New Hexahydrocarbazoles and Spiro Indoles, and Their Affinity for D_2 Dopamine and 5-HT_{2A} Serotonin Receptors

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In a search for novel atypical antipsychotics, the synthesis of new hexahydrocarbazoles and spiro indoles *N*-substituted with a 3-(dimethylamino)propyl chain is described, together with the results of an *in vitro* evaluation of their affinities for D_2 and 5-HT_{2A} receptors.

Key words hexahydrocarbazole; spiroindole; D_2 dopamine receptor; 5-HT_{2A} serotonin receptor

The indole structure is present in a large number of antipsychotic drugs, of which oxypertine[1] is the prototype. Like many other antipsychotics, oxypertine is ineffective against the negative symptoms of schizophrenia and provokes significant extrapyramidal side effects (EPS), which are one of the main factors limiting its use as an antipsychotic treatment. Although there is no indole structure in clozapine,[2] the prototype of "atypical" or "non-classical" antipsychotics (which do not cause EPS and are effective against the negative symptoms of schizophrenia),[3] it is present in other compounds classed as atypical antipsychotics, including roxindole,[4] sertindole[5] and, more recently, the carbazole derivatives rimcazole[6] and flutroline.[7]

In our search for new atypical antipsychotics derived from indole we thought it of interest to compare the activities of compounds in which cyclohexane is fused to the indole pyrrole ring (hexahydrocarbazoles) with those of the corresponding spiro compounds, in which the cyclohexane meets the pyrrole ring at just one carbon and, therefore, has greater rotational freedom. We describe here the synthesis of a series of compounds of such types (in both series the "tail" on the indole nitrogen was an *N*,*N*-dimethylaminopropyl chain), and report their activities at D_2 dopamine and 5-HT_{2A} serotonin receptors.

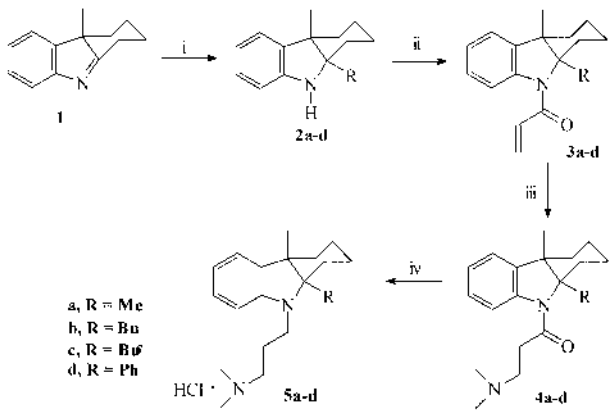
The hexahydrocarbazole derivatives **5a**—**d** were prepared from 4a-methyl-2,3,4,4a-tetrahydro-1*H*-carbazole (**1**), following a novel route shown in Chart 1. Treatment of **1** with the appropriate lithium derivatives afforded the *cis*-fused 9a-substituted 4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazoles **2a**, **b**, **d** in far better yields (82—92%) than those achieved by the method previously described,[8] and allowed us to obtain for the first time **2c**, as a mixture of diastereomers that were isolated and characterized.

Alkylation of the nitrogen of these hexahydrocarbazoles was first attempted by the classical method of treating them with 3-(dimethylamino)propyl chloride in the presence of a variety of bases (Na_2CO_3 in EtOH/H_2O, 50% NaOH/Bu_4NI in toluene, NaH in tetrahydrofuran (THF), LiBu in THF) but this failed. Only 10% of the alkylation product of **2a** was obtained when using NaH in the presence of 18-crown-6 ether in THF, and these conditions also failed when applied to the other hexahydrocarbazoles **2b**—**d**.[9] As the problem seemed to be due to the steric hindrance about the position 9, we changed the strategy by seeking a less bulky and more reactive reagent.

Reaction of compounds **2** with acryloyl chloride in the presence of triethylamine produced the 9a-substituted 9-acryloyl-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazoles **3a**—**d** (59—89% yield), which, upon treatment with dimethylamine, afforded the 9a-substituted 9-[3-(dimethylamino)-propanoyl]-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazoles **4a**—**d** (85—87% yield), and reduction of the amide group with diborane prepared from $NaBH_4$ and $BF_3 \cdot Et_2O$ gave stable boron complexes that, upon hydrolysis with 2 N HCl, gave the hexahydrocarbazoles **5a**—**d** (52—60% yield) as hydrochlorides.

The spiro indole derivatives **12a**—**c** were obtained as shown in Chart 2 from 2′-methylspiro[cyclohexane-1,3′-3*H*-indole] (**8a**), which had previously been obtained by Fischer's synthesis from the phenylhydrazone of cyclohexyl methyl ketone. Treatment of **8a** with a 10 : 1 molar ratio of MeMgI : **8a** in Et_2O/THF allowed insertion on the methyl group rather than the expected addition to the C=N double bond (79% yield); and use of a 15 : 1 molar ratio of MeMgI : **8a** in Et_2O/toluene led to a double insertion, affording **8c** (47% yield). Reduction of the C=N double bond of compounds **8a**—**c** with $LiAlH_4$ in THF yielded the 2′-alkylspiro[cyclohexane-1,3′-indolines] **9a**—**c** (78—89% yield), and a 3-(dimethylamino)propyl side chain was added to the latter by the same synthetic sequence as for compounds **5a**—**d**.[10,11]

Table 1 lists the activities of compounds **5a**—**d** and **12a**—**c** at D_2 dopamine receptors and 5-HT_{2A} serotonin receptors,



Reagents: (i) RLi / hexane or THF; (ii) $CH_2CHCOCl$ / Et_3N; (iii) Me_2NH / Et_2O; (iv) B_2H_6.

