The spatial structures of the major diastereomers **7a,b** were determined in NOE experiments. Irradiation of a solution of indoline **7a** in DMSO-d_6 at the resonance frequency of the methyl protons revealed the NOE for the

Table 1. Stereoselective reduction of 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles **6a** (R^1 = Me) and **6b** (R^1 = Ph)

R^1	Conditions			Substrate : $NaBH_3CN$	*dr* (%)	Conversion (%)
	Solvent	*T*/°C	*t*/h			
Me	AcOH	25	4	1 : 4	91	>99
Ph	AcOH	25	7	1 : 4	86	83
Me	MeOH—dioxane—HCl	−70	4	1 : 4	>97	59
Me	MeOH—dioxane—HCl	−50	10	1 : 7	>97	71
Me	MeOH—dioxane—HCl	−10	24	1 : 7	>97	82

C(4)H (3.9%), C(10a)H (2.2%), C(3)H_a (1.2%), and C(6)H protons (0.7%). A similar pattern was obtained for its solution in C_6D_6. These data suggest that the C(10a)H proton is spatially closer to the methyl group than to the C(4)H proton. Irradiation at the resonance frequency of the C(3)H_b proton brought about the NOE for the geminal C(3)H_a proton (15.4%) and the C(4)H proton (3.3%). For compound **7b** in DMSO-d_6, the NOE for the C(4)H proton (4.3%) was observed upon irradiation at the resonance frequency of the C(10a)H proton, thus indicating their spatial vicinity. These data suggest that the reduction of compound **6a** predominantly gives the (4*R**,10a*R**)-isomer, while the reduction of compound **6b** yields the (4*R**,10a*S**)-isomer.

The reduction of optically active indole *R*-**6a** in the MeOH—HCl system at −10 °C afforded indoline (4*R*,10a*R*)-**7a**, $[\alpha]_D^{23}$ −35.0 (*c* 2.0, MeOH). The other enantiomer was not detected by HPLC with a chiral stationary phase.

Experimental

IR spectra were recorded on a UR-20 instrument (Nujol or neat compounds). Rotation values were measured on a Jasco DIP-360 polarimeter (589 nm). GC-MS studies were performed with a Carlo Erba/Kratos Fractovap Series 4200 gas-liquid chromatograph (Ultra-1 column, Hewlett Packard, 25 m × 0.2 mm, phase layer thickness 0.33 μm, helium as a carrier gas (1 mL min^{-1}), flow separator 1 : 10, evaporator temperature 280 °C, temperature gradient 150—280 °C (5 deg min^{-1}), ITD-700 MS detector (Finnigan MAT), EI, 70 eV, mass range *m*/*z* 45—400). The enantiomeric excess was determined by HPLC (column 280 × 4 mm, Vancomycin-immobilized silica gel, flow rate 0.7 mL min^{-1}). ^{1}H NMR spectra were recorded on a Bruker AMX-400 spectrometer (400.13 MHz) in DMSO-d_6 (unless otherwise specified) with Me_4Si as the internal standard. 2D COSY and HMBC NMR spectra were recorded on a Bruker DRX-500 spectrometer (500.13 (^{1}H) and 125.76 MHz (^{13}C)). NOE experiments were performed on a Bruker AM-360 spectrometer. Melting points were measured in open capillaries and are given uncorrected. Compounds were purified by chromatography on silica gel 60 (0.040—0.063 mm, Merck Co.). The course of the reactions was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates and GC-MS.

Ethyl 2-(2-cyanoindol-1-yl)propionate (3a). Ethyl 2-bromopropionate (4.2 g, 23 mmol) and K_2CO_3 (3.2 g, 23 mmol) were added to a solution of 2-cyanoindole[3] (3 g, 21 mmol) in DMF (20 mL). The reaction mixture was stirred at 50 °C for 6 h and then water (150 mL) was added. The products were extracted with ether (4×50 mL). The extract was washed with water (5×50 mL) and brine (100 mL) and dried with anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with AcOEt—light petroleum (1 : 25) as an eluent. The yield of compound **3a** was 4.8 g (94%). Found (%): C, 68.96; H, 5.89; N, 11.12. $C_{14}H_{14}N_2O_4$. Calculated (%): C, 69.41; H, 5.82; N, 11.56. IR, ν/cm^{-1}: 1740 (C=O); 2240 (C≡N). ^{1}H NMR, δ: 1.15 (t, 3 H, C<u>H</u>$_3$CH$_2$, *J* = 7.1 Hz); 1.76 (d, 3 H, C<u>H</u>$_3$CH, *J* = 7.4 Hz); 4.40 (m, 2 H, CH$_3$C<u>H</u>$_2$); 5.80 (q, 1 H, CH$_3$C<u>H</u>, *J* = 7.4 Hz); 7.20 (t, 1 H, *J* = 7.65 Hz); 7.41 (t, 1 H, *J* = 7.8 Hz); 7.47 (s, 1 H, C(3)H); 7.62 (d, 1 H, *J* = 8.5 Hz); 7.66 (d, 1 H, *J* = 8.1 Hz). MS, *m*/*z* (I_{rel} (%)): 242 $[M]^+$ (23), 169 $[M - CO_2Et]^+$ (100), 142 (6), 115 (8).

