Synthesis and Stereochemistry of Oxazolo[4',5':1,2]benz[5,4,3-*c,d*]-indole Derivatives as Intermediates on the Way to a Selective Dopamine Autoreceptor Agonist

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Dedicated to Prof. Dr. G. Rücker, Bonn, on the occasion of his 65th birthday

An expedient and practical variant of the synthesis of the selective dopamine autoreceptor agonist **5** from the benzindolone **1** is described. The reaction sequence includes a two-fold epimerization at the α-position of the lactam function. The structure of the intermediate **9a** was confirmed by X-ray structure analysis.

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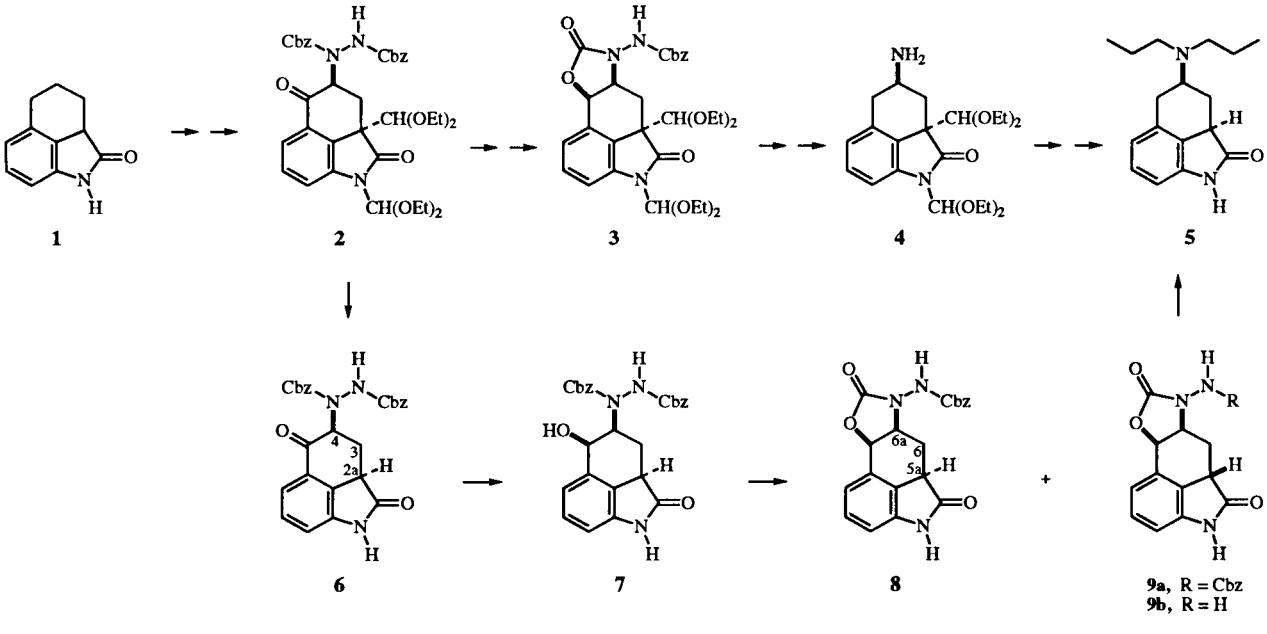
Selective agonists at the presynaptically localized dopamine autoreceptor inhibit dopamine synthesis, release and neuronal firing and, thus, can serve as atypical neuroleptics for the treatment of schizophrenia [1,2]. Previously, we have reported synthesis and pharmacological investigations of the novel aminobenzindolone **5** [3,4]. According to receptor binding studies and functional *in vivo* experiments, this tricyclic ergoline analog showed strong and selective activity at the dopamine D-2 autoreceptor. For a diastereoselective synthesis of **5** the diethoxymethyl protected hydrazino ketone **2**, which is readily available from tetrahydrobenz-[*c,d*]indole-2(1*H*)-one **1**, was used as an educt. The key steps of the synthesis were the introduction of a nitrogen equivalent into position 4 by a diastereoselective electrophilic amination and a reductive degradation of **2** by *cis* selective lithium triethylborohydride reduction followed by hydrogenolysis of the thus formed oxazolidinone **3**. In contrast to previous experiences when we established this methodology based on tetralones [3,5,6], the hydrogenolytic cleavage of the endocyclic benzylic position and the *N,N*-bond of **3** required high pressure (50 bar) and was only possible successively. Thus, three reaction steps had been necessary to afford the primary amine **4**. Obviously, this is due to the steric demand of the protecting group in position 2a which makes it difficult for the molecule to approach to the catalyst.

