A Convenient Synthetic Route to Spiro[indole-3,4′-piperidin]-2-ones

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Starting from 1-[(*tert*-butoxy)carbonyl]piperidine-4-carboxylic acid and 2-bromoaniline, the spiro[indole-3,4′-piperidin]-2-one system was obtained in three high-yielding steps: anilide formation, *N*(1)-protection, and intramolecular cyclization under Pd catalysis as the key reaction. The preparation of the corresponding 2-bromoanilide was studied. In extension, the same sequence was developed with 4-methyl- and 4-nitro-2-bromoaniline. In the key step, the NO_2 group led to a rather diminished yield. The transformation of the protected spiro[indole-3,4′-piperidin]-2-one to the corresponding unprotected dihydroindoles is discussed.

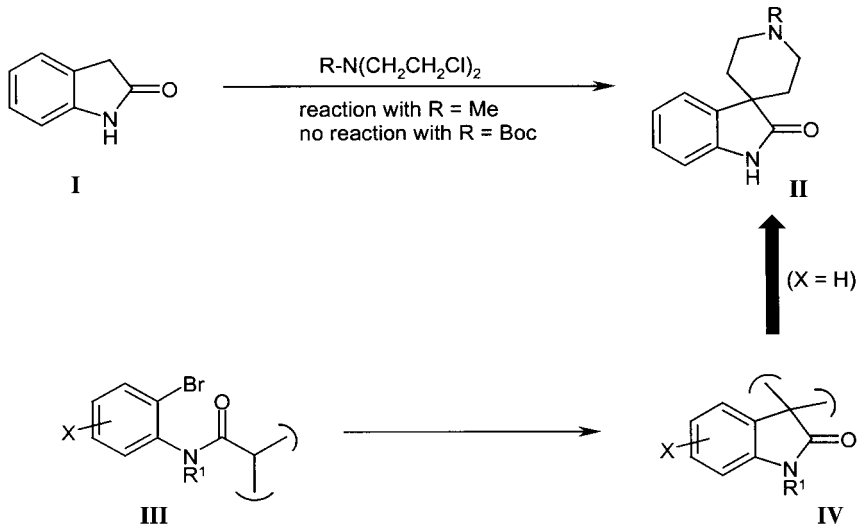
Introduction. – 1,2-Dihydrospiro[indole-3,4′-piperidines] and 1,2-dihydro[indole-3,4′-piperidin]-2-ones are key moieties of a variety of biologically active compounds, such as growth hormone secretagogues (*Ibutamoren*, *MK-0677*) [1], neurokinin antagonists [2], oxytocin antagonists [3], monoamine transporter inhibitors [4], and bradykinin antagonists [5]. For the ability of certain molecular units to interact with certain receptors, the term 'privileged structures' has been coined [6]. This has led to a significant interest in developing efficient methods for their preparation.

The reduction of the C=O group of the 3,3-disubstituted dihydroindol-2-ones, leading to the corresponding dihydroindoles is a well-investigated literature procedure [7]. With sodium bis(2-methoxyethoxy)aluminium hydride as the reducing agent, this transformation is carried out with an excellent yield [7]. Therefore, the 1,2-dihydrospiro[3*H*-indole-3,4′-piperidin]-2-ones are appropriate targets for a general and flexible synthesis of different phenyl substituted derivatives.

The most straightforward route to 1,2-dihydrospiro[3*H*-indole-3,4′-piperidin]-2-ones involves the conversion of indolone **I** with the highly toxic and carcinogenic 2,2′-dichloro-*N*-methyldiethylamine hydrochloride to give the spirocyclic compound **II** [5] (*Scheme 1*). The *N*-Me group should be removed in a two-step procedure involving demethylation with 2,2,2-trichloroethyl chloroformate and cleavage of the corresponding carbamate with Zn. However, treatment of **I** with *N*-[(*tert*-butoxy)carbonyl]-2,2′-dichloro-*N*-methyldiethylamine to prepare the corresponding **II** was unsuccessful [5].

The preparation of indol-2-ones of general structure **IV** by means of a Pd-catalyzed intramolecular amide arylation of a variety of 2′-bromoanilides **III** has recently been described [8] (*Scheme 1*), stating that both electron-withdrawing (*i.e.*, X = 4′-CN) and electron-donating (*i.e.*, X = 4′-OMe) substituents on the aromatic ring of the

Scheme 1. *Synthetic Routes to 1,2-Dihydrospiro[3*H*-indole-3,4′-piperidin]-2-ones*



2′-bromoanilide substrate are tolerated. To our knowledge, the application of this intramolecular α-arylation of amides for the synthesis of 1,2-dihydrospiro[3*H*-indole-3,4′-piperidin]-2-ones has not been described.

To realize this concept, the preparation of these spiropiperidines from commercially available 1-[(*tert*-butoxy)carbonyl]piperidine-4-carboxylic acid (**2**, *N*-Boc-isonipecotic acid) is reported in the present communication.

