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SYNTHESIS OF 2-ACYLTETRAHYDRO-β-CARBOLINES BY AN INTRAMOLECULAR α-AMIDOALKYLATION REACTION

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Abstract: 2-Acyltetrahydro-β-carbolines **7** have been obtained by cyclization of adducts **5** from imines **3** of tryptamine **1** and aldehydes **2** with acyl chlorides **4** as a result of an intramolecular α-amidoalkylation reaction in the presence of bases as N,N-dimethylaniline or Et_3N.

β-Carboline moiety is a central feature of many indole alkaloids. Consequently, the large majority of indol alkaloid syntheses incorporate at some crucial stage the synthesis of this type of skeleton.[1] The original Pictet-Spengler reaction was successfully extended to the synthesis of tetrahydro-β-carbolines and provided one of the most versatile and general approaches to this system. It was found that the yields of tetrahydro-β-carbolines obtained by Pictet-Spengler reaction can be improved in an aprotic media and the mechanism of the cyclization was extensively studied.[2-7] Concerning the mechanism of the reaction of tryptamine and tryptophan derivatives two possible pathways have been proposed, which involve a direct attack at the indole 2-position or attack at 3-position to form a spiroindolenium intermediate.[8] However, regardless of the path which is followed, it is the electrophilic nature of the imine double bond which is the driving force

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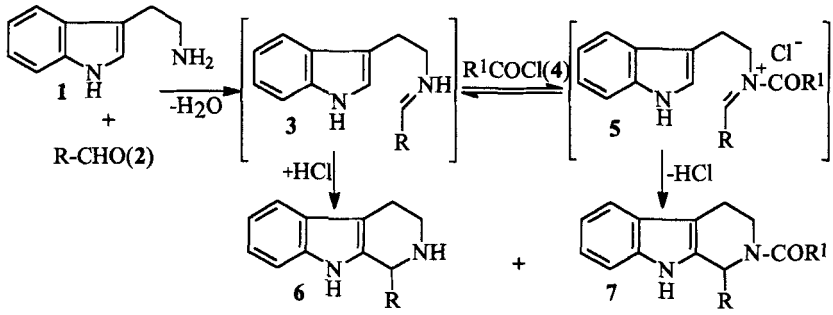
in this reaction. It was well established for the last several years that the N-iminium ions involved in the Pictet-Spengler's reaction are much less electrophilic then those of the corresponding N-acyliminium ions used in the intramolecular α-amidoalkylation reaction and that was successfully explored for synthesis of N-acyltetrahydroisoquinolines.[9]

Looking for further synthetic applications of the intramolecular α-amido-alkylation reaction as an extended variation of Pictet-Spengler method we investigated the reaction of adducts **5** obtained from imines **3** of tryptamine **1** and aldehydes **2** with acyl chlorides **4** for synthesis of 2-acyltetrahydro-β-carbolines **7**. Imines **3**, obtained from tryptamine **1** and the corresponding aldehydes **2** were used without isolation and purification because of their instability.



It was found that the reaction of imines **3** with acyl chlorides **4** in organic solvents as dichloromethane proceeded at room temperature with evolution of hydrogen chloride and afforded a mixture of two products, which were identified as the corresponding tetrahydro-β-carbolines **6** and 2-acyltetrahydro-β-carbolines **7** (Table 1, Method A). It was assumed that the presence of **6** in the reaction mixture is a result of the Pictet-Spengler reaction from the evolved hydrogen chloride at the cyclization of adducts **5**. Supporting this assumption was the finding that the yield of **6** depended on the nature of the substituents in the aromatic ring of the aldehyde of **3**. The presence of electron withdrawing groups led to increased yields of **6**(Table 1,