For a more expedient synthesis of the final product **5** we planned to remove the diethoxymethyl group [7] before the reductive reaction steps. Thus, the amination product **2** was treated with trifluoroacetic acid to give **6** under complete retention at C-2a. We expect that this is due to thermodynamic control, because the *cis* configuration allows an equatorial orientation of the hydrazine substituent. The relative configuration of **6** was assigned by ^{1}H nmr spectroscopy

Scheme 1



when the coupling constants of H-3_{ax} (q, J = 12 Hz) indicated an antiperiplanar orientation in relation to H-4 and H-2a. Due to *steric approach control* [8] treatment of **6** with lithium triethylborohydride at -78° gave an exclusive equatorial attack of the keto group resulting in formation of the *cis* hydrazino alcohol **7**. For a complete conversion of the ketone **6** it was necessary to employ an excess of the reducing agents. Obviously, the acidic protons in the positions 1 and 2a lead to consumption of approximately one equivalent. Depending on the work up conditions, it could be controlled whether **7** was isolated (hydrolysis at dry ice temperature) or oxazolidinone formation was allowed (hydrolysis after warming up to room temperature). Spectroscopic analysis of the crude product showed that two diastereomeric oxazolidinones were formed in a 5:1 ratio. Interestingly, only the minor isomer **8** gave the characteristic coupling pattern for H-6_{ax} (q, J = 11.7 Hz) indicating *cis* configuration between H-5a and H-6a. For the major isomer **9a** the respective values (J = 13.9, 12.5, 2.9 Hz) indicated an approximately equatorial disposition for H-6a which is only possible after epimerization at C-2a. Recrystallization gave **9a** as a single diastereomer. The structure of **9a**, including an oxazolidinone moiety which is positioned almost perpendicularly onto the half-chair of the cyclohexene fragment, was confirmed by single crystal X-ray analysis (Figure 1). This structural feature which we observed also for conformationally more flexible oxazolidinone fused tetralin derivatives [5,6] seems to be the driving force for the epimerization reaction. Hydrogenation of **9a** under atmospheric pressure resulted in *N,N*-bond cleavage and reductive ring opening at the benzylic C,O bond when Raney-Ni was used as a catalyst whereas selective removal of the Cbz group to give **9b** was observed under the influence of Pd/C. Without isolation of the primary amine obtained under Raney-Ni catalysis, the reaction sequence was completed by reductive alkylation (propionaldehyde, sodium cyanoborohydride) to give the target product **5**. The spectroscopic data of the product were identical with those of the material obtained *via* **3** indicating a thermodynamically favored equatorial disposition of the amino group and thus, a further epimerization at C-2a after cleavage of the oxazolidinone ring.

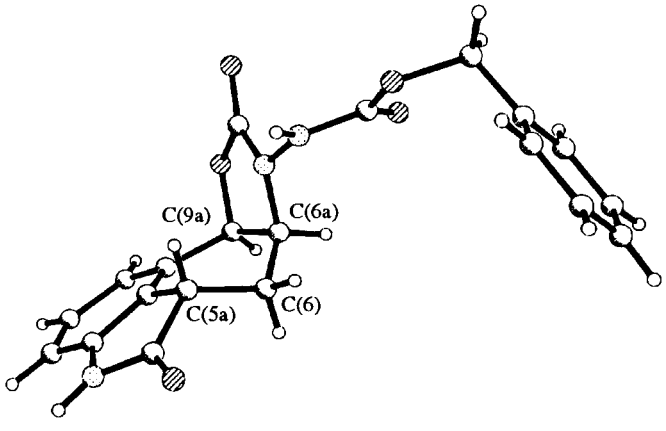


Figure 1. X-ray structure of compound **9a**.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from sodium/benzophenone, immediately before use. All liquid reagents were also purified by distillation. Tetrahydrobenz[*c,d*]indole-2(1*H*)-one (**1**) was purchased from Aldrich Inc. Unless otherwise noted reactions were conducted under dry nitrogen. Evaporations of final product solutions were done *in vacuo* with a rotatory evaporator. Flash chromatography was carried out with 230-400 mesh silica gel. Melting points were obtained on a Büchi melting point apparatus, and are uncorrected. The ir spectra were observed on a Perkin Elmer 881 spectrometer. The mass spectra were obtained on a Varian CH7 instrument, the nmr spectra on a Jeol JNM-GX 400 spectrometer at 400 MHz, using tetramethylsilane as internal standard, and the elemental analyses were determined on a Heraeus CHN Rapid instrument.

