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DIASTEREODIRECTED SYNTHESIS OF 1-ARYL-4-PHENYL-β-CARBOLINES

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A diastereodirected Pictet–Spengler reaction has been carried out to give the previously unknown 1-aryl(alkyl)-4-phenyl-β-carbolines and it has been found that all of the β-carbolines diastereomers obtained have predominantly the R,R*-configuration. The diastereoselectivity of the given reaction is 44-70%.*

Keywords: β-carbolines, β-phenyltryptamine, diastereoselective synthesis, Pictet–Spengler reaction.

We have demonstrated a high diastereoselectivity of α-phenyl-*nor*-gramine in the Michael reaction with cyclic ketones and acetoacetic ester [1, 2]. The present work is concerned with a study of the diastereoselectivity of the reaction of β-phenyltryptamine (**1**) with aromatic and aliphatic aldehydes (the Pictet–Spengler reaction [3]).

Two routes are possible for the reaction studied, i.e. at the phenyl ring to give a tetrahydroquinoline [3] or at the pyrrole ring of the indole to give a β-carboline [4, 5]. We propose that the reaction will involve the participation of the indole ring as a result of its π-excessive nature. In [4], the synthesis of 1-unsubstituted 4-phenyl-β-carbolines was described and it was shown that they possess marked biological activity.

The previously proposed mechanism for the Pictet–Spengler reaction includes a stage of formation of a spiro[3H-indole-3,2'-pyrrolidine] derivative which subsequently rearranges to a β-carboline [6-8]. On this basis we propose that the reaction in our case using differently structured aldehydes and β-phenyltryptamine as starting materials occurs *via* the formation of intermediate **2**. It is known that the diastereoselectivity is determined by stereoelectronic or spatial factors [9]. In this connection, in the intermediate the substituents in position 2 and 4 of the pyrrolidine ring must be maximally removed from one another, i.e. they have a *trans* arrangement. The rearrangement of compound **2** to the β-carboline system is evidently influenced by the same steric factors to form mainly the (*R**,*R**)-1-aryl(alkyl)-4-phenyl-β-carbolines **3** (here, and subsequently, the * indicates the relative configuration).

The structures of the compounds prepared were investigated using one- and two-dimensional NMR spectroscopy. The ^{1}H and ^{13}C NMR one- dimensional spectra show two sets of signals of differing intensity which correspond to two diastereomers (the signals were assigned by analysing two-dimensional COSY, HSQC, and HMBC spectra). The spatial structure of each of the diastereomers was revealed using two-dimensional H-H NOE (NOESY) spectroscopy which allows one to identify the close positioned protons.

We have studied the configuration of both diastereomers in the case of compounds **3a,b**. In all of the compounds studied the H-3 protons have a clear equatorial or axial nature as shown by the shape of the H-3 and H-3a proton signals in the ^{1}H NMR spectra. This makes easier the identification of the configuration of the