Methyl (2-cyanoindol-1-yl)phenylacetate (3b) was obtained analogously with methyl mesyloxy(phenyl)acetate as an alkylating agent. The yield of compound **3b** was 69%. Found (%): C, 74.23; H, 4.80; N, 9.59. $C_{18}H_{14}N_2O_2$. Calculated (%): C, 74.47; H, 4.86; N, 9.65. IR, ν/cm^{-1}: 705 (Ph); 1750 (C=O); 2235 (C≡N). ^{1}H NMR, δ: 3.83 (s, 3 H, OMe); 7.12 (s, 1 H, C<u>H</u>Ph); 7.23 (t, 1 H, *J* = 7.5 Hz); 7.29—7.45 (m, 6 H); 7.57 (s, 1 H, C(3)H); 7.72 (d, 2 H, *J* = 8.1 Hz). MS, *m*/*z* (I_{rel} (%)): 290 $[M]^+$ (4), 231 $[M - CO_2Me]^+$ (4), 121 (10), 89 (14), 77 (13), 59 (100).

Ethyl (*R*)-2-(2-cyanoindol-1-yl)propionate (*R*-3a). A solution of diisopropyl azodicarboxylate (4.44 g, 22 mmol) in anhydrous THF (5 mL) was added dropwise at 0 to 5 °C under argon to a solution of triphenylphosphine (5.87 g), 2-cyanoindole (2.11 g, 15 mmol), and ethyl (*S*)-2-hydroxypropionate (2.61 mL, 22 mmol) in anhydrous THF (50 mL). The reaction mixture was left at ~20 °C for 48 h, whereupon the solvent was removed *in vacuo* and the residue was chromatographed on silica gel with AcOEt—light petroleum (1 : 25) as the eluent. The yield of compound *R*-**3a** was 2.54 g (71%), $[\alpha]_D^{20}$ −18.0 (*c* 2.0, $CHCl_3$). Its spectra are in agreement with the data for racemic ethyl 2-(2-cyanoindol-1-yl)propionate (**3a**).

Ethyl 2-(2-(*tert*-butoxycarbonylaminomethyl)indol-1-yl)propionate (5). Nickel dichloride hexahydrate (5 mg, 0.2 mmol) was added to a solution of ethyl 2-(2-cyanoindol-1-yl)propionate (**3a**) (0.5 g, 2 mmol) and Boc_2O (0.87 g, 4 mmol) in anhydrous MeOH (15 mL). Then $NaBH_4$ (0.53 g, 14 mmol) was added in portions at 0 to 5 °C. The reaction mixture was stirred at ~20 °C for 1 h, whereupon the solvent was removed *in vacuo*. The residue was dissolved in AcOEt (50 mL), washed with a solution of $NaHCO_3$ (2×20 mL) and brine, and dried with anhydrous Na_2SO_4. The extract was concentrated *in vacuo* and the residue was chromatographed on silica gel with light petroleum—EtOAc (10 : 1) as an eluent. The yield of compound **5** was 0.51 g (74%). Found (%): C, 65.26; H, 7.54; N, 7.79. $C_{19}H_{26}N_2O_4$. Calculated (%): C, 65.87; H, 7.56; N, 8.09. IR, ν/cm^{-1}: 1710 (NHC=O); 1735 (C=O); 3390 (N—H). MS, *m*/*z* (I_{rel} (%)): 346 $[M]^+$ (36), 290 $[M - H_2C{=}C(CH_3)_2]^+$ (68), 245 (23), 230 (15), 200 (27), 171 (32), 156 (100), 144 (38), 130 (54), 57 (83). ^{1}H NMR, δ: 1.09 (t, 3 H, C<u>H</u>$_3$CH$_2$, *J* = 7.1 Hz); 1.39 (s, 9 H, CMe$_3$); 1.62 (d, 3 H, C<u>H</u>$_3$CH, *J* = 7.4 Hz); 4.11 (m, 2 H, CH$_3$C<u>H</u>$_2$); 4.30 (m, 2 H, C<u>H</u>$_2$NH); 5.80 (q, 1 H, CH$_3$C<u>H</u>, *J* = 7.4 Hz); 6.31 (s, 1 H, C(3)H); 6.99 (t, 1 H, *J* = 6.9 Hz); 7.06 (t, 1 H, *J* = 7.7 Hz); 7.17 (d, 1 H, *J* = 8.3 Hz); 7.38 (br.s, 1 H, NH); 7.49 (d, 1 H, *J* = 7.5 Hz).

