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Synthesis of 1-aryl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles (1,2,3,4-tetrahydro-β-carbolines) under high pressures

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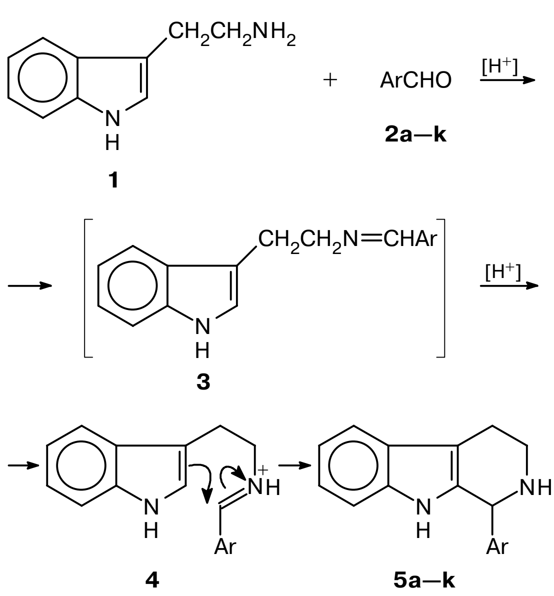
The reactions of aromatic aldehydes with tryptamine (**1**) in solvents of different polarity were studied. The yields of carbolines in the chosen media decrease with an increase in the donating properties of the aryl substituent, but they markedly increase at a high pressure (5 kbar), especially for compounds with electron-donating aryl groups. The phase transition of dioxane at 5 kbar also sharply increases the yields of the target products.

Key words: carbolines, tryptamine, aromatic aldehydes, Pictet—Spengler reaction, high pressure.

1,2,3,4-Tetrahydro-β-carboline is a structural fragment of many biologically active alkaloids[1] such as reserpine, tetrahydroharmine, and yohimbine. Its 1-alkyl derivatives are usually obtained by the Pictet—Spengler reaction,[2] *i.e.*, by condensation of tryptamine (**1**) with aliphatic aldehydes in an acidic media to form intermediate Schiff bases that undergo *in situ* cyclization into carbolines. This reaction is widely dealt with in the literature.[1] However, the behavior of aromatic aldehydes in the Pictet—Spengler reaction has been discussed only in a single work.[3] It was shown that the yields of carboline derivatives are high only for ArCHO with electron-withdrawing substituents (NO_2 and Cl) and rather low in the case of electron-donating groups (Me, OMe, and NMe_2).

The goal of our work is to carry out the reactions of tryptamine (**1**) with aromatic aldehydes **2a—k** (Scheme 1, Table 1) both at ambient and high pressure (5 kbar) and study how the phase transition of a solvent influences the yield of carbolines. It is known[1] that an intramolecular electrophilic cyclization of protonated intermediate **4** is the key stage in the synthesis, and hence this process can be significantly accelerated at elevated pressure (entropic factor).

Scheme 1



Aldehydes with different electronic properties were studied (in Table 1, the aldehydes appear in the order of decreasing electron-withdrawing and increasing electron-donating properties of an aromatic substituent). All syntheses were carried out in MeOH (a standard solvent for the Pictet—Spengler reaction), CH_2Cl_2, and dioxane. The reaction mixtures were refluxed at ambient pressure for 10 h and kept at ~20 °C at a pressure of 5 kbar for 1 h (see Table 1). Hydrogen chloride was used as an acid catalyst in the ratios close to those in Ref. 3.

At ambient pressure, the yields of carbolines **5** gradually decreased with an increase in the donating properties of the aryl substituent, being for alkyl- and alkoxy derivatives ~30% in MeOH and <1% in CH_2Cl_2 and dioxane. Such a result was also noted earlier[3] and is probably due to a decreased electrophilicity of intermediate **4** with an electron-donating Ar group.

As expected, the yields of carbolines **5** at 5 kbar in all of the solvents were much higher than those at ambient pressure, the products from any aldehydes being obtained (see Table 1).

It was also found that the course of the reaction under study is largely affected by the solvent. In low-polarity media (CH_2Cl_2 and dioxane), the yields of compounds **5** at ambient pressure were appreciably lower

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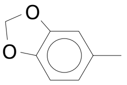
Table 1. Yields of 1-aryl-1,2,3,4-tetrahydro-β-carbolines (**5a—k**) in the Pictet—Spengler reaction under different conditions

