Diastereoselective synthesis of 1,1-disubstituted 4-phenyl-2,3,4,9-tetrahydrospiro-β-carbolines from β-phenyltryptamine and isatin derivatives

B. B. Semenov,[a]★ K. A. Novikov,[a] V. N. Azev,[b] and V. V. Kachala[c]

[a]*D. I. Mendeleev University of Chemical Technology, 9 Miusskaya pl., 125047 Moscow, Russian Federation. Fax: +7 (095) 200 4204. E-mail: semenovb@mail.ru*
[b]*Tufts University, 62 Talbot Ave., 02155 Medford, USA. E-mail: vazev02@tufts.edu*
[c]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (095) 135 5328. E-mail: kachala@ioc.ac.ru*

The reaction of β-phenyltryptamine with isatin derivatives is diastereoselective (*de* 66—88%) and affords earlier unknown 1,1-disubstituted 4-phenyl-2,3,4,9-tetrahydrospiro-β-carbolines based on phenyltryptamine and isatins. The study by NMR (NOESY) spectroscopy showed the (*R**,*R**)-configuration of the predominant diastereomers of the resulting 2,3,4,9-tetrahydrospiro-β-carbolines.

Key words: β-carbolines, 2,3,4,9-tetrahydrospiro-β-phenyltryptamine, Piktet—Spengler reaction, diastereoselective synthesis, NMR spectroscopy.

The Piktet—Spengler reaction[1] is widely used for the syntheses (including diastereoselective synthesis) of various 2,3,4,9-tetrahydrospiro-β-carboline derivatives. As the most close analogies, we should mention the synthesis of 2,3,4,9-tetrahydrospiro-β-carbolines with substituents at the C(4) atom, 4-phenyl-substituted 2,3,4,9-tetrahydrospiro-β-carbolines containing no substituents at the C(1) and C(3) atoms,[2—5] 1,1,3,4-tetrasubstituted β-carbolines with a phenyl group at the C(4) atom,[6] and 4-phenyl-substituted 2,3,4,9-tetrahydrospiro-β-carboline derivatives containing no substituents at the C(1) atom.[7]

We have previously found[8,9] high diastereoselectivity in the Michael reaction of α-phenyl-*nor*-gramine with cyclic ketones and acetoacetic ester. Continuing these studies, we studied the diastereoselectivity of the Piktet—Spengler reaction[10] using the reactions between racemic β-phenyltryptamine (**1**) and substituted isatins (Scheme 1) as an example. We obtained earlier unknown 1,1-disubstituted 4-phenyl-β-carbolines **3** and **4**.

Taking into account the structure of tryptamine **1**, only two different routes of the Piktet—Spengler reaction can be proposed[10]: the route involving tryptamine **1** at the phenyl ring to form tetrahydroquinoline and the route at the pyrrole ring of indole to form 2,3,4,9-tetrahydrospiro-β-carboline.[7,11] Based on the published data,[12] we supposed that the reaction involves the indole bicycle because of its π-excessive character.

A mechanism of the Piktet—Spengler reaction including the formation of the spiro[3*H*-indole-3.3´-pyrrolidine] followed by its rearrangement to 2,3,4,9-tetrahydrospiro-β-carboline has previously[1,13,14] been proposed. Therefore, we expected the interaction to involve similar intermediate **3** (see Scheme 1). It is known[15] that diastereoselectivity of the reaction is determined by stereoelectronic and spatial factors. According to this, the intermediates in the pyrrolidine ring of intermediate **3** should be remote from each other at a maximum distance. Similar factors induce, most likely, the predominant formation of (*R**,*R**)-1,1-disubstituted 4-phenyl-2,3,4,9-tetrahydrospiro-β-carbolines **4** by the rearrangement of intermediate **3** to the 2,3,4,9-tetrahydrospiro-β-carboline system.

The structures of the compounds were confirmed by 1D and 2D NMR spectroscopy. The ^{1}H and ^{13}C NMR spectra contained two sets of signals with different intensities corresponding to two diastereomers **4** and **5**. The signals were assigned by an analysis of the 2D COSY, TOCSY, HSQC, and HMBC spectra (Fig. 1). The ratio of diastereomers was determined by a comparison of the integral intensities of the signals of the H(3a), H(3), and H(4) protons in the ^{1}H NMR spectra of the resulting