Chart 1

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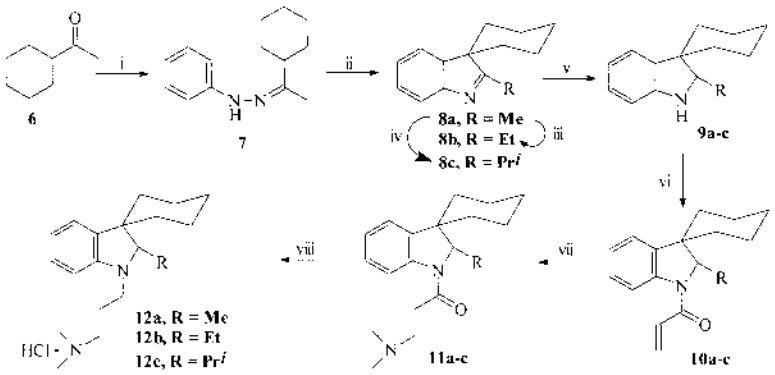

Reagents: (i) $PhNHNH_2$; (ii) AcOH; (iii) MeMgI 10 eq / Et_2O–THF; (iv) MeMgI 15 eq / Et_2O–toluene; (v) $LiAlH_4$ / THF; (vi) $CH_2CHCOCl$ / Et_3N; (vii) Me_2NH / Et_2O; (viii) B_2H_6.

Chart 2

Table 1. Inhibition Constants (pK_i) at D_2 and 5-HT_{2A} receptors[a)]

	p*K*i (D_2)	pK_i (5-HT_{2A})	pK_i (5-HT_{2A})/pK_i (D_2)
5a	5.52	5.57	1.00
5b	6.11	5.84	0.95
5c-I	6.08	6.14	1.00
5d	6.12	6.34	1.03
12a	5.97	6.23	1.04
12b	5.98	6.70	1.12
12c	5.93	6.08	1.02
Clozapine	7.00	8.30	1.19

a) Inhibition constants (pK_i) for *in vitro* inhibition of the binding of ^{3}H-ketanserine to rat frontal cortex membranes (5-HT_{2A}) and of ^{3}H-spiperone to striatal membranes (D_2). These assays have been described elsewhere.[13,14] pK_i values were calculated using the Cheng-Prusoff equation;[15] results shown are means of three inhibition curves constructed with each drug.

together with those of the reference compound clozapine. All seven new compounds inhibit both the binding of ^{3}H-spiperone to D_2 receptors (with pK_i values of 5.52—6.12) and the binding of ^{3}H-ketanserine to 5-HT_{2A} receptors (with pK_i values of 5.57—6.70). According to the criterion of Meltzer (the ratio between 5-HT_{2A}- and D_2-blocking activities),[12] **12b** (pK_i (5-HT_{2A}/D_2) ratio 1.12) is very close to that of Clozapine (1.19), the prototype atypical antipsychotic.

In conclusion, we have developed a synthetic strategy for the practical, efficient preparation of a series of hexahydrocarbazoles and spiro indole derivatives of potential value as antipsychotics. The high pK_i (5-HT_{2A}/D_2) ratio of the spiro indole derivative **12b** suggests that the development of atypical antipsychotics containing a spiro group is worth pursuing further.

Experimental

Melting points are uncorrected and were determined in a Reichert stage microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer 681 spectrophotometer. ^{1}H-NMR spectra (200 MHz) were recorded on a Bruker WM-200-SY spectrometer, using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard (chemical shifts in δ values, *J* in Hz). Flash chromatography was performed on silica gel (Merck 60, 230—240 mesh); analytical TLC was performed on pre-coated silica gel plates (Merck 60 F_{254}, 0.25 mm).

General Procedure for the Synthesis of 9a-Substituted 4a-Methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazoles (2) To 1.5 g (8.1 mmol) of **1**[8] in 19 ml dry toluene at −10 °C and protected from sunlight was added a solution of the organolithium reagent (12.5 mmol) in hexane or THF, and the reaction mixture was stirred at −10 °C for 3 h. Work up included hydrolysis with 25 ml 1 : 1 toluene–water, extraction with dichloromethane (DCM), drying of the pooled organic phases over $MgSO_4$ and evaporation of the solvents *in vacuo*. The orange oil obtained was purified by silica gel column chromatography using 5 : 1 hexane–EtOAc as eluent. Data for compounds **2a**—**d** are as follows:

4a,9a-Dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**2a**): 82% from **1**; slighty yellowish oil; hydrochloride mp 222—224 °C. IR (film): 3340, 740 cm^{-1}. ^{1}H-NMR: 1.10 (s, 3H, CH_3-4a), 1.18 (s, 3H, CH_3-9a), 1.30—1.70 (m, 7H, $(CH_2)_3$ +H-1), 1.85 (m, 1H, H-1), 3.33 (s, 1H, NH), 6.62 (d, 1H, *J*=7.3 Hz, H-8), 6.76 (t, 1H, *J*=6.8 Hz, H-6), 6.98 (m, 2H, H-5 +H-7).

9a-Butyl-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**2b**): 92% from **1**; slighty yellowish oil; hydrochloride mp 221—223 °C. IR (film): 3350, 730 cm^{-1}. ^{1}H-NMR: 0.86 (t, 3H, *J*=5.0 Hz, CH_3-Bu), 1.05 (s, 3H, CH_3-4a), 1.20—1.70 (m, 13H, $(CH_2)_3$+$(CH_2)_3$+H-1), 1.85 (m, 1H, H-1), 3.31 (s, 1H, NH), 6.52 (d, 1H, *J*=7.8 Hz, H-8), 6.66 (t, 1H, *J*=7.2 Hz, H-6), 6.95 (m, 2H, H-5+H-7).