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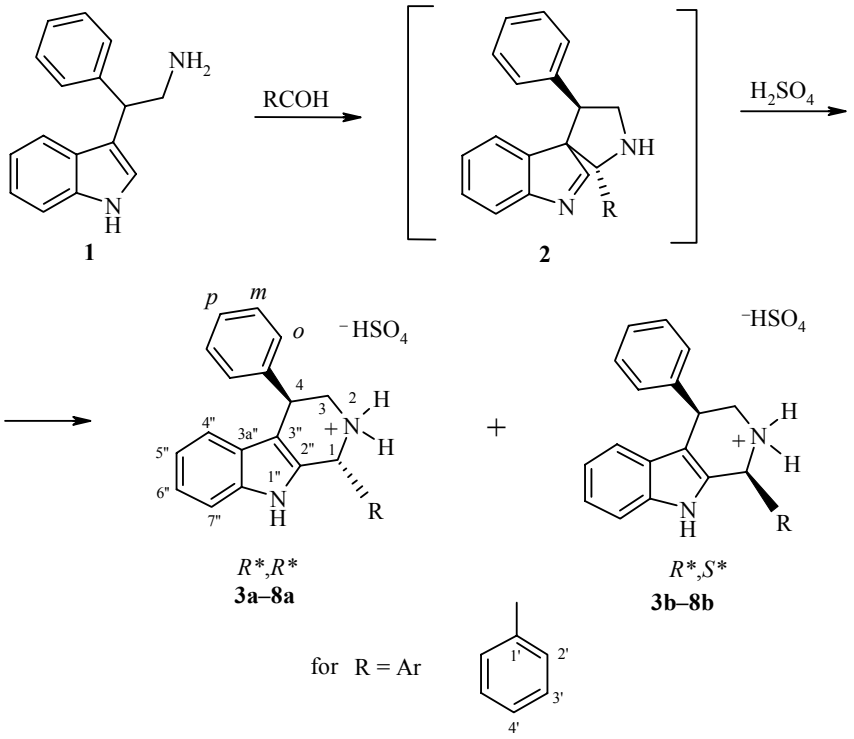

3 R = Me, **4** R = Ph, **5** R = *p*-ClC_6H_4, **6** R = *p*-$MeOC_6H_4$, **7** R = *p*-$O_2NC_6H_4$, **8** R = *m*-$O_2NC_6H_4$

diastereomers. The NOESY spectrum of the minor 1*S**,4*R**-isomer shows correlations between the 1-CH_3 group protons, (H-1'), and the axial H-3a proton (see Fig. 1).

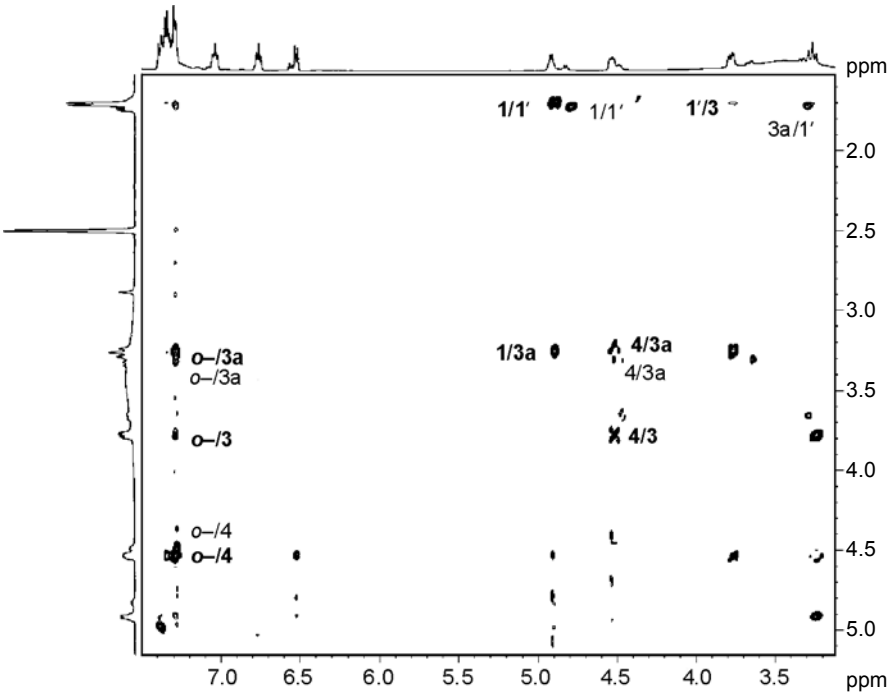

Fig. 1. Part of the NOESY spectrum of compounds **3a,b** (bold type for the 1*R**,4*R**-isomer).