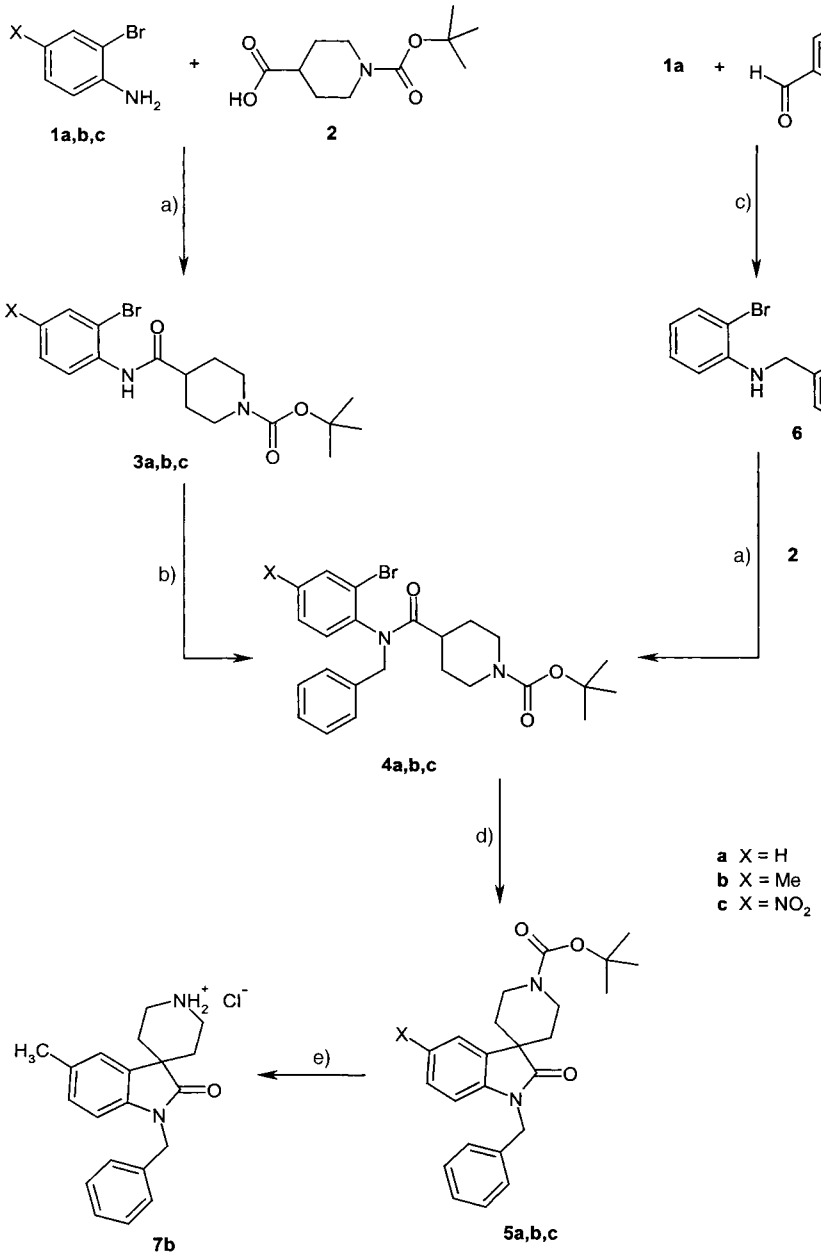
Results and Discussion. – For this purpose, the 2′-bromoanilides **3a**–**c** had to be prepared from *N*-Boc-isonipecotic acid (**2**) and the selected 2-bromoanilines **1a**–**c**, which, in turn, had to be protected by *N*-benzylation to give **4a**–**c**, representing the key intermediates for the cyclization step to the target compounds **5a**–**c** (*Scheme 2*).

Initial attempts, however, to prepare the 2′-bromoanilide **3a** from 2-bromoaniline **1a** and the acid-sensitive starting compound **2** by means of several peptide-coupling techniques (*e.g.*, DCC, DMF; EDC, HOBt, NMM, THF or DMF; 2,4-dinitrobenzenesulfonyl chloride, Et_3N, DMAP, MeCN; $POCl_3$, Et_3N, CH_2Cl_2) gave only a low yield or failed completely.

At this stage, the low reactivity of 2-bromoaniline **1a** was studied briefly in a test system (*Scheme 3*). Thus, the imidazolide **8** was prepared from the acid **2**. After addition of **1a** to a solution of **8** and stirring the mixture for 24 h, not even a trace of product was formed, whereas after addition of aniline to the same reaction mixture, conversion was almost complete within 40 minutes to give anilide **9**. On the other hand, the less nucleophilic pyridin-2-amine **10** reacted smoothly with the imidazolide **8** to give the *N*-(pyridin-2-yl)carboxamido compound **11**. These experiments clearly demonstrate the drastic *o*-bromo effect of these anilines due to steric hindrance.

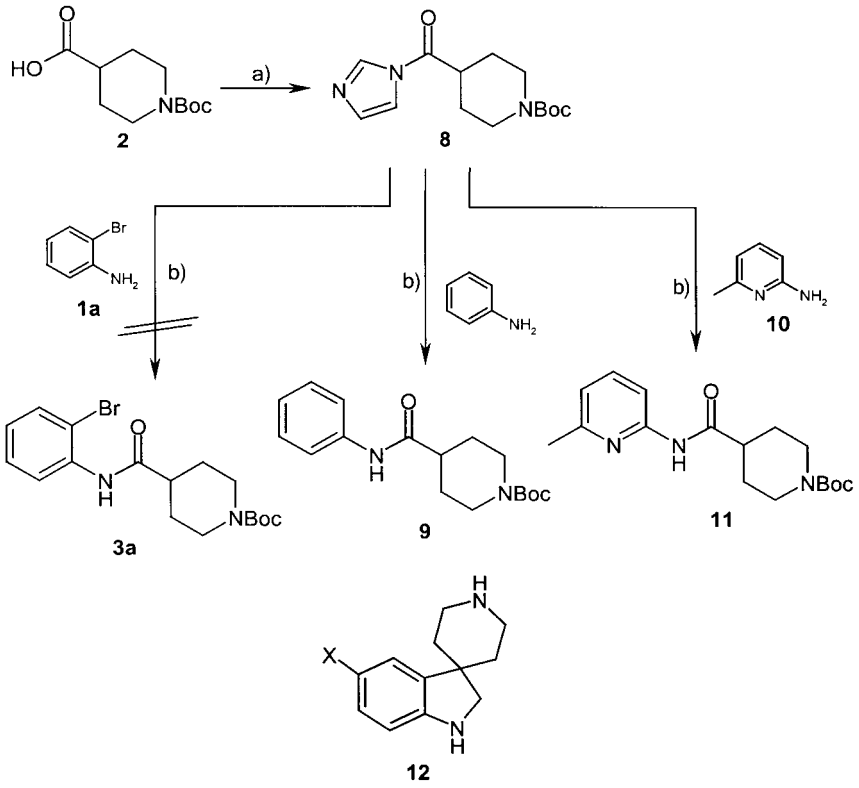
Finally, it was found that the only method to obtain the 2′-bromoanilides **3a**–**c** in high yield involves formation of the acid chloride of **2** under non-acidic conditions ($SOCl_2$, pyridine, CH_2Cl_2) and subsequent *in situ* reaction with the anilides **1a**–**c** in the