4a-Methyl-9a-(1-methylpropyl)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**2c**): Following the general procedure, a light yellow oil was obtained (82%) as a mixture of two diastereomers of the title compound, that were separated by column chromatography on silica gel (20 : 1 hexane–THF as eluent).

Diastereomer 4a*RS*,9a*SR*,1′*SR* (**2c**-I): Colorless oil; hydrochloride mp 249—251 °C. IR (film): 3350, 745 cm^{-1}. ^{1}H-NMR: 0.95 (t, 3H, *J*=6.9 Hz, CH_3-*sec*-Bu), 1.05 (d, 3H, *J*=6.9 Hz, CH_3-*sec*-Bu), 1.15 (s, 3H, CH_3-4a), 1.20—2.10 (m, 11H, $(CH_2)_4$+CH_2CH-*sec*-Bu), 3.71 (s, 1H, NH), 6.58 (d, 1H, *J*=7.6 Hz, H-8), 6.73 (td, 1H, *J*=7.5, 0.8 Hz, H-6), 6.96 (d, 1H, *J*=7.6 Hz, H-5), 7.00 (td, 1H, *J*=7.4, 1.4 Hz, H-7).

Diastereomer 4a*RS*,9a*SR*,1′*RS* (**2c**-II): White solid, mp 58—60 °C; hydrochloride mp 239—241 °C. IR (KBr): 3350, 745 cm^{-1}. ^{1}H-NMR: 0.93 (t, 3H, *J*=6.8 Hz, CH_3-*sec*-Bu), 0.97 (d, 3H, *J*=6.7 Hz, CH_3-*sec*-Bu), 1.12 (s, 3H, CH_3-4a), 1.21—2.12 (m, 11H, $(CH_2)_4$+CH_2CH-*sec*-Bu), 3.65 (s, 1H, NH), 6.57 (d, 1H, *J*=7.7 Hz, H-8), 6.72 (td, 1H, *J*=7.5, 0.8 Hz, H-6), 6.96 (d, 1H, *J*=7.7 Hz, H-5), 6.99 (td, 1H, *J*=7.6, 1.3 Hz, H-7).

4a-Methyl-9a-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**2d**): 87% from **1**; white solid, mp 88—90 °C, hydrochloride mp 265—267 °C. IR (KBr): 3340, 760, 755, 705 cm^{-1}. ^{1}H-NMR: 0.74 (s, 3H, CH_3-4a), 1.4—1.9 (m, 6H, $(CH_2)_3$), 2.10 (m, 2H, CH_2), 3.91 (s, 1H, NH), 6.74 (d, 1H, *J*=7.4 Hz, H-8), 6.77 (t, 1H, *J*=7.3 Hz, H-6), 6.99 (d, 1H, *J*=6.8 Hz, H-7), 7.08 (td, 1H, *J*=7.5, 1.2 Hz, H-5), 7.30 (m, 3H, H-3′+H-4′+H-5′), 7.70 (m, 2H, H-2′+H-6′).

General Procedure for the Synthesis of 9a-Substituted 9-Acryloyl-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazoles (3) To a mixture of 2.1 mmol **2** in 8 ml dry toluene and 0.41 ml (2.95 mmol) triethylamine, kept at 0 °C, was added dropwise acryloyl chloride (3.16 mmol). The reaction mixture was stirred for 4 h. A work up as above for compound **2** led to dark oily residues that were purified by silica gel column chromatography using 6 : 1 DCM–hexane (for **3a**), 9 : 1 EtOAc–hexane (for **3b**—**c**), or DCM (for **3d**) as eluent. Data for compounds **3a**—**d** are as follows:

9-Acryloyl-4a,9a-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**3a**): 87% from **2a**; clear orange oil; IR (film): 1655, 1615, 950, 750 cm^{-1}. ^{1}H-NMR: 1.12 (s, 3H, CH_3-4a), 1.22—1.61 (m, 4H, $(CH_2)_2$), 1.47 (s, 3H, CH_3-9a), 1.79—2.11 (m, 4H, $(CH_2)_2$), 5.76 (dd, 1H, *J*=10.1, 1.9 Hz, C<u>H</u>H=CH), 6.44 (dd, 1H, *J*=16.9, 1.9 Hz, CH<u>H</u>=CH), 6.73 (dd, 1H, *J*=16.9, 10.1 Hz, CH_2=C<u>H</u>), 7.0—7.7 (m, 4H, arom).

9-Acryloyl-9a-butyl-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole

(**3b**): 72% from **2b**; clear orange oil; IR (film): 1650, 1615, 995, 955, 750 cm^{-1}. ^{1}H-NMR: 0.78 (t, 3H, J=6.8 Hz, CH_3-Bu), 1.01—1.32 (m, 4H, $(CH_2)_2$), 1.30 (s, 3H, CH_3-4a), 1.32—1.69 (m, 9H, $(CH_2)_4$+H-1), 3.25 (dt, 1H, J=15.1, 2.7 Hz, H-1), 5.75 (dd, 1H, J=10.1, 2.1 Hz, CHH=CH), 6.45 (dd, 1H, J=17.2, 2.1 Hz, CHH=CH), 6.75 (dd, 1H, J=17.2, 10.1 Hz, CH-acryloyl), 6.93—7.31 (m, 4H, arom).