Correlations were also revealed between the phenyl *ortho* protons, H-4, and both H-3 and H-3a protons. This supports an equatorial positioning of the phenyl group in the six-membered ring and an axial position for the methyl group in this ring and is supported by the presence of a correlation between the methyl group protons and H-3a. Different correlations are found in the main isomer. Hence the *ortho* protons of the phenyl group have the same cross peak with the H-3 and H-3a protons but proton H-1 interacts with the axial H-3a proton thus pointing to an axial positioning in this ring. This fact, and the absence of a correlation between the methyl group protons and the axial H-3a proton lead us to infer a *trans* arrangement for the phenyl and methyl groups in the six-membered ring. In both cases a correlation is observed between the H-4 proton and equatorial H-3e proton. It should be noted that the signals for the protons on the N-2 atom are strongly broadened hence the correlation of peaks could not be made and structural information not deduced. Hence the configuration of the pair of compounds **3a** and **3b** were established; the first being the 1*R**,4*R**- and the second the 1*S**,4*R**-isomer (Fig. 2).

The structure of the remaining compounds was established similarly. In the case of the predominant 1*R**,4*R**-isomers the NOESY spectra showed a correlation of the axial H-3a proton with the *ortho* protons of the phenyl ring, H-4, and the H-1 proton and this unambiguously points of to a *trans* arrangement for the substituents at positions 1 and 4. In the example of the minor 1*S**,4*R**-diastereomers a characteristic correlation is seen between H-3a and the *ortho* protons of the phenyl ring, H-4, and also with the *ortho* protons (H-1') of the aryl substituent at C-1. This proves a *cis* positioning of the substituents at positions 1 and 4. Fig. 3 shows a part of the NOESY spectrum for compounds **5a,b**.

The method proposed by us leads to the preparation of compounds **3-8** with a known diastereomeric excess of *R**,*R**-diastereomers and with different substituents in the position 1 of the β-carboline ring.

TABLE 1. Diastereomers Ratio for Compounds **3-8**

Diastereomers	*de*, %*	Diastereomers	*de*, %*
3a (1*R**,4*R**) : **3b** (1*S**,4*R**)	44	**6a** (1*R**,4*R**) : **6b** (1*S**,4*R**)	64
4a (1*R**,4*R**) : **4b** (1*S**,4*R**)	70	**7a** (1*R**,4*R**) : 7**b** (1*S**,4*R**)	62
5a (1*R**,4*R**) : **5b** (1*S**,4*R**)	62	**8a** (1*R**,4*R**) : 8**b** (1*S**,4*R**)	56

* *de* denotes the diastereoselectivity of the reaction

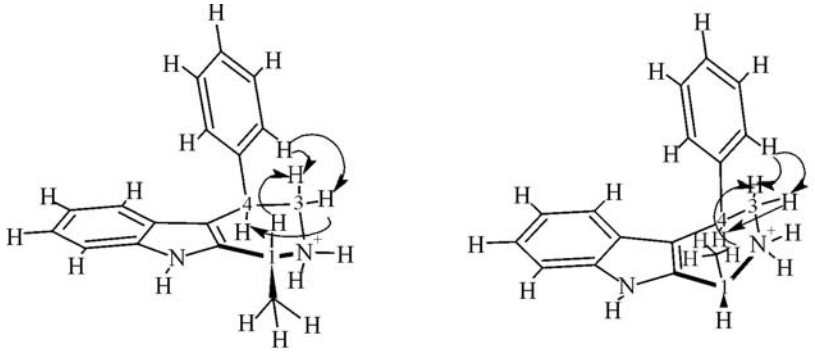

Fig. 2. Correlation interactions in compounds **3a,b**.