Compound, Ar	Yields of **5a—k · HCl** (%)						M.p. of **5 · HCl**/°C		M$^+$ *m/z*
	Ambient pressure, 10 h			5 kbar, 20 °C, 1 h			Our data	Literature data[3]	
	MeOH, 65 °C	CH_2Cl_2, 40 °C	Dioxane, 101 °C	MeOH	CH_2Cl_2	Dioxane			
5a, 4-$CF_3C_6H_4$	91	40	47	97	72	94	283—285[a]	—	316
5b, 4-$O_2NC_6H_4$	88	36	35	91	60	90	242—245	240—250 (decomp.)	293
5c, 3-O_2N-4-ClC_6H_3	69	28	29	85	62	88	268—270	270 (decomp.)	327
5d, 3-$O_2NC_6H_4$	65	15	21	88	63	89	271—273[b]	—	293
5e, 4-ClC_6H_4	62	16	17	85	70	87	282—284	280—281	282
5f, Ph	35	3	2	87	60	91	268—270	267—270	248
5g, *m*-Tol	33	<1	<1	89	69	90	250—251	248—251	262
5h, *p*-Tol	34	<1	<1	81	57	85	285—287	283—286	262
5i, 	30	<1	<1	78	50	87	272—275	270—273	292
5j, 4-$MeOC_6H_4$	33	<1	<1	80	51	90	283—285	283—285	278
5k, 4-$EtOC_6H_4$	27	<1	<1	78	49	78	271—274[c]	—	292

[a] Found (%): C, 61.49; H, 4.30; N, 7.59. $C_{18}H_{16}ClF_3N_2$. Calculated (%): C, 61.28; H, 4.57; N, 7.94.

[b] Found (%): C, 61.82; H, 5.11; N, 13.09. $C_{17}H_{16}ClN_3O_2$. Calculated (%): C, 61.92; H, 4.89; N, 12.74.

[c] Found (%): C, 69.75; H, 6.10; N, 8.55. $C_{19}H_{21}ClN_2O$. Calculated (%): C, 69.40; H, 6.44; N, 8.52.

than in MeOH, and carbolines **5g—k** from aldehydes with electron-donating substituents were formed in very small amounts.

Of interest is also the solvent effect on the reaction at 5 kbar. Although the use of high pressure markedly increased the yields of carbolines **5** in CH_2Cl_2, they were lower than in MeOH (5 kbar). In most cases, the yields in dioxane (5 kbar) are even higher than in MeOH (5 kbar), as opposed to the reactions at ambient pressure. Such an unusual jump in the yields of compounds **5** in dioxane can be explained by its phase transition at a pressure of 5 kbar. The crystallization of the solvent increases the concentration of the reagents and can also cause a specific "cell effect" which lowers the transition state energy, thus facilitating the reaction (entropic factor).[4]

Experimental

^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer in DMSO-d_6. The chemical shifts are referred to the δ scale with Me_4Si as the standard. Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument (EI, 70 eV). Melting points of hydrochlorides **5a—k** were determined on a Boetius hot stage. The notation "<1%" in Table 1 means that hydrochlorides **5** were not isolated, but their presence (in trace amounts) in the reaction mixtures was proved by mass spectrometry (M$^+$).

All reagents and solvents (Aldrich) were used without additional purification.

1-(4-Trifluoromethylphenyl)-1,2,3,4-tetrahydro-β-carboline hydrochloride (5a · HCl). A. Experiment in MeOH at $P = 1$ bar. A mixture of tryptamine **1** (10 mmol) and aldehyde **2a** (10 mmol) in 3 mL of MeOH was treated with a solution of HCl (10.5 mmol) in MeOH. The volume of MeOH was brought to 10 mL, and the reaction mixture was refluxed for 10 h. After cooling, hydrochloride (**5a · HCl**) was filtered off and recrystallized from MeOH. The filtrates were concentrated to give an additional amount of crystals. The total yield was 91%. ^{1}H NMR, δ: 3.00—3.50 (m, 4 H, CH_2CH_2); 6.00 (s, 1 H, $C\underline{H}—N^+H_2$); 7.00—7.85 (m, 8 H, H_{arom}); 10.40 (br.s, 2 H, $N^+\underline{H}_2$); 10.80 (s, 1 H, NH).

B. Experiment in CH_2Cl_2 at $P = 1$ bar. A mixture of compound **1** (10 mmol) and aldehyde **2a** (10 mmol) in 3 mL of CH_2Cl_2 was treated with a solution of HCl (10.5 mmol) in CH_2Cl_2. The volume of CH_2Cl_2 was brought to 10 mL, and the reaction mixture was refluxed for 10 h and evaporated to dryness. After MeOH (5 mL) was added, hydrochloride **5a · HCl** was filtered off. An additional amount of the hydrochloride was isolated from the filtrate. The total yield of **5a · HCl** was 40%.

C. Experiment in dioxane at $P = 1$ bar was carried out as described for CH_2Cl_2, using a solution of HCl in dioxane. The yield of **5a · HCl** was 47%.