9-Acryloyl-4a-methyl-9a-(1-methylpropyl)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole. Diastereomer 4a*RS*,9a*SR*,1′*SR* (**3c**-I): 89% from **2c**-I; clear orange oil; IR (film): 1650, 1610, 750 cm^{-1}. ^{1}H-NMR: 0.65 (t, 3H, J=7.2 Hz, CH_3-*sec*-Bu), 0.97 (d, 3H, J=6.7 Hz, CH_3-*sec*-Bu), 0.71—1.72 (m, 10H, $(CH_2)_3$+CH_2CH-*sec*-Bu+H-1), 1.38 (s, 3H, CH_3-4a), 3.2 (m, 1H, H-1), 5.70 (dd, 1H, J=10.0, 2.0 Hz, CHH=CH), 6.43 (dd, 1H, J=16.8, 2.0 Hz, CHH=CH), 6.70 (dd, 1H, J=16.8, 10.0 Hz, CH acryloyl), 6.90—7.22 (m, 4H, arom).

Diastereomer 4a*RS*,9a*SR*,1′*RS* (**3c**-II): 93% from **2c**-II; clear orange oil. IR (film): 1650, 1610, 750 cm^{-1}. ^{1}H-NMR: 0.71 (t, 3H, J=6.8 Hz, CH_3-*sec*-Bu), 0.79 (d, 3H, J=7.2 Hz, CH_3-*sec*-Bu), 0.89—1.78 (m, 10H, $(CH_2)_3$+CH_2CH-*sec*-Bu+H-1), 1.38 (s, 3H, CH_3-4a), 3.21 (m, 1H, H-1), 5.71 (dd, 1H, J=10.0, 2.1 Hz, CHH=CH), 6.44 (dd, 1H, J=16.8, 2.1 Hz, CHH=CH), 6.70 (dd, 1H, J=16.8, 10.0 Hz , CH-acryloyl), 6.90—7.21 (m, 4H, arom).

9-Acryloyl-4a-methyl-9a-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**3d**): 59% from **2d**; orange solid mp 112—113 °C. IR (KBr): 1650, 750, 740, 700 cm^{-1}. ^{1}H-NMR: 0.75 (s, 3H, CH_3-4a), 1.20—1.89 (m, 6H, $(CH_2)_3$), 2.25 (m, 1H, H-1), 2.6 (m, 1H, H-1), 5.40 (m, 1H, CHH=CH), 5.95 (m, 1H, CHH=CH), 6.35 (m, 1H, CH-acryloyl), 7.30 (m, 8H, arom), 8.51 (m, 1H, H-8).

General Procedure for the Synthesis of 9a-Substituted 9-[3-(Dimethylamino)propanoyl]-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazoles (4) Dimethylamine was bubbled into a solution of 1.85 mmol **3** in 25 ml Et_2O at 0 °C, over 20 min, and the reaction mixture was then stirred for 2 h. After the solvent and excess dimethylamine were removed, the resulting residue was purified by silica gel column chromatography, using 1 : 1 EtOAc–EtOH as eluent. Compounds **4a**—**d** were all slighty yellowish oils. Other data are as follows:

9-[3-(Dimethylamino)propanoyl]-4a,9a-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**4a**): 86% from **3a**; hydrochloride mp 219—221 °C. IR (film): 1650, 750 cm^{-1}. ^{1}H-NMR: 1.09 (s, 3H, CH_3-4a), 1.45 (s, 3H, CH_3-9a), 1.30—1.92 (m, 8H, $(CH_2)_4$), 2.28 (s, 6H, $N(CH_3)_2$), 2.85 (m, 4H, $OCCH_2CH_2N$), 7.72 (m, 4H, arom).

9a-Butyl-9-[3-(Dimethylamino)propanoyl]-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**4b**): 85% from **3b**; hydrochloride mp 207—208 °C. IR (film): 1650, 750 cm^{-1}. ^{1}H-NMR: 0.78 (t, 3H, J=6.1 Hz, CH_3-Bu), 1.02—1.71 (m, 13H, $(CH_2)_3$+$(CH_2)_3$+H-1), 1.30 (s, 3H, CH_3-4a), 2.27 (s, 6H, $N(CH_3)_2$), 2.62—3.01 (m, 4H, $OCCH_2CH_2N$), 3.22 (m, 1H, H-1), 7.00—7.21 (m, 4H, arom).

9-[3-(Dimethylamino)propanoyl]-4a-methyl-9a-(1-methylpropyl)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole. Diastereomer 4a*RS*,9a*SR*,1′*SR* (**4c**-I): 87% from **3c**-I; hydrochloride mp 229—231 °C. IR (film): 1650, 750 cm^{-1}. ^{1}H-NMR: 0.64 (t, 3H, J=6.9 Hz, CH_3-*sec*-Bu), 0.93 (d, 3H, J=6.8 Hz, CH_3-*sec*-Bu), 1.36 (s, 3H, CH_3-4a), 0.71—1.72 (m, 10H, $(CH_2)_3$+CH_2CH-*sec*-Bu+H-1), 2.26 (s, 6H, $N(CH_3)_2$), 2.62—2.90 (m, 4H, $OCCH_2CH_2N$), 3.22 (m, 1H, H-1), 7.03—7.22 (m, arom).

Diastereomer 4a*RS*,9a*SR*,1′*RS* (**4c**-II): 87% from **3c**-II; hydrochloride mp 228—230 °C. IR (film): 1650, 750 cm^{-1}. ^{1}H-NMR: 0.67 (t, 3H, J=6.8 Hz, CH_3-*sec*-Bu), 0.77 (d, 3H, J=7.2 Hz, CH_3-*sec*-Bu), 1.36 (s, 3H, CH_3-4a), 0.72—1.73 (m, 10H, $(CH_2)_3$+CH_2CH-*sec*-Bu+H-1), 2.25 (s, 6H, $N(CH_3)_2$), 2.61—2.92 (m, 4H, $OCCH_2CH_2N$), 3.22 (m, 1H, H-1), 7.02—7.21 (m, 4H, arom).