4-Methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-3-one (4a). ***A.*** Trifluoroacetic acid (0.33 mL, 4.3 mmol) was added to a solution of ethyl 2-(2-(*tert*-butoxycarbonylaminomethyl)indol-1-yl)propionate (**5**) (0.15 g, 0.43 mmol) in 2 mL of CH_2Cl_2. The reaction mixture was kept at room temperature for 2 h and then diluted with CH_2Cl_2 to 10 mL, washed with a solution of $NaHCO_3$ (2×5 mL), and dried with anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was recrystallized from EtOH to give compound **4a** (80 mg, 92%).

B. Nickel dichloride hexahydrate (0.25 g, 1 mmol) was added to a solution of ethyl 2-(2-cyanoindol-1-yl)propionate (**3a**)

(2.5 g, 10.3 mmol) in 75 mL of anhydrous methanol. Then $NaBH_4$ (2.74 g, 72 mmol) was added in portions at 0 to 5 °C. The reaction mixture was stirred at room temperature for 2 h, whereupon the solvent was removed *in vacuo*. The residue was dissolved in 200 mL of AcOEt, washed with a solution of $NaHCO_3$ (2×100 mL) and brine, and dried with anhydrous Na_2SO_4. The extract was concentrated *in vacuo* and the residue was recrystallized from EtOH to give compound **4a** (1.4 g, 63%), m.p. 220—222 °C (from ethanol). Found (%): C, 71.46; H, 5.92; N, 13.55. $C_{12}H_{12}N_2O$. Calculated (%): C, 71.98; H, 6.04; N, 13.99. IR, ν/cm^{-1}: 1670 (C=O); 3200 (N—H). ^{1}H NMR, δ: 1.52 (d, 3 H, CH_3, J = 6.8 Hz); 4.53 (dd, 1 H, C(1)H_a, J = 16.3 Hz, J = 4.4 Hz); 4.69 (d, 1 H, C(1)H_b, J = 16.3 Hz); 5.02 (q, 1 H, $CH_3C\underline{H}$, J = 6.8 Hz); 6.33 (s, 1 H, C(10)H); 7.04 (t, 1 H, J = 7.4 Hz); 7.11 (t, 1 H, J = 7.4 Hz); 7.51 (t, 2 H); 8.39 (br.d, 1 H, NH). MS, m/z (I_{rel} (%)): 200 [M]$^+$ (82), 185 [M – Me]$^+$ (60), 156 (58), 130 (100), 115 (71), 77 (91), 63 (72).

(*R*)-4-Methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-3-one (*R*-4a) was obtained as described for 4-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-3-one (**4a**) in procedure ***B***. The yield of compound *R*-**4a** was 0.5 g (65%), m.p. 221—222 °C; $[\alpha]_D^{23}$ –91.5 (*c* 1.3, MeOH). Its spectral characteristics agree with the data for the racemate.

4-Phenyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-3-one (4b) was obtained as described for 4-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-3-one (**4a**) in procedure ***B***. The yield of compound **4b** was 65%. Found (%): C, 77.50; H, 5.18; N, 10.35. $C_{17}H_{14}N_2O$. Calculated (%): C, 77.84; H, 5.38; N, 10.68. IR, ν/cm^{-1}: 710 (Ph), 1775 (C=O), 3330 (N—H). ^{1}H NMR, δ: 4.64—4.75 (m, 2 H, CH_2); 6.18 (s, 1 H, PhC$\underline{H}$); 6.47 (s, 1 H, C(10)H); 6.98—7.06 (m, 2 H); 7.11 (d, 2 H, J = 6.3 Hz); 7.25—7.35 (m, 4 H); 7.55 (d, 1 H, J = 6.6 Hz); 8.51 (br.s, 1 H, NH). MS, m/z (I_{rel} (%)): 262 [M]$^+$ (27), 218 (62), 128 (21), 115 (28), 103 (28), 89 (90), 77 (100), 62 (47), 51 (56), 44 (55), 39 (81).