TABLE 2. ^{1}H NMR Spectra of Compounds **3-8**

Protons	Chemical shifts, δ, ppm											
	3a (1*R**,4*R**)	**3b** (1*S**,4*R**)	**4a** (1*R**,4*R**)	**4b** (1*S**,4*R**)	**5a** (1*R**,4*R**)	**5b** (1*S**,4*R**)	**6a** (1*R**,4*R**)	**6b** (1*S**,4*R**)	**7a** (1*R**,4*R**)	**7b** (1*S**,4*R**)	**8a** (1*R**,4*R**)	**8b** (1*S**,4*R**)
H-1	4.91	4.75	5.89	5.76	5.75	5.58	5.76	5.60	5.89	5.70	5.92	5.75
H-2	—	—	—	—	—	—	—	—	—	—	—	—
H-3	3.79	3.56	3.67	3.41	3.59	3.37	3.60	3.39	3.60	3.40	3.65	3.40
H-3a	3.20	3.22	3.38	2.85	3.16	2.82	3.19	2.89	3.17	2.81	3.20	2.82
H-4	4.55	4.41	4.60	4.46	4.51	4.36	4.61	4.42	4.51	4.37	4.56	4.39
H-1'	1.61	1.64	—	—	—	—	—	—	—	—	—	—
H-2'	—	—	7.43	7.44	7.45	7.45	7.38	7.30	7.68	8.06	8.30	—*
H-3'	—	—	7.49	—	7.56	7.51	7.00	7.02	8.30	8.39	—	—
H-4'	—	—	7.44	—*	—	—	—	—	—	—	8.31	—*
H-5'	—	—	—	—	—	—	3.78	3.76	—	—	7.78	—*
H-6'	—	—	—	—	—	—	—	—	—	—	7.89	—*
o-H	7.28	7.31	7.29	7.35	7.30	7.32	7.30	7.30	7.31	—*	7.29	—*
m-H	7.35	7.35	7.35	—*	7.32	7.32	7.30	7.30	7.33	—*	7.33	—*
p-H	7.35	7.35	7.31	—*	7.32	7.32	7.26	7.26	7.37	—*	7.29	—*
H-1"	11.33	11.29	10.76	11.02	10.71	10.94	10.67	10.94	10.74	10.99	10.77	11.02
H-4"	6.53	6.58	6.58	6.69	6.59	6.69	6.59	6.72	6.64	—*	6.61	—*
H-5"	6.76	6.78	6.74	6.80	6.74	6.79	6.74	6.80	6.78	—*	6.76	—*
H-6"	7.04	7.08	6.99	7.03	6.98	7.01	6.97	7.00	6.99	—*	6.99	—*
H-7"	7.40	7.40	7.27	7.32	7.25	7.30	7.31	7.36	7.26	—*	7.25	—

* Signal not assigned.

TABLE 3. ^{13}C NMR Spectra of Compounds **3-8**

Atoms	Chemical shifts, δ, ppm									
	3a (1*R**,4*R**)	**3b** (1*S**,4*R**)	**4a** (1*R**,4*R**)	**4b** (1*S**,4*R**)	**5a** (1*R**,4*R**)	**5b** (1*S**,4*R**)	**6a** (1*R**,4*R**)	**6b** (1*S**,4*R**)	**7a*** (1*R**,4*R**)	**8a***[2] (1*R**,4*R**)
C-1	49.0	47.3	56.9	54.6	55.9	54.0	56.5	54.6	56.0	56.0
C-3	48.5	44.9	49.7	46.2	50.6	47.3	50.3	47.1	49.9	50.1
C-4	37.4	36.8	38.4	38.2	39.6	39.6	38.8	38.9	38.7	39.2
C-1'	16.7	17.9	—*[3]	—*[3]	139.1	—*[3]	129.7	129.7	145.6	139.9
C-2'	—	—	129.6	—*[3]	131.1	129.3	130.7	130.5	130.7	123.9
C-3'	—	—	129.3	—*[3]	128.3	128.3	114.2	114.1	123.6	147.8
C-4'	—	—	129.3	—*[3]	—*[3]	—*[3]	159.8	159.5	147.7	123.6
C-5'	—	—	—	—	—	—	55.4	55.8	—	130.2
C-6'	—	—	—	—	—	—	—	—	—	136.0
i-	140.3	140.3	141.4	—*[3]	142.8	141.5	142.0	142.7	141.9	141.9
o-	128.2	128.2	128.4	128.4	128.2	128.2	128.4	128.4	128.3	128.3
m-	128.3	128.3	128.4	—*[3]	128.2	128.2	128.4	128.4	128.3	128.3
p-	127.3	127.2	127.1	—*[3]	126.5	126.7	127.0	126.8	126.8	126.8
C-2"	132.0	132.5	131.7	—*[3]	134.1	133.7	133.0	133.4	132.0	132.1
C-3"	108.2	107.3	110.4	110.3	110.6	109.2	110.5	110.4	110.6	110.7
C-3a"	125.0	125.0	125.2	—*[3]	125.7	126.2	125.6	125.8	125.3	125.4
C-4"	118.8	118.8	118.9	118.8	118.7	118.5	118.9	118.7	118.8	118.8
C-5"	118.8	118.8	118.7	118.7	118.3	118.4	118.7	118.8	118.6	118.6
C(6")	121.4	121.5	121.3	121.3	120.8	120.8	121.3	121.4	121.2	121.2
C(7")	111.4	111.4	111.6	111.6	111.3	111.5	111.6	111.5	111.4	111.4
C-7a"	136.4	136.3	136.6	136.5	136.3	136.4	136.7	136.6	136.5	136.5