9-[3-(Dimethylamino)propanoyl]-4a-methyl-9a-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**4d**): 85% from **3d**; hydrochloride mp 184—186 °C. IR (film): 1650, 750, 700 cm^{-1}. ^{1}H-NMR: 0.80 (s, 3H, CH_3-4a), 1.19—2.01 (m, 8H, $(CH_2)_4$), 2.26 (s, 6H, $N(CCH_3)_2$), 2.28—2.70 (m, 4H, $OCCH_2CH_2N$), 7.01—7.32 (m, 8H, arom), 8.50 (m, 1H, H-8).

General Procedure for the Synthesis of 9a-Substituted 9-[3-(Dimethylamino)propyl]-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazoles (5) To a solution of 9.6 mmol $NaBH_4$ in 2 ml dry THF, kept at 0 °C under Ar, $BF_3 \cdot Et_2O$ (12.8 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min and then **4** (1.6 mmol) was added. After stirring at room temperature for a further 18 h, the reaction mixture was hydrolyzed by addition of 15 ml 2 N HCl, the THF was removed, and the resulting mixture was refluxed for 1.5 h. After cooling, the reaction mixture was neutralized with NaOH and extracted with DCM, and the extracts were dried over Na_2SO_4. Evaporation of the solvent left a brown oil that was purified by silica gel column chromatography using 2 : 1 EtOAc–EtOH as eluent. Compounds **5a**—**d** were all slighty yellowish oils. Other data are as follows:

9-[3-(Dimethylamino)propyl]-4a,9a-dimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**5a**): 60% from **4a**; hydrochloride mp 165—167 °C. IR (film): 750 cm^{-1}. ^{1}H-NMR: 1.05 (s, 3H, CH_3-4a), 1.10 (s, 3H, CH_3-9a), 1.29—1.80 (m, 10H, $(CH_2)_4$+CH_2-β), 2.25 (s, 6H, $N(CH_3)_2$), 2.40 (t, 2H, J=7.2 Hz, CH_2-α), 2.95 (t, 2H, J=7.2 Hz, CH_2-γ), 6.42 (d, 1H, J= 7.0 Hz, H-8), 6.65 (td, 1H, J=6.5, 0.9 Hz, H-6), 6.91 (dd, 1H, J=6.5, 0.9 Hz, H-5), 7.05 (td, 1H, J=7.0, 1.7 Hz, H-7).

9a-Butyl-9-[3-(dimethylamino)propyl]-4a-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**5b**): 52% from **4b**; hydrochloride mp 181—183 °C. IR (film): 750 cm^{-1}. ^{1}H-NMR: 0.79 (t, 3H, J=7.0 Hz, CH_3-Bu), 0.88—1.71 (m, 14H, $(CH_2)_4$+$(CH_2)_3$), 1.21 (s, 3H, CH_3-4a), 1.86 (quint, 2H, J=7.4 Hz, CH_2-β), 2.32 (s, 6H, $N(CH_3)_2$), 2.45, 2.47 (2t, 2H, J=7.6, 7.2 Hz, CH_2-γ), 3.04 (td, 2H, J=7.4 Hz, CH_2-α), 6.34 (d, 1H, J=7.7 Hz, H-8), 6.61 (d, 1H, J=7.2 Hz, H-6), 6.86 (dd, 1H, J=7.1, 1.2 Hz, H-5), 7.02 (td, 1H, J=7.6, 1.3 Hz, H-7).

9-[3-(Dimethylamino)propyl]-4a-methyl-9a-(1-methylpropyl)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole. Diastereomer 4a*RS*,9a*SR*,1′*SR* (**5c**-I): 59% from **4c**-I; hydrochloride mp 152—154 °C. IR (film): 750 cm^{-1}. ^{1}H-NMR: 0.82 (m, 3H, CH_3-*sec*-Bu), 0.87 (d, 3H, J=7.0 Hz, CH_3-*sec*-Bu), 1.23 (s, 3H, CH_3-4a), 1.30—1.72 (m, 11H, $(CH_2)_4$+CH_2CH-*sec*-Bu), 1.91 (m, 2H, CH_2-β), 2.34 (s, 6H, $N(CH_3)_2$), 2.50 (t, 2H, J=7.2 Hz, CH_2-γ), 3.11 (m, 2H, CH_2-α), 6.27 (d, 1H, J=7.7 Hz, H-8), 6.58 (t, 1H, J=7.2 Hz, H-6), 6.82 (d, 1H, J=7.1 Hz, H-5), 7.01 (t, 1H, J=7.5 Hz, H-7).

Diastereomer 4a*RS*,9a*SR*,1′*RS* (**5c**-II): 47% from **4c**-II; hydrochloride mp 170—172 °C. IR (film): 750 cm^{-1}. ^{1}H-NMR: 0.69 (d, 3H, J=6.6 Hz, CH_3-*sec*-Bu), 0.81 (t, 3H, J=6.0 Hz, CH_3-*sec*-Bu), 1.28 (s, 3H, CH_3-4a), 1.29—1.71 (m, 11H, $(CH_2)_4$+CH_2CH-*sec*-Bu), 1.90 (m, 2H, CH_2-β), 2.58 (s, 6H, $N(CH_3)_2$), 2.91 (t, 2H, J=7.2 Hz, CH_2-γ), 3.05 (m, 2H, CH_2-α), 6.31 (d, 1H, J=7.7 Hz, H-8), 6.59 (t, 1H, J=7.2 Hz, H-6), 6.83 (d, 1H, J=7.1 Hz, H-5), 7.01 (t, 1H, J=7.5 Hz, H-7).