Scheme 2



a) 1. $SOCl_2$, pyridine, CH_2Cl_2, r.t.; 2. Et_3N, 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2; **3a**, 71%, **3b**: 84%, **3c**: 67%, **4a**: 86%. b) BnCl, KF-Al_2O_3, MeCN/1,2-dimethoxyethane (DME), r.t.; **4a**: 80%, **4b**, 95%, **4c**: 86%. c) 1. Toluene, reflux; 2. $NaBH_4$, MeOH, r.t.; 54% (as HCl salt). d) *t*-BuONa, [Pd(dba)$_2$], 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene (BINAP), dioxane, 95–110°; **5a**: 80%, **5b**: 78%, **5c**: 22%. e) **5b**, HCl in dioxane, Et_2O; 86%.

Scheme 3



a) 1,1′-Carbonyldiimidazole (CDI), CH_2Cl_2, r.t., 87%. b) THF, r.t.; **3a**: no reaction, **9**: fast reaction, **11**: 73% (crude).

presence of Et_3N and 4-(dimethylamino)pyridine (DMAP). Even the least nucleophilic aniline **1c** could be converted easily under severer conditions.

To protect the anilide N-atom, benzylation was performed with BnCl, KF-Al_2O_3 [9]. Very clean reactions did actually occur, and the *N*-Bn anilides **4a**–**c** could be isolated in very high yield, but very long reaction times were usually required for complete conversion.

Additionally, an alternative route was developed, exemplified by the preparation of **4a** (*Scheme 2*). Thus, reductive amination of benzaldehyde with **1a** to *N*-benzyl-2-bromoaniline **6** and subsequent anilide formation with acid **2** in the usual way proceeded without any complications.

With the key intermediates **4a**–**c** in hand, their Pd-mediated cyclizations were performed under the conditions described in [8] (*t*-BuONa, [Pd(dba)$_2$], *rac*-BINAP, (2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene), dioxane, 100°, 3–4.5 h). As expected, the unsubstituted anilide **4a** and the more electron-rich derivative **4b** reacted smoothly (*ca.* 80% yield) to yield the spirocycles **5a** and **5b**. The cyclization of the electron-deficient anilide **4c** represented a particular challenge, as it is well-known [10] that aromatic NO_2 compounds are rapidly affected, undergoing side reactions under

these harsh conditions. Nevertheless, as in the other cases, the cyclization took place and the nitro derivative **5c** could easily be isolated in pure state – albeit in low yield – after 3 h. No further attempts at optimization to enhance the yield were undertaken.

In addition, the *N*-Boc protecting group was removed in the case of **5b** to yield the spiropiperidine hydrochloride **7b**.

Conclusions and Perspectives. – An easy and efficient preparative route to 1,2-dihydrospiro[3*H*-indole-3,4′-piperidin]-2-ones is presented. The readily prepared 2′-bromoanilides **4a**–**c** were cyclized by Pd catalysis to afford the spiro compounds **5a**,**b** in high yield. An aromatic NO_2 substituent, however, limited the applicability.

Furthermore, overall conversion to the 1,2-dihydrospiro[3*H*-indole-3,4′-piperidines] **12** should be possible following literature procedures for similar compounds: reduction of the C=O group of 1,2-dihydroindol-2-ones as mentioned before (*Red-Al*, toluene [7] or $LiAlH_4$, Et_2O [11]) and subsequent *N*-debenzylation (H_2, Pd/C [12], or irradiation [13]) or, *vice versa*, *N*-debenzylation (Na, liq. NH_3 [14]) prior to reduction of the C=O group [7].

Proceeding from the commercially available isomeric piperidine- and pyrrolidine-carboxylic acids, investigations of the syntheses of the corresponding unprotected – hitherto unknown – 1,2-dihydrospiro[indole-piperidines] and 1,2-dihydrospiro[indole-pyrrolidines] are in progress.

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Experimental Part

General. 1-[(*tert*-Butoxy)carbonyl]piperidine-4-carboxylic acid was purchased from *Chess* and KF-Al_2O_3 from *Fluka*. TLC: *Merck 60 F-254* silica-gel plates. Flash-column chromatography (FC): silica gel (*Baker*, 30–60 μm). The portions of solvents in solvent mixtures are given in parts by volume. M.p.: *HWS Labortechnik SGV 500 Plus* melting-point apparatus; uncorrected. IR Spectra: *Bruker 85 IFS 48 IR* or *Perkin-Elmer FT 1710* spectrophotometer. ^{1}H-NMR Spectra: *Bruker AC 200*, *Avance 200*, *WM 250*, or *Avance 400* spectrometer; chemical shifts (δ) in ppm relative to TMS. MS: electron impact (EI or fast atom bombardement, with a *Micromass VG 70-70E* or *70-250SE*, or with a *Finigan MAT 312* at 70 eV, respectively; *m*/*z*, relative intensity in %). High-resolution (HR) mass spectra (peak matching method): *Autospec M* or *VG-Autospec* from *Micromass*. Elemental microanalyses: *Elementar vario EL* (Hanau, Germany) CHNOS elemental analyzer.