4-Methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole hydrochloride (6a). 4-Methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-3-one (**4a**) (0.95 g, 4.75 mmol) was added in portions (to prevent very vigorous boiling) to a suspension of $LiAlH_4$ (0.45 g, 11.9 mmol) in anhydrous THF (12 mL). The reaction mixture was refluxed for 10 h and cooled to room temperature. Water (0.5 mL) was carefully added; then 15% KOH (0.5 mL) and an additional 0.5 mL of water were added. Then the mixture was stirred at ~20 °C for 30 min. The precipitate was filtered off and washed with THF (50 mL). The filtrate was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (50 mL), washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was dissolved in a small amount of anhydrous ether; 4 *M* HCl (1.2 mL, ~4.75 mmol) in dioxane was added with cooling. The precipitate that formed was filtered off, washed with anhydrous ether, dried, and recrystallized from ethanol. The yield of salt **6a** was 0.76 g (72%), m.p. 251—252 °C (from ethanol). Found (%): C, 64.42; H, 6.83; N, 12.44. $C_{12}H_{14}N_2$·HCl. Calculated (%): C, 64.71; H, 6.79; N, 12.58. IR, ν/cm^{-1} (for the free base): 760, 780, 3060, 3390 (N—H). ^{1}H NMR, δ: 1.52 (d, 3 H, CH_3, J = 6.6 Hz); 3.57 (dd, 1 H, C(3)H_a, J = 13.2 Hz, J = 3.5 Hz); 3.69 (dd, 1 H, C(3)H_b, J = 16.3 Hz, J = 4.9 Hz); 4.44 (d, 1 H, C(1)H_a, J = 15.7 Hz); 4.52 (d, 1 H, C(1)H_b, J = 15.7 Hz); 4.81—4.90 (m, 1 H, $CH_3C\underline{H}$); 6.40 (s, 1 H, C(10)H); 7.06 (t, 1 H, J = 7.4 Hz); 7.15 (t, 1 H, J = 7.6 Hz); 7.49 (d, 1 H, J = 8.0 Hz); 7.54 (d, 1 H, J = 7.8 Hz); 10.00 (br.s, 2 H, NH_2^+). MS (for the free base), m/z (I_{rel} (%)): 186 [M[$^+$ (47), 157 (62), 130 (100), 117 (49), 102 (30), 89 (48), 63 (55).

(*R*)-4-Methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole hydrochloride (*R*-6a). (*R*)-4-Methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-3-one (*R*-**4a**) (0.1 g, 5 mmol) was added to a 1 *M* solution of a borane—THF complex (1.1 mL, ~1.1 mmol). The reaction mixture was left for 24 h, whereupon methanol (1 mL) was added dropwise. Volatile compounds were removed *in vacuo*. The residue was dissolved in 2 mL of dilute HCl (1 : 1). The mixture was heated with stirring for 1 h, cooled to 0 °C, and alkalified with 30% KOH to pH ~12. The product was extracted with $CHCl_3$ (5×10 mL). The extract was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed *in vacuo*; the residue was dissolved in anhydrous ether and 4 *M* HCl (in dioxane, 0.13 mL, ~5 mmol) was added with cooling. The precipitate that formed was filtered off, washed with anhydrous ether, and dried to give compound *R*-**6a** (0.87 g, 78%), m.p. 249—251 °C (from ethanol); $[\alpha]_D^{20}$ –40.2 (*c* 0.8, MeOH). Its spectral characteristics agree with the data for the racemate.