9-[3-(Dimethylamino)propyl]-4a-methyl-9a-phenyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole (**5d**): 59% from **4d**; hydrochloride mp 184—185 °C. IR (film): 1650, 750, 700 cm^{-1}. ^{1}H-NMR: 0.78 (s, 3H, CH_3-4a), 1.50—2.12 (m, 10H, $(CH_2)_4$+CH_2-β), 2.19 (s, 6H, $N(CH_3)_2$), 2.27 (t, 2H, J=7.3 Hz, CH2-γ), 2.95 (m, 2H, CH_2-α), 6.51 (d, 1H, J=7.7 Hz, H-8), 6.67 (t, 1H, J=7.2 Hz, H-6), 6.87 (dd, 1H, J=6.9, 0.8 Hz, H-5), 7.11 (td, 1H, J=7.6, 1.1 Hz, H-7), 7.31 (m, 5H, Ph).

2′-Ethylspiro[cyclohexane-1,3′-3*H*-indole] (8b) To a solution of 25 mmol MeMgI in 7 ml anhydrous Et_2O at 0 °C, a solution of 500 mg (2.5 mmol) **8a** was added dropwise. The mixture was stirred at 0 °C for 4 h and then hydrolyzed with 30 ml aqueous NH_4Cl and extracted with dichloromethane. The solvent was removed and the residual brown oil was purified by silica gel column chromatography using 5 : 1 hexane–EtOAc as eluent. **8b** was isolated as a yellow solid, mp 105—107 °C, 79% yield. IR (KBr): 2920, 2860, 1670, 1570, 1450, 1350, 750 cm^{-1}. ^{1}H-NMR: 1.25 (m, 2H, CH_2), 1.35 (t, 3H, J=7.3 Hz, CH_3CH_2), 1.49—2.20 (m 8H, $(CH_2)_4$), 2.60 (q, 2H, J=7.3 Hz, CH_3CH_2), 7.18 (t, 1H, J=8.1 Hz, H-5′), 7.35 (t, 1H, J=6.5 Hz, H-6′), 7.62 (d, 1H, J=6.5 Hz, H-7′), 7.72 (d, 1H, J=8.2 Hz, H-4′).

2′-Isopropylspiro[cyclohexane-1,3′-3*H*-indole] (8c) To a solution of 37.7 mmol MeMgI in 40 ml anhydrous Et_2O at 0 °C, a solution of 500 mg (2.5 mmol) **8a** in 20 ml anhydrous toluene was added dropwise. The flask was protected from the light, and the reaction mixture was stirred at room temperature for 60 h and then hydrolyzed with 30 ml aqueous NH_4Cl and extracted with dichloromethane. The solvent was removed and the residual brown oil was purified by silica gel column chromatography using 3 : 1 hexane–EtOAc as eluent. **8c** was isolated as a yellow solid, mp 75—77 °C (hexane), 47% yield. IR (KBr): 2920, 1630, 1590, 740 cm^{-1}. ^{1}H-NMR: 1.30 (d, 6H, J=6.8 Hz, $(CH_3)_2CH$), 1.81—2.12 (m, 10H, $(CH_2)_5$), 2.97 (sept, 1H, J=6.8 Hz, $(CH_3)_2CH$), 7.15 (td, 1H, J=7.1, 1.1 Hz, H-5′), 7.33 (td, J=7.4, 1.1 Hz, H-6′), 7.60 (d, 1H, J=7.5 Hz, H-7′), 7.71 (d, 1H, J=7.5 Hz, H-4′).

General Procedure for the Synthesis of 2′-Alkylspiro[cyclohexane-1,3′-indolines] (9) To a solution of 10 mmol $LiAlH_4$ in 8 ml anhydrous THF, 3.5 mmol **8** in 16 ml THF as added. The reaction mixture was stirred for 4 h and then hydrolysed with 50 ml 1 : 1 THF–H_2O and extracted with dichloromethane. The pooled organic phases were dried over Na_2SO_4, the solvents were removed and the oily residue obtained was purified by silicagel column chromatography using 7 : 1 hexane–EtOAc as eluent. Compounds **9a**—**c** were all slighty yellowish oils. Other data are as follows:

2′-Methylspiro[cyclohexane-1,3′-indoline] (**9a**): 89% from **8a**; hydrochloride mp 157—159 °C. IR (film): 3040, 1590, 1580, 750 cm^{-1}. ^{1}H-NMR: 1.14 (d, 3H, J=6.5 Hz, CH_3-2′), 1.30—1.82 (m, 10H, $(CH_2)_5$), 3.4 (br s, 1H, NH), 3.72 (q, 1H, J=6.5 Hz, H-2′), 6.63 (d, 1H, J=7.4 Hz, H-7′),

6.74 (td, 1H, J=7.4, 1.1 Hz, H-5′), 7.15 (d, 1H, J=7.4 Hz, H-4′), 7.73 (td, 1H, J=7.4, 1.1 Hz, H-6′).

2′-Ethylspiro[cyclohexane-1,3′-indoline] (**9b**): 78% from **8b**; picrate mp 238—240 °C. IR (film): 3380, 1610, 750 cm^{-1}. ^{1}H-NMR: 1.00 (t, 3H, J=7.4 Hz, C$\underline{H}_3$CH$_2$), 1.31—1.82 (m, 12H, (CH$_2$)$_5$+CH$_2$), 3.50 (dd, 1H, J=10.2, 2.9 Hz, H-2′), 3.95 (br s, 1H, NH), 6.62 (d, 1H, J=7.4 Hz, H-7′), 6.71 (td, 1H, J=7.4, 0.9 Hz, H-5′), 7.02 (td, 1H, J=7.4, 1.1 Hz, H-6′), 7.19 (dd, 1H, J=7.4, 1.1 Hz, H-4′).