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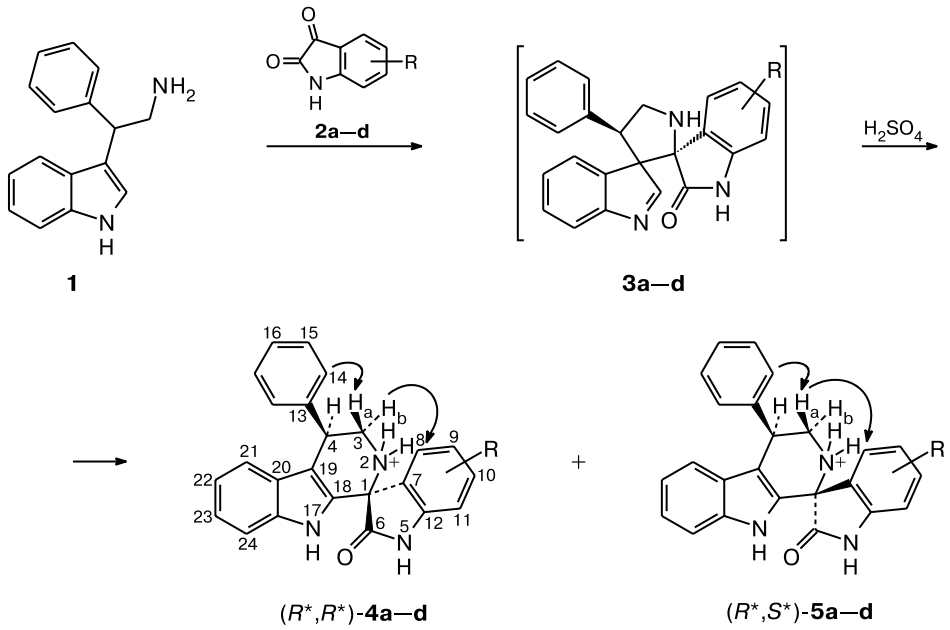
Scheme 1



2, 3: R = H (**a**), 5-Br (**b**), 5,7-Br_2 (**c**), 5-NO_2 (**d**); **4, 5:** R = H (**a**), 9-Br (**b**), 9,11-Br_2 (**c**), 9-NO_2 (**d**)

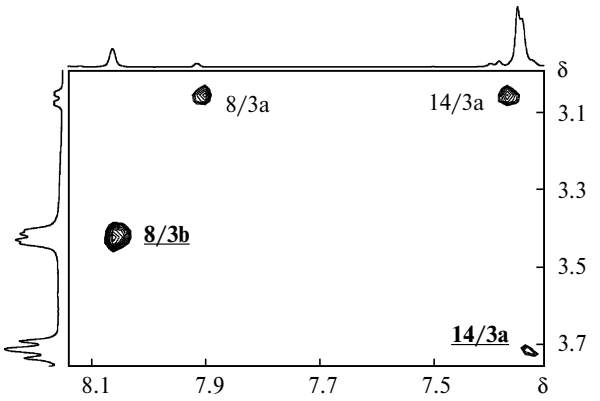


Fig. 1. Fragment of the NOESY spectrum of compounds **4d** and **5d** (the signals of the 1*R**,4*R**-isomer are shown in bold type and underlined).

compounds. The corresponding diastereoselectivities of the reactions are given in Table 1. The chemical shifts of signals in the ^1H and ^{13}C NMR spectra of the compounds under study are presented in Tables 2 and 3, respectively. The spatial structure of each diastereomer was proved by 2D NOESY spectroscopy, revealing closely arranged protons (the correlations are shown by arrows in Scheme 1). In both cases, the configurations were assigned using the correlation between the H(4) and H(3a) protons, which indicated their *cis*-arrangement ("at one side" of the cycle).

For the prevailing 1*R**,4*R**-isomers, the NOESY spectra exhibited correlations of the H(3a) proton with the *ortho*-protons of the phenyl ring (H(14)) and of the H(3b) proton with the H(8) proton, which indicates unambiguously the *trans*-arrangement of substituents at the C(1) and C(4) atoms. For the minor 1*R**,4*S**-isomers, the characteristic correlations of the H(3a) proton with the *ortho*-protons of the phenyl group (H(14)) and with the H(8) proton were detected, which evidenced for the *cis*-arrangement of the substituents at the C(1) and C(4) atoms.

It should be noted that the signals of protons at the N(2) atom are strongly broadened and, hence, they give no correlation peaks and bear no structural information.

The method proposed in this work enables one to obtain a diastereomeric excess of *R**,*R**-diastereomers of 1,1,4-trisubstituted 2,3,4,9-tetrahydrospiro-β-carbolines by the Piktet—Spengler reaction of β-phenyltryptamine with substituted isatins.

Table 1. Diastereoselectivity of the reactions affording pairs of diastereomers of compounds **4a—d** and **5a—d**

Diastereomers of compounds **4** and **5**	*de* (%)★
(1*R**,4*R**)-**4a** : (1*S**,4*R**)-**5a**	88
(1*R**,4*R**)-**4b** : (1*S**,4*R**)-**5b**	72
(1*R**,4*R**)-**4c** : (1*S**,4*R**)-**5c**	72
(1*R**,4*R**)-**4d** : (1*S**,4*R**)-**5d**	66

★ In all cases, the (1*R**,4*R**)-diastereomer of **4** predominates.