Syntheses. tert-*Butyl 4-[[(2-Bromophenyl)amino]carbonyl]piperidine-1-carboxylate* (**3a**). $SOCl_2$ (0.80 ml, 11.01 mmol) was added, under N_2 and at r.t., to a mixture of N-*[(*tert-*butoxy)carbonyl]piperidine-4-carboxylic acid* (**2**; 2.115 g, 9.22 mmol), pyridine (1.90 ml, 23.56 mmol), and CH_2Cl_2 (13 ml) while stirring. After 25 min, a soln. of 2-bromoaniline (1.748 g, 10.16 mmol), Et_3N (4.50 ml, 32.33 mmol), and DMAP (113 mg, 0.92 mmol) in CH_2Cl_2 (16 ml) was added dropwise, and stirring was continued for 14 h. (TLC control: *t*-BuOMe/petroleum ether 1:1). The mixture was added to 2N HCl (100 ml), followed by extraction with *t*-BuOMe (100 ml). The org. phase was washed with 2N HCl (2 × 100 ml) and then with sat. Na_2CO_3 soln. (100 ml), and dried (Na_2SO_4). After inoculation, the product was crystallized from Et_2O to yield 2.514 g (71.1%) of **3a**. White solid. M.p. 137–139°. IR (KBr): 3294, 2926, 1693, 1668, 1581, 1527, 1173. ^{1}H-NMR ((D_6)DMSO): 9.41 (br. *s*, 1 H); 7.65 (*dd*, *J* = 1.5, 8.0, 1 H); 7.54 (*dd*, *J* = 1.7, 8.0, 1 H); 7.36 (*ddd*, *J* = 1.5, 7.6, 7.8, 1 H); 7.14 (*ddd*, *J* = 1.7, 7.7, 7.7, 1 H); 3.98 (*d*, *J* = 13.2, 2 H); 2.85–2.75 (*m*, 2 H); 2.69–2.57 (*m*, 1 H); 1.82 (*dd*, *J* = 3.2, 13.2, 2 H); 1.57–1.42 (*m*, *J* = 4.3, 12.7, 2 H); 1.41 (*s*, 9 H). FAB-MS: 385 (19), 383 (20, $M^{+\cdot}$), 329 (68), 327 (73), 249 (40), 112 (100). Anal. calc. for $C_{17}H_{23}BrN_2O_3$ (383.29): C 53.26, H 6.06, N 7.31, O 12.52; found: C 53.40, H 6.10, N 7.40, O 12.60.

tert-*Butyl 4-[[(2-Bromo-4-methylphenyl)amino]carbonyl]piperidine-1-carboxylate* (**3b**). In a flask with a reflux condenser, $SOCl_2$ (6.10 ml, 83.92 mmol) was added, under N_2 and at r.t., to a mixture of **2** (16.496 g, 71.95 mmol), pyridine (14.5 ml, 179.83 mmol), and CH_2Cl_2 (100 ml) while stirring vigorously. After 25 min, a soln. of 2-bromo-4-methylaniline (14.722 g, 79.13 mmol), Et_3N (35.0 ml, 251.46 mmol), DMAP (0.894 g,

7.32 mmol) in CH_2Cl_2 (120 ml) was added dropwise within 25 min, and stirring was continued for 14 h (TLC control: Et_2O/petroleum ether 1:2). The mixture was concentrated, added to 2N HCl (200 ml), and extracted with *t*-BuOMe (150 ml). The org. phase was washed with 2N HCl (2 × 200 ml), then with sat. Na_2CO_3 soln. (200 ml), and dried (Na_2SO_4). The crude product was crystallized from Et_2O/petroleum ether to yield 23.873 g (83.5%) of **3b**. White solid. M.p. 143–144°. IR (KBr): 3259, 2977, 1700, 1653, 1519, 1425, 1176. ^{1}H-NMR ((D$_6$)DMSO): 9.34 (br. *s*, 1 H); 7.47 (*d*, *J* = 1.9, 1 H); 7.37 (*d*, *J* = 8.2, 1 H); 7.16 (*dd*, *J* = 1.9, 8.2, 1 H); 3.96 (*d*, *J* = 13.3, 2 H); 2.85–2.70 (*m*, 2 H); 2.65–2.57 (*m*, 1 H); 2.27 (*s*, 3 H); 1.80 (*dd*, *J* = 2.9, 13.2, 2 H); 1.55–1.42 (*m*, 2 H); 1.40 (*s*, 9 H). EI-MS: 398 (4), 396 (5, $M^{+\bullet}$), 341 (7), 339 (8), 297 (26), 295 (27), 57 (100). Anal. calc. for $C_{18}H_{25}BrN_2O_3$ (397.32): C 54.41, H 6.35, Br 20.11, N 7.05, O 12.08; found: C 53.90, H 6.30, Br 19.80, N 7.00, O 12.20.

tert-*Butyl 4-[[(2-Bromo-4-nitrophenyl)amino]carbonyl]piperidine-1-carboxylate* (**3c**). While stirring vigorously at r.t., $SOCl_2$ (1.90 ml, 26.14 mmol) was slowly added dropwise, under N_2, to a soln. of **2** (5.152 g, 22.47 mmol) and pyridine (4.50 ml, 55.81 mmol) in CH_2Cl_2 (30 ml). Stirring was continued for 20 min. Subsequently, 2-bromo-4-nitroaniline (5.361 g, 24.70 mmol) and DMAP (4.121 g, 33.73 mmol) in CH_2Cl_2 (40 ml) were added dropwise within 15 min. The mixture was stirred at r.t. for 16 h; then Et_3N (6.0 ml, 43.1 mmol) was added. The mixture was then refluxed for 4.5 h and stirred at r.t. for a further 14 h (TLC control: Et_2O/petroleum ether 3:1). The mixture was added to 2N HCl (150 ml) and extracted with Et_2O (150 ml). The org. phase was washed first with 4N HCl (2 × 150 ml) and then sat. Na_2CO_3 soln. (150 ml). The Na_2CO_3 soln. was extracted twice with Et_2O (100 and 50 ml), the combined Et_2O phases were dried (Na_2SO_4), and the solvent was removed. A total of 6.49 g (67.4%) of pure **3c** was obtained by crystallization from CH_2Cl_2/Et_2O. M.p. 162–164°. IR (KBr): 3341, 2991, 1716, 1669, 1584, 1530, 1502, 1342, 1153. ^{1}H-NMR ((D$_6$)DMSO): 9.69 (br. *s*, 1 H); 8.47 (*d*, *J* = 2.6, 1 H); 8.23 (*dd*, *J* = 2.6, 9.0, 1 H); 8.04 (*d*, *J* = 9.0, 1 H); 3.99 (*d*, *J* = 13.2, 2 H); 2.88–2.70 (*m*, 3 H); 1.85 (*dd*, *J* = 3.2, 13.4, 2 H); 1.66–1.42 (*m*, 2 H); 1.41 (*s*, 9 H). FAB-MS: 430 (11), 428 (12, $M^{+\bullet}$), 374 (17), 372 (18), 217 (45), 91 (100). Anal. calc. for $C_{17}H_{22}BrN_3O_5$ (428.29): C 47.67, H 5.19, Br 18.65, N 9.81, O 18.68; found: C 47.60, H 5.20, Br 18.40, N 9.90, O 18.70.