2′-Isopropylspiro[cyclohexane-1,3′-indoline] (**9c**): 86% from **8c**; picrate mp 136—138 °C. IR (film): 3400, 1610, 750 cm^{-1}. ^{1}H-NMR: 0.65 (d, 3H, J=6.6 Hz, C$\underline{H}_3$CH), 1.00 (d, 3H, J=6.6 Hz, C$\underline{H}_3$CH), 1.29—1.90 (m, 10H, (CH$_2$)$_5$), 2.03 (sept d, 1H, J=6.6, 2.7 Hz, (CH$_3$)$_2$C$\underline{H}$), 3.40 (d, 1H, J=2.7 Hz, H-2′), 3.85 (br s, 1H, NH), 6.57 (d, 1H, J=6.9 Hz, H-7′), 6.66 (td, 1H, J=6.9, 1.0 Hz, H-5′), 7.00 (td, 1H, J=6.9, 1.0 Hz, H-6′), 7.09 (d, 1H, J=7.6 Hz, H-4′).

1′-Acryloyl-2′-alkylspiro[cyclohexane-1,3′-indolines] (10) Compounds **10** were prepared as described for compounds **3**. Data for compounds **10a**—**c** are as follows:

1′-Acryloyl-2′-methylspiro[cyclohexane-1,3′-indoline] (**10a**): 80% from **9a**; clear yellow solid, mp 76—78 °C. IR (KBr): 1640, 1610, 1600, 750 cm^{-1}. ^{1}H-NMR: 1.20 (d, 3H, J=6.6 Hz, CH$_3$), 1.19—2.02 (m, 10H, (CH$_2$)$_5$), 4.50, 4.80 (two m, 1H, H-2′, two chain conformers), 5.82 (dd, 1H, J=11.5, 1.6 Hz, C$\underline{H}$H=CH), 6.60 (m, 2H, CH$\underline{H}$=C$\underline{H}$), 7.01—7.32 (m, 4.5H, arom), 8.23 (m, 0.5H, H-7′ of a chain conformer).

1′-Acryloyl-2′-ethylspiro[cyclohexane-1,3′-indoline] (**10b**): 91% from **9b**; yellow oil. IR (film): 1640, 1610, 1590, 980, 960, 750 cm^{-1}. ^{1}H-NMR: 0.85 (m, 3H, C$\underline{H}_3$CH$_2$), 1.1—2.0 (m, 12H, (CH$_2$)$_5$+CH$_2$), 4.40, 4.53 (two m, 1H, H-2′, two chain conformers), 5.80 (dd, 1H, J=10.6, 1.6 Hz, C$\underline{H}$H=CH), 6.39—6.88 (m, 2H, CH$\underline{H}$=C$\underline{H}$), 7.01—7.32 (m, 4.5H, arom), 8.15 (m, 0.5H, H-7′ of a chain conformer).

1′-Acryloyl-2′-isopropylspiro[cyclohexane-1,3′-indoline] (**10c**): 81% from **9c**; low melting, yellow wax. IR (KBr): 1650, 1620, 1600, 755 cm^{-1}. ^{1}H-NMR: 0.39 (d, 1.5H, J=6.5 Hz, C$\underline{H}_3$CH of a chain conformer), 0.42 (d, 1.5H, J=6.6 Hz, C$\underline{H}_3$CH of a chain conformer), 1.04 (d, 1.5H, J=6.9 Hz, C$\underline{H}_3$CH of a chain conformer), 1.12 (d, 1.5H, J=6.9 Hz, CH$_3$CH of a chain conformer), 1.21—2.09 (m, 10H, (CH$_2$)$_5$), 4.35, 4.77 (two m, 1H, H-2′), 5.78 (dd, 1H, J=10.1, 2.2 Hz, C$\underline{H}$H=CH), 6.51—6.98 (m, 2H, CH$\underline{H}$=C$\underline{H}$), 7.02—7.23 (m, 4.5H, arom), 8.08 (d, 0.5H, J=7.9 Hz, H-7′ of a chain conformer).

2′-Alkyl-1′-[3″-(dimethylamino)propanoyl]spiro[cyclohexane-1,3′-indolines] (11) Compounds **11** were prepared as described for compounds **4**. Compounds **11a—c** were all, slighty yellowish, oils. Other data are as follows:

1′-[3″(Dimethylamino)propanoyl]-2′-methylspiro[cyclohexane-1,3′-indoline] (**11a**): 90% from **10a**; hydrochloride mp 207—209 °C. IR (film): 1650, 1605, 760 cm^{-1}. ^{1}H-NMR: 1.20 (d, 3H, J=7.3 Hz, CH$_3$), 1.11—1.92 (m, 10H, (CH$_2$)$_5$), 2.30 (s, 6H, N(CH$_3$)$_2$), 2.59—2.92 (m, 4H, OCCH$_2$CH$_2$N), 4.39, 4.85 (q and m, 1H, J=7.3 Hz, H-2′, two chain conformers), 7.01—7.29 (m, 4.5H, arom), 8.12 (d, 0.5H, J=7.8 Hz, H-7′ of a chain conformer).