Table 2. Chemical shifts of the signals in the ^{1}H NMR spectra (δ) of compounds **4** and **5**

Proton	δ							
	(1*R**,4*R**)-**4a**	(1*S**,4*R**)-**5a**	(1*R**,4*R**)-**4b**	(1*S**,4*R**)-**5b**	(1*R**,4*R**)-**4c**	(1*S**,4*R**)-**5c**	(1*R**,4*R**)-**4d**	(1*S**,4*R**)-**5d**
3a	4.13	3.44	3.88	3.16	3.63	3.03	3.71	3.06
3b	3.79	3.98	3.97	3.63	3.37	4.02	3.41	4.03
4	4.80	4.68	4.57	4.40	4.37	4.29	4.45	4.34
5	11.31	11.28	11.14	11.02	11.08	10.99	11.41	11.25
8	7.45	7.43	7.47	7.36	7.33	7.28	8.06	7.91
9	7.13	7.15	—	—	—	—	—	—
10	7.52	7.46	7.62	7.54	7.75	7.73	8.33	8.29
11	7.16	7.20	7.04	6.98	—	—	7.21	7.18
14	7.41	7.40	7.38	7.38	7.33	7.33	7.35	7.35
15	7.40	7.40	7.38	7.38	7.32	7.32	7.35	7.35
16	7.33	7.34	7.31	7.31	7.25	7.25	7.28	7.26
17	10.97	11.08	10.88	10.91	10.76	10.81	10.76	10.81
21	6.58	6.70	6.59	6.83	6.62	6.93	6.60	6.95
22	6.77	6.82	6.76	6.83	6.73	6.82	6.75	6.85
23	7.03	7.08	7.01	7.04	6.97	7.03	6.98	7.03
24	7.25	7.28	7.23	7.23	7.20	7.21	7.18	7.20

Table 3. Chemical shifts of the signals in the ^{13}C NMR spectra (δ) of compounds **4** and **5**

Atom C	δ							
	(1*R**,4*R**)-**4a**	(1*S**,4*R**)-**5a**	(1*R**,4*R**)-**4b**	(1*S**,4*R**)-**5b**	(1*R**,4*R**)-**4c**	(1*S**,4*R**)-**5c**	(1*R**,4*R**)-**4d**	(1*S**,4*R**)-**5d**
1	59.7	60.3	60.2	61.3	61.9	62.2	60.4	60.9
3	45.2	46.8	46.2	47.3	47.8	47.4	47.5	47.5
4	37.1	37.2	38.3	38.3	39.8	38.5	39.4	38.1
6	172.6	170.9	174.3	173.1	177.1	175.0	177.3	178.4
7	124.9	126.6	130.2	132.4	134.8	135.9	131.4	133.1
8	126.2	125.7	128.3	128.3	126.2	126.1	120.6	119.8
9	122.8	122.7	114.0	114.0	114.0	113.9	142.3	142.2
10	131.7	131.2	133.6	132.7	134.1	133.9	126.9	126.5
11	111.2	111.6	112.7	112.5	103.4	103.5	110.4	110.3
12	143.1	142.7	142.3	142.0	141.8	141.8	149.3	149.3
13	140.7	140.3	141.9	141.7	143.1	144.3	142.8	144.2
14	128.7	128.6	128.6	128.6	128.3	128.2	128.2	128.1
15	128.5	128.5	128.4	128.4	128.2	128.2	128.2	128.2
16	127.5	127.2	127.1	126.5	126.8	126.5	126.5	126.1
18	127.5	127.6	128.6	128.6	131.0	131.3	132.2	130.6
19	112.0	111.9	112.5	112.0	113.9	113.8	113.3	112.4
20	125.0	125.1	125.2	125.5	125.6	125.5	125.5	125.8
21	119.2	119.1	119.1	118.8	119.0	118.6	119.0	118.6
22	119.0	119.0	118.9	118.8	118.5	118.5	118.5	118.5
23	122.2	122.2	121.9	121.7	121.4	121.5	121.4	121.4
24	111.7	111.7	111.6	111.5	111.4	111.4	111.3	111.3
25	136.8	136.8	136.6	136.6	136.4	136.4	136.4	136.4

Experimental

NMR spectra were recorded on a Bruker DRX-500 spectrometer (^{1}H, 500.13; ^{13}C, 125.76 MHz) in DMSO-d_6 at 30 °C using Me_4Si as an internal standard. 2D HSQC and HMBC spectra were obtained using a gradient procedure. Mass spectra (EI, 70 eV) were measured on a Finnigan MAT SSQ-710 spectrometer.