tert-*Butyl 4-[[(Benzyl)(2-bromophenyl)amino]carbonyl]piperidine-1-carboxylate* (**4a**). *Method A:* The anilide **3a** (2.981 g, 7.78 mmol) was dissolved in MeCN (35 ml), and BnCl (1.20 ml, 10.42 mmol) as well as KF-Al_2O_3 (3.56 g, *ca.* 19.6 mmol) were added. The mixture was stirred at r.t. for 72 h (TLC control: *t*-BuOMe/petroleum ether 1:1). The solid substance was filtered by suction, and the solvent was removed. Crystallization from Et_2O yielded 2.933 g (79.7%) of pure **4c**. M.p. 120–122°.

Method B: A mixture of PhCHO (4.75 g, 44.8 mmol) and *2-bromoaniline* (**1a**) (7.07 g, 41.1 mmol) in toluene (40 ml) was refluxed on a water separator for 110 min, and the toluene (30 ml) was thereafter distilled off. After removal of the remaining solvent on a rotary evaporator, the residue was dissolved in dry MeOH (75 ml). While cooling in a water bath, $NaBH_4$ (7.0 g, 185.0 mmol) was added in portions during 48 h. After removal of the solvent, 0.1N NaOH (80 ml) was added, followed by extraction with CH_2Cl_2 (3 × 80 ml). The org. phase was dried (Na_2SO_4) and completely freed from solvent, yielding the known N-*benzyl-2-bromoaniline* (**6**) [15] as a raw product (8.35 g), the spectroscopic data of which conform with those given in the literature. This raw product (3.203 g) was taken up in Et_2O (20 ml), mixed with 4.0M HCl in dioxane (3.2 ml, 12.8 mmol), and left to stand for 14 h. It was decanted from the precipitate, which was then dissolved in boiling MeOH (5 ml). After cooling, the product was crystallized by slowly adding Et_2O (15 ml). Crystallization was completed at 0°, and the crystals were, after decantation of the solvent, washed with Et_2O: *N*-Benzyl-2-bromoaniline hydrochloride (**6** · HCl; 2.544 g, 69.7%; total yield, calculated on 2-bromoaniline: 54.0%). IR (KBr): 2880, 2846, 2608, 2576, 1474, 754. ^{1}H-NMR ((D$_6$)DMSO): 7.40 (*dd*, *J* = 1.5, 7.8, 1 H); 7.33–7.19 (*m*, 5 H); 7.06 (*ddd*, *J* = 1.5, 7.3, 8.3, 1 H); 6.52 (*dd*, *J* = 1.5, 8.3, 1 H); 6.48 (*ddd*, *J* = 1.5, 7.3, 7.8, 1 H); 6.37 (br. *s*, 2 H); 4.41 (*s*, 2 H). EI-MS: 263 (2), 261 (2, $[M-1]^{+\bullet}$), 173 (100), 171 (99), 92 (34). HR-MS: 261.0155 (calc. for $C_{13}H_{12}BrN$ $[M-H]^{+\bullet}$: 261.0153).

To a stirred soln. of **2** (5.372 g, 23.43 mmol) and pyridine (4.60 ml, 57.17 mmol) in CH_2Cl_2 (30 ml), $SOCl_2$ (2.14 ml, 29.44 mmol) was slowly added dropwise under N_2 and at r.t., and stirring was continued for 75 min. Subsequently, a soln. of **6** (raw product; 4.818 g of 69.7% purity, 12.82 mmol), Et_3N (6.30 ml, 45.26 mmol), and DMAP (159 mg, 1.30 mmol) in CH_2Cl_2 (30 ml) was swiftly added dropwise, and the mixture was stirred for a further 20 h (TLC control: *t*-BuOMe/petroleum ether 1:1). The mixture was concentrated and poured into 2N HCl (100 ml), followed by extraction with *t*-BuOMe (100 ml). The org. phase was washed with 2N HCl (100 ml) and then with sat. Na_2CO_3 soln. (100 ml), and dried (Na_2SO_4). Crystallization from Et_2O/petroleum ether yielded 5.220 g (86.0%) of **4a**. IR (KBr): 1691, 1651, 1475, 1433, 1403, 1229, 1168. ^{1}H-NMR ((D$_6$)DMSO): 7.82–7.77 (*m*, 1 H); 7.36–7.23 (*m*, 5 H); 7.16 (*dd*, *J* = 2.2, 7.8, 2 H); 7.06–7.01 (*m*, 1 H); 5.35 (*d*, *J* = 14.6, 1 H); 4.11 (*d*, *J* = 14.6, 1 H); 3.94–3.79 (*m*, 2 H); 2.45–2.39 (*m*, 1 H); 2.15–2.04 (*m*, 1 H); 1.64–1.54 (*m*, 3 H); 1.47–1.39

(*m*, 2 H); 1.38 (*s*, 9 H). FAB-MS: 475 (17), 473 (18, $M^{+\cdot}$), 419 (47), 317 (48), 91 (100). Anal. calc. for $C_{24}H_{29}BrN_2O_3$ (473.41): C 60.88, H 6.19, Br 16.88, N 5.92, O 10.14; found: C 60.90, H 6.30, Br 16.40, N 5.90, O 10.20.