* Compound **7b** (1*S**,4*R**). Signals of C-1-C-4 and *i*-C-C-7a" not assigned.

*[2] Compound **8b** (1*S**,4*R**). Signals not assigned.

*[3] Signal not assigned.

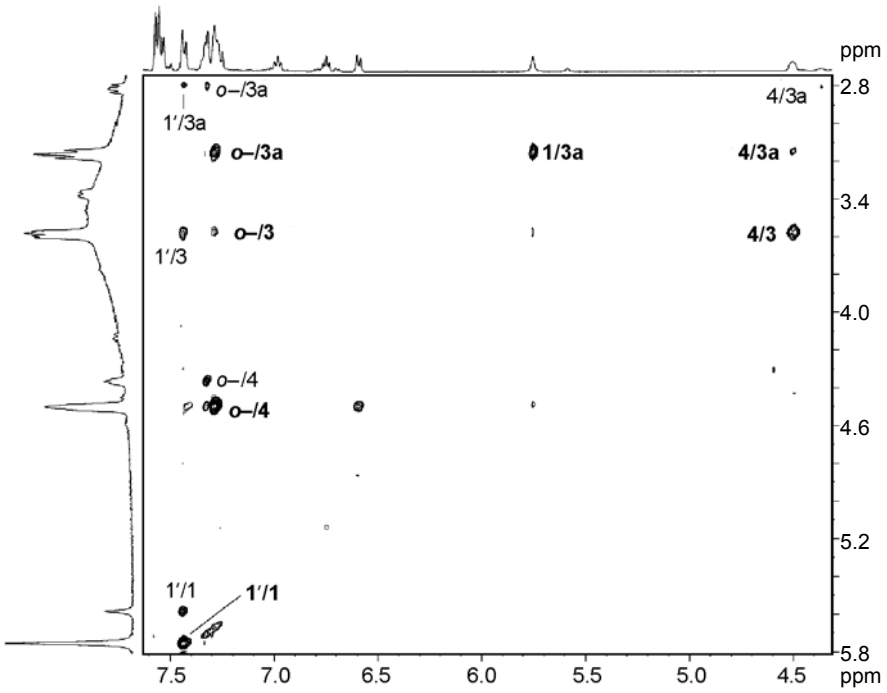

Fig. 3. Part of the NOESY spectrum of compounds **5a,b** (bold type for the 1*R**,4*R**-isomer).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were taken on a Bruker DRX-500 instrument (500 and 125 MHz respectively) using DMSO-d_6 solvent at 30°C using Bruker standard methods. Two-dimensional HSQC and HMBC spectra were obtained using a gradient method. The internal standard was TMS. Mass spectra were recorded on a Finnigan MAT SSQ-710 spectrometer with an electron ionizing energy of 70 eV.