β-Phenyltryptamine (1). Freshly prepared Raney nickel (1 g) was added to a solution of 3-(2-nitro-1-ethylphenyl)indole[16] (26.6 g, 0.1 mol) in 94% EtOH (100 mL), and then hydrazine hydrate (50 mL, 1 mol) was added dropwise. The reaction mixture was refluxed for 60 h; if reflux was interrupted, a new portion of the catalyst (1 g) was added. After the reaction mixture was cooled, and the catalyst was filtered off and washed with hot EtOH (3×10 mL). The filtrate was concentrated to

dryness. The residue was dissolved in anhydrous Et_2O, and excess saturated solution of HCl in Et_2O was added to the resulting solution. The hydrochloride formed was filtered off, suspended in Et_2O, and shaken with excess 20% solution of KOH. The ethereal extract was dried with $MgSO_4$, and the solvent was evaporated. Compound **1** was obtained in 90% yield (21 g), m.p. 131—132 °C (*cf.* Ref. 16: m.p. 131—132 °C (AcOEt)).

5-Bromoindole-2,3(1*H*)-dione (2b) was obtained by a previously described procedure.[17a]

5,7-Dibromoindole-2,3(1*H*)-dione (2c). Molecular bromine (40 g, 0.5 mol) was added dropwise to a mixture of isatin **2a** (30 g, 0.2 mol) and concentrated H_2SO_4 (80 mL) at a temperature below 0 °C with vigorous stirring. The reaction mixture was stored for 1 h at this temperature. After the mixture was warmed to room temperature, it was left to stand for 16 h. Molecular bromine (40 g, 0.5 mol) and AcOH (300 mL) were added to the mixture, and the solution was refluxed until the bromine color disappeared. The mixture was poured onto ice, and the precipitate formed was filtered off and washed with an aqueous solution of K_2CO_3 and water to the neutral reaction in the filtrate. Compound **2c** was obtained in 95% yield (59 g), m.p. 253 °C (*cf.* Ref. 17a: m.p. 252 °C).

5-Nitroindole-2,3(1*H*)-dione was synthesized by a known procedure.[17b]

Compounds 4 and 5 (general procedure). Concentrated H_2SO_4 (1 g) was added to a mixture of β-phenyltryptamine **1** (5 mmol) and the corresponding isatin **2** (5 mmol) in water (40 mL). The reaction mixture was refluxed for 50 h and cooled. A precipitate of 2,3,4,9-tetrahydrospiro-β-carboline sulfates was filtered off and triply washed with boiling isopropyl alcohol. The bases were obtained by suspending the corresponding sulfates in excess aqueous 10% solution of K_2CO_3.

(*R,*R**)- and (*R**,*S**)-4-Phenyl-2,3,4,9-tetrahydrospiro[β-carboline-1,3´-indol]-2´(1´*H*)-one sulfates 4a and 5a.** The yield was 0.83 g (46%), m.p. >300 °C. Found (%): C, 79.23; H, 5.40; N, 11.45 (base). $C_{24}H_{19}N_3O$. Calculated (%): C, 78.88; H, 5.24; N, 11.50 (base). Mass spectrum, m/z (I_{rel} (%)): 365 $[M]^+$ (10).

(*R,*R**)- and (*R**,*S**)-5´-Bromo-4-phenyl-2,3,4,9-tetrahydrospiro[β-carboline-1,3´-indol]-2´(1´*H*)-one sulfates 4b and 5b.** The yield was 1.33 g (60%), m.p. 263 °C (with decomp.). Found (%): C, 64.99; H, 4.20; N, 9.30 (base). $C_{24}H_{18}BrN_3O$. Calculated (%): C, 64.88; H, 4.08; N, 9.46 (base). Mass spectrum, m/z (I_{rel} (%)): 444 $[M]^+$ (15).

(*R,*R**)- and (*R**,*S**)-5´,7´-Dibromo-4-phenyl-2,3,4,9-tetrahydrospiro[β-carboline-1,3´-indol]-2´(1´*H*)-one sulfates 4c and 5c.** The yield was 1.98 g (76%), m.p. >300 °C. Found (%): C, 55.29; H, 3.3; N, 7.89 (base). $C_{24}H_{17}Br_2N_3O$. Calculated (%): C, 55.09; H, 3.27; N, 8.03 (base). Mass spectrum, m/z (I_{rel} (%)): 523 $[M]^+$ (15).

(*R,*R**)- and (*R**,*S**)-5´-Nitro-4-phenyl-2,3,4,9-tetrahydrospiro[β-carboline-1,3´-indol]-2´(1´*H*)-one sulfates 4d and 5d.** The yield was 0.8 g (39%), m.p. 246 °C. Found (%): C, 70.59; H, 4.53; N, 13.55 (base). $C_{24}H_{18}N_4O_3$. Calculated (%): C, 70.23; H, 4.42; N, 13.65 (base). Mass spectrum, m/z (I_{rel} (%)): 410 $[M]^+$ (15).

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