1′-[3″-(Dimethylamino)propanoyl]-2′-ethylspiro[cyclohexane-1,3′-indoline] (**11b**): 94% from **10b**; hydrochloride mp 213—215 °C. IR (film): 1650, 1600, 755 cm^{-1}. ^{1}H-NMR: 0.85 (m, 3H, C$\underline{H}_3$CH$_2$), 1.20—2.00 (m, 12H, (CH$_2$)$_5$+CH$_2$), 2.28, 2.30 (two s, 6H, N(CH$_3$)$_2$), 2.80—2.85 (m, 4H, OCCH$_2$CH$_2$N), 4.30 (dd, 0.5H, J=7.8, 4.1 Hz, H-2′ of a chain conformer), 4.87 (dd, 0.5H, J=9.9, 3.5 Hz, H-2′ of a chain conformer), 7.01—7.32 (m, 4.5H, arom), 8.02 (d, 1H, J=7.8 Hz, H-7′ of a chain conformer).

1′-[3″-(Dimethylamino)propanoyl]-2′-isopropylspiro[cyclohexane-1,3′-indoline] (**11c**): 97% from **10c**; hydrochloride mp 192—194 °C. IR (film): 1650, 1595, 750 cm^{-1}. ^{1}H-NMR: 0.38 (d, 1.5H, J=6.7 Hz, C$\underline{H}_3$CH of a chain conformer), 0.42 (d, 1.5H, J=6.7 Hz, C$\underline{H}_3$CH of a chain conformer), 1.04 (d, 1.5H, J=7.0 Hz, C$\underline{H}_3$CH of a chain conformer), 1.09 (d, 1.5H, J=7.0 Hz, C$\underline{H}_3$CH of a chain conformer), 1.20—2.21 (m, 10H, (CH$_2$)$_5$), 2.27, 2.29 (two s, 6H, N(CH$_3$)$_2$), 2.60—2.90 (m, 4H, OCCH$_2$CH$_2$N), 4.24 (d, 0.5H, J=1.7 Hz, H-2′ of a chain conformer), 4.84 (d, 0.5H, J=1.5 Hz, H-2′ of a chain conformer), 7.00—7.23 (m, 4.5H, arom), 7.92 (d, 0.5H, J=7.9 Hz, H-7′ of a chain conformer).

2′-Alkyl-1′-[3″-(dimethylamino)propyl]spiro[cyclohexane-1,3′-indolines] (12) Compounds **12** were prepared as described for compounds **5**. Compounds **12a**—**c** were all clear, slighty orange, oils. Other data are as follows:

1′-[3″-(Dimethylamino)propyl]-2′-methylspiro[cyclohexane-1,3′-indoline] (**12a**): 56% from **11a**; hydrochloride mp 147—148 °C. IR (film): 1600, 740 cm^{-1}. ^{1}H-NMR: 1.05 (d, 3H, J=6.7 Hz, CH$_3$), 1.30—1.90 (m, 12H, (CH$_2$)$_5$+CH$_2$-β), 2.32 (s, 6H, N(CH$_3$)$_2$), 2.45 (m, 2H, CH$_2$-γ), 3.20 (m, 2H, CH$_2$-α), 3.51 (q, 1H, J=6.7 Hz, H-2′), 6.37 (d, 1H, J=7.5 Hz, H-7′), 6.61 (td, 1H, J=7.5, 1.2 Hz, H-5′), 7.05 (dd, 1H, J=7.5, 1.7 Hz, H-4′), 7.11 (td, 1H, J=7.5, 1.2 Hz, H-6′).

1′-[3″-(Dimethylamino)propyl]-2′-ethylspiro[cyclohexane-1,3′-indoline] (**12b**): 62% from **11b**; hydrochloride mp 157—159 °C. IR (film): 1600, 730 cm^{-1}. ^{1}H-NMR: 0.75 (t, 3H, J=7.4 Hz, C$\underline{H}_3$CH$_2$), 1.20—2.09 (m, 14H, (CH$_2$)$_5$+CH$_2$-2′+CH$_2$-β), 2.23 (s, 6H, N(CH$_3$)$_2$), 2.32 (m, 2H, CH$_2$-γ), 3.20 (m, 2H, CH-α), 3.40 (t, 1H, J=4.6 Hz, H-2′), 6.32 (d, 1H, J=7.7 Hz, H-7′), 6.55 (td, 1H, J=7.5, 0.8 Hz, H-5′), 7.02 (td, 1H, J=7.5, 1.4 Hz, H-4′), 7.05 (d, 1H, J=7.5 Hz, H-6′).

1′-[3″-(Dimethylamino)propyl]-2′-isopropylspiro[cyclohexane-1,3′-indoline] (**12c**): 63% from **11c**; hydrochloride mp 160—162 °C. IR (film): 1600, 730 cm^{-1}. ^{1}H-NMR: 0.64 (d, 3H, J=6.7 Hz, C$\underline{H}_3$CH), 1.10 (d, 3H, J=7.2 Hz, C$\underline{H}_3$CH), 1.20—1.92 (m, 12H, (CH$_2$)$_5$+CH$_2$-β), 2.02 (sept, 1H, J=7.0 Hz, C$\underline{H}$(CH$_3$)$_2$), 2.23 (s, 6H, N(CH$_3$)$_2$), 2.30 (m, 2H, CH$_2$-γ), 3.36 (s, 1H, H-2′), 3.40 (m, 2H, CH$_2$-α), 6.30 (d, 1H, J=7.7 Hz, H-7′), 6.53 (td, 1H, J=7.5, 0.6 Hz, H-5′), 6.93 (dd, 1H, J=7.0, 1.1 Hz, H-4′), 7.01 (td, 1H, J=7.5, 1.1 Hz, H-6′).

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