tert-*Butyl 4-[[(Benzyl)(2-bromo-4-methylphenyl)amino]carbonyl]piperidine-1-carboxylate* (**4b**). BnCl (9.00 ml, 78.17 mmol) and KF-Al_2O_3 (27.11 g, *ca.* 149.1 mmol) were added to a soln. of **3b** (23.706 g, 59.66 mmol) in 1,2-dimethoxyethane (110 ml) and stirred at r.t. for 9 days (TLC control: *t*-BuOMe/petroleum ether 1:1). The solid substance was filtered by suction over *Celite*, the solvent was removed, and the residue was dried *in vacuo* at an increased temp. A non-crystallizable, highly viscous mass (30.487 g) resulted. A portion thereof (1.242 g) was purified by FC (silica gel; *t*-BuOMe/petroleum ether 3:4): semi-solid, sticky mass of **4b** (1.130 g), resulting in a 95.4% yield of the reaction. IR (KBr): 1695, 1662, 1493, 1401, 1365, 1231, 1168. ^{1}H-NMR ((D$_6$)DMSO): 7.68 (*d*, *J* = 1.8, 1 H); 7.31–7.21 (*m*, 4 H); 7.16–7.11 (*m*, 3 H); 6.89 (*d*, *J* = 8.0, 1 H); 5.35 (*d*, *J* = 14.6, 1 H); 4.05 (*d*, *J* = 14.6, 1 H); 3.93–3.79 (*m*, 2 H); 2.45–2.35 (*m*, 1 H); 2.30 (*s*, 3 H); 2.18–2.06 (*m*, 1 H); 1.64–1.53 (*m*, 3 H); 1.46–1.40 (*m*, 1 H); 1.38 (*s*, 9 H). FAB-MS: 489 (6), 487 (7, $M^{+\cdot}$), 433 (34), 431 (35), 91 (100). Anal. calc. for $C_{25}H_{31}BrN_2O_3$ (487.44): C 61.59, H 6.42, N 5.75, O 9.85; found: C 61.50, H 6.60, N 5.60, O 10.10.

tert-*Butyl 4-[[(Benzyl)(2-bromo-4-nitrophenyl)amino]carbonyl]piperidine-1-carboxylate* (**4c**). BnCl (3.00 ml, 26.06 mmol) and KF-Al_2O_3 (9.09 g, *ca.* 50.0 mmol) was added to a soln. of **3c** (8.530 g, 19.92 mmol) in MeCN (60 ml) and DME (75 ml), and stirred at r.t. for 13 days. After 9 days, additional BnCl (1.00 ml, 8.69 mmol), and, after 10.3 days, additional KF-Al_2O_3 (3.02 g, *ca.* 16.6 mmol) were added (TLC control: Et_2O/petroleum ether 3:1). The carrier was filtered by suction over *Celite*, the solvent was removed, and the product was purified by FC (silica gel; *t*-BuOMe/petroleum ether 1:1): 8.878 g, (86.0%) of **4c**. Colorless foam. M.p. 60–63°. IR (KBr): 1691, 1672, 1581, 1527, 1476, 1346, 1168. ^{1}H-NMR ((D$_6$)DMSO): 8.61 (*d*, *J* = 2.6, 1 H); 8.20 (*dd*, *J* = 2.6, 8.7, 1 H); 7.36 (*d*, *J* = 8.7, 1 H); 7.31–7.24 (*m*, 4 H); 7.17 (*d*, *J* = 8.0, 1 H); 5.29 (*d*, *J* = 14.7, 1 H); 4.26 (*d*, *J* = 14.7, 1 H); 3.88 (*d*, *J* = 13.0, 2 H); 3.81 (*d*, *J* = 12.3, 1 H); 2.51–2.45 (*m*, 1 H); 2.15–2.08 (*m*, 1 H); 1.64–1.55 (*m*, 2 H); 1.41–1.38 (*m*, 2 H); 1.37 (*s*, 9 H). FAB-MS: 520 (12), 518 (13, $M^{+\cdot}$), 464 (14), 462 (15), 91 (100). Anal. calc. for $C_{24}H_{28}BrN_3O_5$ (518.41): C 55.60, H 5.45, N 8.11, O 15.43; found: C 55.90, H 5.60, N 7.90, O 15.20.

tert-*Butyl 1-Benzyl-1,2-dihydro-2-oxospiro[(3*H*-indole-3,4′-piperidine]-1′-carboxylate* (**5a**). *t*-BuONa (2.713 g, 28.23 mmol), [Pd(dba)$_2$] (0.542 g, 0.94 mmol), and *rac*-BINAP (0.876 g, 1.41 mmol) were added to a soln. of **4a** (8.887 g, 18.77 mmol) in dry dioxane (1.65 ml). The mixture was stirred in a closed flask under N_2 at 100–110° for 4.5 h. 0.5N Citric acid (150 ml) was added, the soln. was diluted with H_2O (50 ml) and extracted with CH_2Cl_2 (1 × 100 and 2 × 50 ml). The org. phase was dried (Na_2SO_4) and liberated from solvent. A crystalline raw product was obtained from Et_2O/petroleum ether. FC of the raw product over silica gel with Et_2O/petroleum ether 14:13 and of the mother liquor with *t*-BuOMe/petroleum ether 5:9 produced 5.874 g (79.7%) of **5a**. Colorless crystals. M.p. 118–119°. IR (KBr): 1712, 1686, 1609, 1487, 1452, 1433, 1366, 1248. ^{1}H-NMR ((D$_6$)DMSO): 7.51 (*d*, *J* = 6.8, 1 H); 7.36–7.16 (*m*, 6 H); 7.15 (*t*, *J* = 7.4, 1 H); 6.89 (*d*, *J* = 7.7, 1 H); 4.90 (*s*, 2 H); 3.80–3.65 (*m*, 4 H); 1.75 (*t*, *J* = 6.0, 4 H); 1.45 (*s*, 9 H). FAB-MS: 393 (10, $M^{+\cdot}$), 337 (25), 217 (61), 91 (100). Anal. calc. for $C_{24}H_{28}N_2O_3$ (392.50): C 73.43, H 7.20, N 7.14, O 12.23; found: C 73.30, H 7.20, N 7.20, O 12.20.