D. Experiments at $P = 5$ kbar. Amine **1** (1 mmol), aldehyde **2a** (1 mmol), and a solvent (MeOH, CH_2Cl_2, or dioxane, 0.3 mL) were placed in a 1-mL Teflon tube. The reaction mixture was treated with a solution of HCl (1.05 mmol) in the corresponding solvent. The volume of the solvent was brought to 1 mL, and the reaction mixture was kept at 5 kbar for 1 h and worked up as described above for $P = 1$ bar.

The reactions with aldehydes **2b—k** were carried out in a similar manner. The yields and melting points of hydrochlorides **5a—5k · HCl** and the molecular ions of bases **5a—k** are given in Table 1.

The ^{1}H NMR spectra of hydrochlorides **5b · HCl—5k · HCl**.

5b · HCl, δ: 3.00—3.50 (m, 4 H, CH_2CH_2); 6.15 (s, 1 H, $C\underline{H}—N^+H_2$); 7.00—8.40 (m, 8 H, H_{arom}); 10.30 (br.s, 2 H, $N^+\underline{H}_2$); 10.90 (s, 1 H, NH).

5c · HCl, δ: 2.90—3.60 (m, 4 H, CH_2CH_2); 6.15 (s, 1 H, $C\underline{H}—N^+H_2$); 7.10 and 7.90 (both m, 4 H, H(5), H(6), H(7), H(8)); 7.35 and 7.55 (both d, 2 H, $C_6\underline{H}_2NO_2ClH$, $J = 7$ Hz); 8.25 (s, 1 H, $C_6H_2NO_2Cl\underline{H}$); 10.50 (br.s, 2 H, $N^+\underline{H}_2$); 11.00 (s, 1 H, NH).

5d • HCl, δ: 3.00—3.50 (m, 4 H, CH_2CH_2); 6.10 (s, 1 H, $C\underline{H}—N^+H_2$); 7.00—8.40 (m, 8 H, H_{arom}); 10.20 (br.s, 2 H, $N^+\underline{H}_2$); 10.80 (s, 1 H, NH).

5e • HCl, δ: 3.00—3.50 (m, 4 H, CH_2CH_2); 5.90 (s, 1 H, $C\underline{H}—N^+H_2$); 7.00—7.60 (m, 8 H, H_{arom}); 10.40 (br.s, 2 H, $N^+\underline{H}_2$); 10.80 (s, 1 H, NH).

5f • HCl, δ: 3.00—3.50 (m, 4 H, CH_2CH_2); 5.90 (s, 1 H, $C\underline{H}—N^+H_2$); 7.00—7.50 (m, 9 H, H_{arom}); 10.30 (br.s, 2 H, $N^+\underline{H}_2$); 10.90 (s, 1 H, NH).

5g • HCl, δ: 2.35 (s, 3 H, CH_3); 3.00—3.50 (m, 4 H, CH_2CH_2); 5.80 (s, 1 H, $C\underline{H}—N^+H_2$); 7.00—7.55 (m, 8 H, H_{arom}); 10.20 (br.s, 2 H, $N^+\underline{H}_2$); 10.80 (s, 1 H, NH).

5h • HCl, δ: 2.40 (s, 3 H, CH_3); 3.00—3.50 (m, 4 H, CH_2CH_2); 5.80 (s, 1 H, $C\underline{H}—N^+H_2$); 7.00—7.50 (m, 8 H, H_{arom}); 10.00 (br.s, 2 H, $N^+\underline{H}_2$); 10.75 (s, 1 H, NH).

5i • HCl, δ: 3.00—3.50 (m, 4 H, CH_2CH_2); 5.90 (s, 1 H, $C\underline{H}—N^+H_2$); 6.10 (s, 2 H, OCH_2O); 7.00—7.50 (m, 7 H, H_{arom}); 10.20 (br.s, 2 H, $N^+\underline{H}_2$); 10.80 (s, 1 H, NH).

5j • HCl, δ: 3.00—3.50 (m, 4 H, CH_2CH_2); 3.90 (s, 3 H, OCH_3); 5.90 (s, 1 H, $C\underline{H}—N^+H_2$); 7.00—7.60 (m, 8 H, H_{arom}); 10.10 (br.s, 2 H, $N^+\underline{H}_2$); 10.90 (s, 1 H, NH).

5k • HCl, δ: 1.35 (t, 3 H, $OCH_2C\underline{H}_3$); 3.00—3.50 (m, 4 H, CH_2CH_2); 4.10 (q, 2 H, $OC\underline{H}_2CH_3$); 5.85 (s, 1 H, $C\underline{H}—N^+H_2$); 7.00—7.60 (m, 8 H, H_{arom}); 10.00 (br.s, 2 H, $N^+\underline{H}_2$); 10.85 (s, 1 H, NH).

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