4-Phenyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole (6b). 4-Phenyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-3-one (**4b**) (0.71 g, 2.7 mmol) was added in portions (to prevent very vigorous boiling) to a suspension of $LiAlH_4$ (0.26 g, 6.8 mmol) in 15 mL of anhydrous THF. The reaction mixture was refluxed for 16 h and cooled to room temperature. Water (0.3 mL) was carefully added; then 15% KOH (0.3 mL) and an additional portion of water (0.3 mL) were added. The mixture was stirred at room temperature for 30 min. The precipitate was filtered off and washed with THF (50 mL). The filtrate was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (50 mL), washed with brine, and dried with anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel with $CHCl_3$ as an eluent to give compound **6b** (0.58 g, 87%), m.p. 139—140 °C (from heptane). Found (%): C, 82.08; H, 6.47; N, 11.05. $C_{17}H_{16}N_2$. Calculated (%): C, 82.22; H, 6.49; N, 11.28. IR, ν/cm^{-1}: 715 (Ph), 760, 3325 (N—H). ^{1}H NMR, δ: 2.59 (br.s, 1 H, NH); 3.05 (dd, 1 H, C(3)H_a, J = 13.2 Hz, J = 4.6 Hz); 3.49 (dd, 1 H, C(3)H_b, J = 13.0 Hz, J = 4.8 Hz); 4.11 (d, 1 H, C(1)H_a, J = 16.0 Hz); 4.20 (d, 1 H, C(1)H_b, J = 16.0 Hz); 5.43 (t, 1 H, PhC$\underline{H}$, J = 4.8 Hz); 6.24 (s, 1 H, C(10)H); 6.72 (d, 1 H, J = 8.0 Hz); 6.83 (t, 1 H, J = 7.5 Hz); 6.92 (d, 1 H, J = 7.4 Hz); 7.02 (d, 2 H, J = 6.8 Hz); 7.20—7.31 (m, 3 H); 7.45 (d, 1 H, J = 6.8 Hz). MS, m/z (I_{rel} (%)): 248 [M]$^+$ (38), 218 (36), 204 (31), 130 (18), 116 (31), 103 (94), 89 (100), 77 (77), 63 (49).

4-Methyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indole (7a). ***A.*** Sodium cyanoborohydride (0.23 g, 3.6 mmol) was added to a solution of 4-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole hydrochloride (**6a**) (0.2 g, 0.9 mmol) in glacial AcOH (10 mL). The reaction mixture was stirred at ~20 °C for 4 h and then water (15 mL) was added. The mixture was stirred for an additional 30 min and alkalified with 30% KOH to pH ~12. The product was extracted with $CHCl_3$ (5×15 mL). The extract was washed with brine and dried with Na_2SO_4. The solvent was removed *in vacuo* to give a mixture of diastereomers (0.15 g, 90%); the ratio of the diastereomers was 1 : 10 (^{1}H NMR data).

B. A 4 *M* solution of HCl (1 mL) in dioxane was added to a solution of 4-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole hydrochloride (**6a**) (0.1 g, 0.45 mmol) in 5 mL of anhydrous MeOH. The reaction mixture was cooled to –20 °C and

$NaBH_3CN$ (0.2 g, 3.1 mmol) was added. The mixture was stirred at −10 to −5 °C for 9 h, diluted with water (10 mL), stirred for an additional 30 min, and alkalified with 30% KOH to pH ~12. The product was extracted with $CHCl_3$ (5×15 mL). The extract was washed with brine and dried with Na_2SO_4. The solvent was removed *in vacuo*. The conversion was 82% and the content of the minor diastereomer did not exceed 3% (^{1}H NMR data). The starting compound was separated by column chromatography on silica gel with $CHCl_3$—MeOH (100 : 1) as the eluent. The product was isolated as dihydrochloride and recrystallized from ethanol—ether to give the individual major diastereomer (86 mg, 73%). Found (%): C, 76.08; H, 8.52; N, 14.57. $C_{12}H_{16}N_2$. Calculated (%): C, 76.55; H, 8.57; N, 14.88. IR, ν/cm^{-1} (for the free base): 755 (Ar), 1610 (Ar), 3320 (N—H). ^{1}H NMR ($CDCl_3$), δ: 1.23 (d, 3 H, CH_3, J = 6.8 Hz); 2.16 (br.s, 1 H, NH); 2.50 (dd, 1 H, C(10)H_a, J = 14.9 Hz, J = 9.5 Hz); 2.71 (t, 1 H, C(1)H_a, J = 11.3 Hz); 2.80 (d, 1 H, C(3)H_a, J = 12.2 Hz); 2.91 (dd, 1 H, C(10)H_b, J = 14.9 Hz, J = 7.9 Hz); 3.00—3.10 (m, 2 H, C(1)H_b, C(3)H_b); 3.69—3.75 (m, 2 H, C(4)H, C(10a)H); 6.36 (d, 1 H, C(6)H, J = 8.0 Hz); 6.59 (t, 1 H, C(8)H, J = 7.3 Hz); 7.03—7.06 (m, 2 H, C(7)H, C(9)H). ^{13}C NMR ($CDCl_3$), δ: 11.98 (CH_3); 32.81 (C(10)); 46.52 (C(4)); 49.34 (C(3)); 50.84 (C(1)); 57.31 (C(10a)); 105.36 (C(6)); 116.88 (C(8)); 124.57 (C(9)); 127.34 (C(7)); 128.56 (C(9a)); 150.02 (C(5a)). The signals in the ^{1}H and ^{13}C NMR spectra were assigned from the COSY and HMBC data. MS, m/z (I_{rel} (%)): 188 $[M]^+$ (6), 144 (35), 130 (14), 117 (29), 89 (37), 77 (16), 43 (100).