Dibenzyl 1-{(2a*RS*,4*SR*)-1,2,2a,3,4,5-Hexahydro-2,5-dioxobenz-[*c,d*]indolyl}-1,2-hydrazine dicarboxylate (**6**).

A solution of **2** (3.07 g, 4.45 mmoles, prepared as reported in refs [3,4]) in dichloromethane (30 ml) and TFA (10 ml) was stirred for 45 minutes at rt. After addidion of saturated aqueous sodium bicarbonate and dichloromethane the organic layer was dried (magnesium sulfate) and evaporated and the residue was purified by flash chromatography (petroleum ether-ethyl acetate 2:3) to give **6** (1.71 g, 80%) as colorless crystals, mp 194°; ir (potassium bromide): ν 3280, 1720, 1700 cm^{-1}; ^1H nmr (DMSO-d_6, 100°): δ 2.13 (q, J = 12.0 Hz, 1H, 3-H_{ax}), 2.75-2.78 (m, 1H, 3-H_{eq}), 4.00 (dd, J = 12.0, 4.4 Hz, 1H, 2a-H), 5.04-5.11 (m, 5H, 2 x OCH_2, 4-H_{ax}), 7.00-7.02 (m, 1H, ar), 7.25-7.30 (m, 12H, ar), 9.08 (br-s, 1H, NH), 10.15 (s, 1H, NH); ms: m/z 486 (M^+).

Anal. Calcd for $C_{27}H_{23}N_3O_6$: C, 66.80; H, 4.78; N, 8.65. Found C, 66.75; H, 4.95; N, 8.52.

Dibenzyl 1-{(2a*RS*,4*SR*,5*SR*)-1,2,2a,3,4,5-Hexahydro-5-hydroxy-2-oxobenz[*c,d*]indol-4-yl}-1,2-hydrazinedicarboxylate (**7**).

To a solution of **6** (145 mg, 0.3 mmole) in THF (8 ml) was slowly added lithium triethylborohydride (0.75 ml, 1 *M* solution in THF) at -78°. After being stirred for 90 minutes at -78° saturated aqueous ammonium chloride and dichloromethane were added. The organic layer was dried (magnesium sulfate) and evaporated and the residue was purified by flash chromatography (petroleum ether-ethyl acetace 2:3) to give **7** (90 mg, 62%) as colorless crystals, mp 167-168°; ir (potassium bromide): ν 3280, 1710 cm^{-1}; ^1H nmr (DMSO-d_6, 100°): δ 1.61 (ddd, J = 12.5, 11.7, 11.0 Hz, 1H, 3-H_{ax}), 2.31-2.33 (m, 1H, 3-H_{eq}), 3.47 (dd, J = 11.7, 5.9 Hz, 1H, 2a-H), 4.67-4.69 (m, 1H, 4-H_{ax}), 4.86 (d, J = 4.4 Hz, 1H, 5-H), 5.04-5.11 (m, 4H, 2 x OCH_2), 6.66 (d, J = 7.7 Hz, 1H, 8-H), 6.91 (d, J = 7.7 Hz, 1H, 6-H), 7.10 (t, J =7.7 Hz, 1H, 7-H), 7.29-7.33 (m, 10H, Ph), 9.86 (s, 1H, NH).

Anal. Calcd. for $C_{27}H_{25}N_3O_6$: C, 66.52; H, 5.17; N, 8.62. Found: C, 66.53; H, 5.37; N, 8.42.

Benzyl *N*-{(5a*RS*,6a*SR*,9a*RS*)-4,5,5a,6,6a,7,8,9a-Octahydro-5,8-dioxooxazolo[4',5':1,2]benz[5,4,3-*c,d*]indol-7-yl}carbamate (**8**) and Benzyl *N*-{(5a*RS*,6a*RS*,9a*RS*)-4,5,5a,6,6a,7,8,9a-Octahydro-5,8-dioxooxazolo[4',5':1,2]benz[5,4,3-*c,d*]indol-7-yl}carbamate (**9a**).