β-Phenyltryptamine (1). Hydrazine hydrate (75 ml) was added dropwise over 60 h to a mixture of 3-(2-nitro-1-phenylethyl)indole [10] (26.6 g, 0.1 mol) in 94% alcohol (100 ml) and freshly prepared Raney nickel (1 g) at the temperature of reflux of the mixture. If the reflux stops a further portion of catalyst is added. The product was filtered and the filtered catalyst was washed with hot alcohol (3 × 10 ml). The filtrate was evaporated. The residue was dissolved in anhydrous ether and a saturated solution of HCl in ether was added. The hydrochloride formed was filtered off, suspended in ether, and shaked with an aqueous solution of alkali. The ether solution was dried over $MgSO_4$ and evaporated to give 21 g of product (90%) with mp 131-132°C (mp 131-132°C (ethyl acetate) [10]).

Preparation of Compounds 3-8 (General Method). Conc. H_2SO_4 (0.5 g) was added to a mixture of β-phenyltryptamine (1.18 g, 0.005 mol) and 5% acetaldehyde (37.5 ml, 0.04 mol). The product was refluxed to the solution of compound **1**, cooled, and the precipitated carboline sulphates were filtered off.

^{1}H and ^{13}C NMR spectra are given in Tables 2 and 3.

1-Methyl-4-phenyl-2,3,4,9-tetrahydro-β-carboline Sulfate (3). Yield 50%; mp 218°C (sulfate). Mass spectrum, *m/z* (I_{rel}, %): 262 $[M]^+$ (10). Found, %: C 82.53; H 7.02; N 10.45 (base). $C_{18}H_{18}N_2$. Calculated, %: C 82.41; H 6.92; N 10.68 (base).

1,4-Diphenyl-2,3,4,9-tetrahydro-β-carboline sulphate (4). Yield 60%; mp 228°C (sulfate). Mass spectrum, *m/z* (I_{rel}, %): 234 [M] (14). Found, %: C 86.13; H 6.72; N 7.15 (base). $C_{23}H_{20}N_2$. Calculated, %: C 85.15; H 6.21; N 8.63 (base).

1-(4-Chlorophenyl)-4-phenyl-2,3,4,9-tetrahydro-β-carboline Sulphate (5). Yield 63%; mp 255°C (sulfate). Mass spectrum, *m/z* (I_{rel}, %): 358 $[M]^+$ (14). Found, %: C 77.33; H 5.81; N 7.75 (base). $C_{23}H_{19}ClN_2$. Calculated, %: C 76.98; H 5.34; N 7.81 (base).

1-(4-Methoxyphenyl)-4-phenyl-2,3,4,9-tetrahydro-β-carboline Sulfate (6). Yield 55%; mp 225°C (sulfate). Mass spectrum, *m/z* (I_{rel}, %): 354 $[M]^+$ (20). Found, %: C 81.83; H 6.81; N 8.00 (base). $C_{24}H_{22}N_2O$. Calculated, %: C 81.33; H 6.26; N 7.90 (base).

1-(4-Nitrophenyl)-4-phenyl-2,3,4,9-tetrahydro-β-carboline Sulfate (7). Yield 80%; mp >260°C (sulfate). Mass spectrum, *m/z* (I_{rel}, %): 369 $[M]^+$ (30). Found, %: C 74.33; H 5.05; N 11.40 (base). $C_{23}H_{19}N_3O_2$. Calculated, %: C 74.78; H 5.18; N 11.37 (base).

1-(3-Nitrophenyl)-4-phenyl-2,3,4,9-tetrahydro-β-carboline Sulfate (8). Yield 76%; mp >260°C (sulfate). Mass spectrum, *m/z* (I_{rel}, %): 369 $[M]^+$ (27). Found, %: C 74.43; H 4.95; N 11.40 (base). $C_{23}H_{19}N_3O_2$. Calculated, %: C 74.78; H 5.18; N 11.37 (base).

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