(4*R*,10a*R*)-4-Methyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indole ((4*R*,10a*R*)-7a) was obtained in 76% yield as described for racemate **7a** in procedure ***B***; $[\alpha]_D^{20}$ −35.0 (*c* 2.0, MeOH). Its spectral characteristics agree with the data for the racemate.

4-Phenyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indole (7b) was obtained as described for 4-methyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indole (**7a**) in procedure ***A***. The yield of compound **7b** was 79% (*de* 86%). Found (%): C, 81.29; H, 6.93; N, 11.02. $C_{17}H_{18}N_2$. Calculated (%): C, 81.56; H, 7.25; N, 11.19. IR, ν/cm^{-1}: 715 (Ph), 765, 1610, 3320 (N—H). ^{1}H NMR (C_6D_6), δ: 2.43—2.57 (m, 2 H); 2.61—2.75 (m, 2 H); 2.78—2.88 (m, 2 H); 3.01—3.13 (m, 1 H); 3.73 (dd, 1 H, C(10a)H, J = 10.01 Hz, J = 3.5 Hz); 5.88 (d, 1 H, PhC<u>H</u>, J = 7.3 Hz); 6.67—6.75 (m, 2 H); 6.95—7.24 (m); 7.35 (d, 2 H, J = 6.6 Hz). MS, m/z (I_{rel} (%)): 250 $[M]^+$ (4), 206 (42), 118 (22), 104 (30), 89 (37), 77 (35), 44 (100).

Reduction of 4-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-3-one (4a) with the dimethyl sulfide—borane complex. The complex $BH_3 \cdot Me_2S$ (0.38 g, 5 mmol) was added to a solution of 4-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indol-3-one (**4a**) (0.2 g, 1 mmol) in anhydrous THF (10 mL) and Me_2S was removed. The reaction mixture was refluxed for 12 h and MeOH (5 mL) was added with cooling. The solvent was removed *in vacuo* and the residue was dissolved in 12% HCl (10 mL), refluxed for 1 h, and alkalified with 30% KOH to pH ~12. The product was extracted with dichloromethane (5×20 mL). The extract was washed with brine and dried with anhydrous Na_2SO_4. Volatile compounds were removed *in vacuo* to give a mixture (0.33 g) of 4-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole (**6a**) (25%) and 4-methyl-1,2,3,4,10,10a-hexahydropyrazino[1,2-*a*]indole (**7a**) (75%). Compound **7a** was a 1 : 2 mixture of diastereomers (^{1}H NMR data).

References

1. A. R. Katritzky, A. K. Verma, H.-Y. He, and R. Chandra, *J. Org. Chem.*, 2003, **68**, 4938.
2. Ger. Offen. 2 162 422, *Chem. Abstr.*, 1973, **79**, 66402.
3. F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Nayler, *J. Chem. Soc.*, 1956, **8**, 2854.
4. O. Mitsunobu, *Synthesis*, 1981, 1.
5. A. V. Karchava, M. A. Yurovskaya, T. R. Wagner, B. L. Zybailov, and Y. G. Bundel, *Tetrahedron*: *Asymmetry*, 1995, **6**, 2895.
6. A. V. Kurkin, V. V. Nesterov, A. V. Karchava, and M. A. Yurovskaya, *Khim. Geterotsikl. Soedin.*, 2003, 1665 [*Chem. Heterocycl. Compd.*, 2003 (Engl. Transl.)].
7. S. S. Bhagwat and C. Gude, *Tetrahedron Lett.*, 1994, **35**, 1848.
8. A. Bombrun and G. Casi, *Tetrahedron Lett.*, 2002, **43**, 2187.
9. C. A. Brown, *J. Org. Chem.*, 1970, **35**, 1900.
10. S. Caddick, D. B. Judd, A. K. d. K. Lewis, M. T. Reich, and M. R. V. Williams, *Tetrahedron*, 2003, **59**, 5420.
11. R. J. Sundberg, *Indoles*, Academic Press, London—San Diego—New York—Boston, 1966, 145.

Received October 27, 2004