tert-*Butyl 1-Benzyl-1,2-dihydro-5-methyl-2-oxospiro[3*H*-indole-3,4′-piperidine]-1′-carboxylate* (**5b**). In a closed flask, a soln. of **4b** (916 mg, 1.88 mmol), *t*-BuONa (273 mg, 2.84 mmol), *rac*-BINAP (88 mg, 0.14 mmol), and [Pd(dba)$_2$] (57 mg, 0.10 mmol) in dry dioxane (17 ml) was stirred under N_2 at 95–105° for 4.5 h. The mixture was added to 0.5N citric acid (80 ml) and extracted with CH_2Cl_2 (1 × 100 and 2 × 50 ml). The org. phase was dried (Na_2SO_4) and liberated from solvent. The product **5b** was obtained pure (598 mg, 78.3%) by FC (silica gel; *t*-BuOMe/petroleum ether 5:1). Compound **5b** was crystallizable from Et_2O/petroleum ether. M.p. 151–152°. IR (KBr): 1712, 1681, 1617, 1498, 1418, 1366, 1347, 1244, 1154, 1121. ^{1}H-NMR ((D$_6$)DMSO): 7.35–7.21 (*m*, 6 H); 6.99 (*d*, *J* = 7.7, 1 H); 6.76 (*d*, *J* = 8.0, 1 H); 4.86 (*s*, 2 H); 3.81–3.64 (*m*, 4 H); 2.26 (*s*, 3 H); 1.80–1.65 (*m*, 4 H); 1.45 (*s*, 9 H). FAB-MS: 407 (30, $M^{+\cdot}$), 351 (100), 333 (50), 306 (34), 91 (95). Anal. calc. for $C_{25}H_{30}N_2O_3$ (406.53): C 73.85, H 7.45, N 6.89, O 11.81; found: C 73.30, H 7.50, N 6.80, O 11.70.

tert-*Butyl 1-Benzyl-1,2-dihydro-5-nitro-2-oxospiro[3*H*-indole-3,4′-piperidine]-1′-carboxylate* (**5c**). The anilide **4c** (8.757 g, 16.89 mmol) was dissolved in dry dioxane (150 ml), followed by addition of *t*-BuONa (2.443 g, 25.42 mmol), [Pd(dba)$_2$] (0.492 g, 0.856 mmol), and *rac*-BINAP (0.790 g, 1.27 mmol). The mixture was stirred in a closed flask under N_2, at 95–110° for 3 h, concentrated, and introduced into sat. $NaHCO_3$ soln. (150 ml). Extraction was performed with CH_2Cl_2 (1 × 100 and 2 × 50 ml), the extract was dried (Na_2SO_4) and freed from solvent. FC (silica gel; *t*-BuOMe/petroleum ether 3:4) afforded 1.599 g (21.6%) of **5c**. Yellowish foam. M.p. of 66–67°. IR (KBr): 1717, 1692, 1606, 1527, 1491, 1448, 1424, 1346, 1164. ^{1}H-NMR ((D$_6$)DMSO): 7.92 (*dd*, *J* = 2.1, 8.2, 1 H); 7.84 (*d*, *J* = 8.2, 1 H); 7.69 (*d*, *J* = 2.1, 1 H); 7.39–7.25 (*m*, 5 H); 5.03 (*s*, 2 H); 3.81–3.65 (*m*, 4 H);

1.91–1.75 (*m*, 4 H); 1.45 (*s*, 9 H). FAB-MS: 438 (13, $M^{+\cdot}$), 382 (40), 364 (39), 91 (100). Anal. calc. for $C_{24}H_{27}N_3O_5$ (437.50): C 65.88, H 6.23, N 9.61, O 18.28; found: C 65.80, H 6.40, N 9.20, O 17.90.

*1-Benzyl-1,2-dihydro-5-methyl-2-oxospiro[3*H*-indole-3,4′-piperidin]-1′-ium Hydrochloride* (**7b**). Compound **5b** (458 mg, 1.127 mmol) was taken up in dry dioxane (2.0 ml) and mixed at r.t. with 4.0M HCl in dioxane (4.0 ml) while stirring. Stirring was continued for 1 h, and Et_2O (10 ml) was then swiftly added dropwise while stirring vigorously. Crystallization then started and was completed at 0°. After having been sucked off, **7b** was washed with Et_2O and dried: 358 mg (86.4%). M.p. >260° (dec.). IR (KBr): 2965, 2922, 2718, 2612, 1711, 1602, 1501, 1461, 1351. ^{1}H-NMR ((D$_6$)DMSO): 9.20 (br. *s*, 2 H); 7.36–7.21 (*m*, 5 H); 7.18 (*d*, *J* = 1.7, 1 H); 7.04 (*ddd*, *J* = 0.8, 1.7, 8.0, 1 H); 6.80 (*d*, *J* = 8.0, 1 H); 4.89 (*s*, 2 H); 3.61–3.47 (*m*, 2 H); 3.36–3.26 (*m*, 2 H); 2.29 (*s*, 3 H); 2.25–2.11 (*m*, 2 H); 1.99–1.88 (*m*, 2 H). EI-MS: 306 (69, $[M-1]^{+\cdot}$), 250 (53), 91 (100). HR-MS: 306.1731 (calc. for $C_{20}H_{22}N_2O$ $[M-H]^{+\cdot}$: 306.1732). Anal. calc. for $C_{20}H_{23}ClN_2O \cdot 1/3\ Et_2O$ (367.58): C 69.71, H 7.22, N 7.62, O 5.80; found: C 69.20, H 7.00, N 7.90, O 5.70.