To a solution of **6** (1.03 g, 2.12 mmoles) in THF (65 ml) was slowly added lithium triethylborohydride (5.3 ml, 1 *M* solution in THF) at -78°. After being stirred for 180 minutes at -78° and another 60 minutes at rt saturated aqueous ammonium chloride and ethyl acetate were added. The organic layer was dried (magnesium sulfate) and evaporated and the residue was purified by flash chromatography (petroleum ether-ethyl acetace 2:3) to give a mixture of the diastereomers **8** and **9a** (ratio of isomers: 1:5); ^{1}H nmr data of **8** (DMSO-d_6, 100°): δ 1.10 (q, 11.7 Hz, 1H, 6-H_{ax}), 2.49-2.55 (m, 1H, 6-H_{eq}), 3.32 (dd, J = 11.7, 5.1 Hz, 1H, 5a-H), 4.47 (ddd, J = 11.7, 8.1, 5.1 Hz, 1H, 6a-H), 5.17 (s, 2H, OCH_2), 5.64 (d, J = 8.1 Hz, 1H, 9a-H), 6.83 (d, J = 7.3 Hz, 1H, 3-H), 7.00 (d, J = 8.1 Hz, 1H, 1-H), 7.23 (dd, J = 8.1, 7.3 Hz, 1H, 2-H), 7.30-7.38 (m, 5H, Ph), 9.35 (br-s, 1H, NH), 9.85 (br-s, 1H, NH). Recrystallization of **8,9a** from ethyl acetate afforded pure **9a** (563 mg, 70%) as colorless crystals, mp 186°; ir (potassium bromide): ν 3330, 3230, 1770, 1720, 1700 cm^{-1}; ^{1}H nmr (DMSO-d_6, 130°): δ 1.49 (ddd, J = 13.9, 12.5, 2.9 Hz, 1H, 6-H_{ax}), 2.53 (ddd, J = 13.9, 4.8, 1.9 Hz, 1H, 6-H_{eq}), 3.63 (dd, J = 12.5, 4.8 Hz, 1H, 5a-H), 4.53 (ddd, J = 8.1, 2.9, 1.9 Hz, 1H, 6a-H), 5.17 (s, 2H, OCH_2), 5.66 (d, J = 8.1 Hz, 1H, 9a-H), 6.83 (d, J = 7.3 Hz, 1H, 3H), 6.99 (d, J = 8.1 Hz, 1H, 1-H), 7.21 (dd, J = 8.1, 7.3 Hz, 1H, 2-H), 7.30-7.39 (m, 5H, Ph), 9.35 (br-s, 1H, NH), 9.85 (br-s, 1H, NH); ms: m/z 379 (M^+).

Anal. Calcd. for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.44; H, 4.73; N, 10.75.

(5a*RS*,6a*RS*,9a*SR*)-7-Amino-5a,6a,7,9a-tetrahydrooxazolo-[4',5':1,2]benz [5,4,3-*c,d*]indole-5,8(4*H*,6*H*)-dione (**9b**).

A mixture of **9a** (38 mg, 0.1 mmole) and Pd/C (15 mg, 10%) in methanol (6 ml) was stirred for 1 hour at rt under a balloon of hydrogen. Then, the reaction mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography (dichloromethane-methanol 95:5) to give **9b** (18 mg, 74%) as colorless crystals, mp 196°; ir (potassium bromide): ν 3330, 3200, 1760, 1700 cm^{-1}; ^{1}H nmr (methanol-d_6): δ 1.49 (ddd, J = 13.2, 12.5, 3.7 Hz, 1H, 6-H_{ax}), 2.91 (ddd, J = 13.2, 4.4, 2.2 Hz, 1H, 6-H_{eq}), 3.51 (dd, J = 12.5, 4.4 Hz, 1H, 5a-H), 4.41 (ddd, J = 8.8, 2.9, 2.2 Hz, 1H, 6a-H), 5.62 (d, J = 8.8 Hz, 1H, 9a-H), 6.89 (d, J = 7.3 Hz, 1H, 3-H), 7.07 (d, J = 7.3 Hz, 1H, 1-H), 7.27 (t, J = 7.3 Hz, 1H, 2-H); ms: m/z 245 (M^+).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 59.13; H, 4.89; N, 16.40.

(2a*RS*,4*SR*)-4-Dipropylamino-2a,3,4,5-tetrahydrobenz[*c,d*]-indole-2(1*H*)-one (**5**).

A mixture of **9a** (30 mg, 0.078 mmole) and catalytic amounts of Raney-Ni in methanol (6 ml) was stirred for 24 hours at rt under a balloon of hydrogen. After the reaction mixture was filtered sodium cyanoborohydride (5 mg, 0.08 mmole) and propionaldehyde (28 µl, 0.08 mmole) were added to the filtrate. After being stirred for 14 hours at rt aqueous hydrochloric acid (2 *N*) and ethyl ether were added. The aqueous layer was treated with an excess of sodium carbonate and then extracted with dichloromethane. The organic layer was dried (magnesium sulfate) and evaporated and the residue was purified by flash chromatography (*n*-hexane/isopropanol/dimethylethylamine 95:5:1) to give **5** (2 mg, 10%) as a colorless oil with analytical data being identical with those reported in ref [4].

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