tert-*Butyl 4-(1*H*-Imidazole-1-carbonyl)piperidine-1-carboxylate* (**8**). To a stirred soln. of 1,1′-carbonyldiimidazole (1.162 g, 7.17 mmol) in dry CH_2Cl_2 (11 ml), **2** (1.22 g, 5.32 mmol) was added in portions at r.t. The mixture was stored at 0° for 4.5 h, diluted with Et_2O (22 ml), washed with ice-water and subsequently with ice-cold sat. $NaHCO_3$ soln., and dried (Na_2SO_4). After evaporation of the solvents, **8** (1.291 g, 86.9%) was obtained. Colorless solid. IR ($CHCl_3$): 2981, 1736, 1686, 1475, 1427, 1319, 1166. ^{1}H-NMR ($CDCl_3$): 8.19 (*s*, 1 H); 7.48 (*s*, 1 H); 7.13 (*s*, 1 H); 4.18 (*m*, 2 H); 3.06 (*tt*, *J* = 4.0, 10.9, 1 H); 2.92 (br. *t*, *J* = 11.6, 2 H); 1.93 (br. *d*, *J* = 11.0, 2 H); 1.90–1.79 (*m*, *J* = 4.2, 11.2, 2 H); 1.47 (*s*, 9 H). EI-MS: 279 (18, $M^{+\cdot}$), 222 (63), 206 (62), 179 (28), 156 (49), 128 (39), 112 (98), 84 (36), 82 (36), 69 (100). HR-MS: 279.1581 (calc. for $C_{14}H_{21}N_3O_3$: 279.1583).

tert-*Butyl 4-[(Phenylamino)carbonyl]piperidine-1-carboxylate* (**9**). To **8** (397 mg, 1.34 mmol) in dry THF (1.5 ml), a soln. of 2-bromoaniline (218 mg, 1.27 mmol) in dry THF (1.5 ml) was added under stirring at r.t. TLC Control (*t*-BuOMe/petroleum ether 1:1) revealed that not even a trace of product was formed after more than 24 h. Aniline (119 mg, 1.28 mmol) was now added to the same mixture. This time, product formation was almost complete within 40 min at r.t. (TLC). To identify the product **9**, a sample was purified by FC (silica gel; *t*-BuOMe/petroleum ether 3:1). M.p. 136–137°. IR (KBr): 3317, 2931, 1697, 1665, 1602, 1546, 1441, 1238, 1167. ^{1}H-NMR (CD_3OD): 7.54 (*dd*, *J* = 1.2, 8.7, 2 H); 7.29 (*dd*, *J* = 7.4, 8.7, 2 H); 7.07 (*tt*, *J* = 1.2, 7.4, 1 H); 4.14 (br. *d*, *J* = 13.2, 2 H); 2.83 (br. *t*, *J* = 12.1, 2 H); 2.55 (*tt*, *J* = 4.0, 11.5, 1 H); 1.83 (*dd*, *J* = 2.9, 13.3, 2 H); 1.75–1.54 (*m*, *J* = 4.3, 12.0, 2 H); 1.47 (*s*, 9 H). EI-MS: 304 (6, $M^{+\cdot}$), 247 (51), 203 (98), 147 (100). Anal. calc. for $C_{17}H_{24}N_2O_3$ (304.49): C 67.08, H 7.95, N 9.20, O 15.77; found: C 67.20, H 8.20, N 8.90, O 15.60.

tert-*Butyl 4-{[(6-Methylpyridin-2-yl)amino]carbonyl}piperidine-1-carboxylate* (**11**). A soln. of *2-amino-6-methylpyridine* (**10**; 281 mg, 2.60 mmol) in dry THF (3 ml) was added to **8** (858 mg, 3.07 mmol) in dry THF (5 ml) at r.t., and the mixture was stirred for 45 h. After dilution with *t*-BuOMe (25 ml), the mixture was washed with sat. NH_4Cl soln. (2 × 25 ml) and subsequently with sat. Na_2CO_3 soln. (25 ml). After drying (Na_2SO_4) and removing of the solvents, a solid raw product (898 mg) was obtained. According to ^{1}H-NMR analysis, this material consisted of **11** (610 mg, 73%), **8** (221 mg), and imidazole (67 mg). The desired product was isolated as follows: the solid was taken up in MeCN (10 ml), and 10% aq. NaOH soln. (0.5 ml) was added. After stirring for 15 min at r.t., the mixture was diluted with *t*-BuOMe (50 ml), washed with 10% aq. AcONa/AcOH buffer soln. (2 × 50 ml), sat. Na_2CO_3 soln. (50 ml), and dried (Na_2SO_4). Evaporation of the solvents afforded pure **11** (395 mg, 47.6%), which solidified on standing. M.p. 150–152°. IR ($CHCl_3$): 3416, 2979, 1685, 1520, 1454, 1427, 1237, 1158. ^{1}H-NMR ($CDCl_3$): 8.02 (br. *s*, 1 H); 8.01 (*d*, *J* = 8.3, 1 H); 7.60 (*dd*, *J* = 7.4, 8.3, 1 H); 6.91 (*d*, *J* = 7.4, 1 H); 4.17 (*m*, 2 H); 2.79 (br. *t*, *J* = 11.5, 2 H); 2.45 (*s*, 3 H); 2.40 (*tt*, *J* = 3.8, 11.5, 1 H); 1.91 (br. *d*, *J* = 11.7, 2 H); 1.79–1.68 (*m*, *J* = 4.3, 11.9, 2 H); 1.47 (*s*, 9 H). EI-MS: 319 (13, $M^{+\cdot}$), 262 (11), 218 (21), 163 (100). Anal. calc. for $C_{17}H_{25}N_3O_3$ (319.41): C 63.93, H 7.89, N 13.16, O 15.03; found: C 63.60, H 8.20, N 12.90, O 15.40.

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