Table 1. 2-Acyltetrahydro-β-carbolines **7** and tetrahydro-β-carbolines **6**

Entry	R	R^1	Yields (%)			
			Method **A**		Method **B**	
			6	**7**	**6**	**7**
a	C_6H_5	Me	30	50	-	80
b	C_6H_5	OEt	25	54	traces	78
c	4-NO_2-C_6H_4	Me	43	52	-	95
d	4-NO_2-C_6H_4	OEt	36	58	8	83
e	4-F-C_6H_4	Me	32	45	23	50
f	4-Cl-C_6H_4	Me	-	-	-	85
g	4-Br- C_6H_4	Me	-	-	-	65
h	4-Me-C_6H_4	Me	-	-	-	75
i	3,4$(MeO)_2C_6H_3$	Me	-	-	-	15
j	$C_6H_5CH_2CH_2$	Me	-	-	-	35
k	C_6H_5CH=CH	Me	-	-	-	80
l	C_6H_5CH=CH	OEt	-	-	-	85

Method A, **6c,d**). The successful suppression of this reaction and an effective amidoalkylation cyclization to 2-acyltetrahydro-β-carbolines **7** was achieved when the reaction was carried out in the presence of bases as N,N-dimethylaniline (Table 1, Method **B**) or Et_3N (only for preparation of **7e**). The yield of **7** also depended on the nature of substituents in the aromatic ring of aldehyde of **5**. The presence of electron withdrawing groups increased the electrophilic ability of N-acyliminium ions **5** and led to higher yields (Table 1,

Method B, **7c,d,f**), while the presence of electron donating groups decreased the yields (Table 1, Method B, **7h,g**). The N-acyliminium cyclization of adducts **5** even in the presence of bases is an evidence that they are more electrophilic than the corresponding iminium intermediates. The reaction allows also the syntheses of 1-alkyl-2-acyltetrahydro-β-carbolines (Table 1, Method B, **7g-l**).

Experimental

All melting temperatures were determined using Boettus heat plate apparatus and are uncorrected. The ^{1}H NMR, ^{13}C NMR spectra were recorded on a Bruker 250 MHz spectrometer in the indicated solvent and MS spectra on a Jeol JMS-D300 spectrometer (70 eV).

Imines **3a-d** from tryptamine (3 mmol) and benzaldehyde or 4-nitrobenzaldehyde (3 mmol) were obtained in dichloroethane (10 mL) at reflux for 1 h. Imines **3e-h** from tryptamine (3 mmol) and the corresponding aldehydes (3 mmol) were obtained in methanol (10 mL) after stirring for 2 h at room temperature, while imines **3i-k** with 3,4-dimethoxybenzaldehyde, hydrocinnam-aldehyde and cinnamaldehyde were obtained in methanol in the presence of anh. sodium acetate (3 mmol) by stirring overnight at room temperature. The products, after distillation of the solvent under vacuum were used without further purification.

Synthesis of N-acyltetrahydro-β-carbolines 7; Typical procedures:

Method A: The corresponding acyl chloride **4** (3 mmol) in dichloromethane (3 mL) was added dropwise to a stirred at room temperature solution of the above obtained imines **3** (3 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 1 h at room temperature and then water (30 mL) was added. The mixture was extracted with CH_2Cl_2 (3x20 mL), the combined extract was dried (Na_2SO_4) and the solvent was removed by distillation. The products **7a** and **7c** were purified by recrystallization from methanol, while the others were purified by column chromatography on a neutral Al_2O_3, using a mixture of p. ether/ether (1:1) as an eluent. The acidic water solution was basified with Na_2CO_3, then extracted with dichloromethane (3x20 mL) and the solvent removed by distillation. The isolated products **6** were purified by column chromatography on silica gel, using ether as eluent.

Method B: Acyl chloride **4** (3 mmol) in dichloromethane (3 mL) was added dropwise at room temperature to a stirred solution of the above obtained imines **3** (3 mmol) and N,N-dimethylaniline (3 mmol) or Et_3N (for preparation of **7e**) in dichloromethane (5 mL). The mixture was stirred at room temperature for 1 h, then

dichloromethane (20 mL) was added and the solution was washed with 10% aq. HCl (3x20 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed by distillation. Products **7a** and **7c** were purified by recrystallization from methanol, while the other products **7** were purified by column chromatography on a neutral Al_2O_3, using a mixture of p. ether/ether (1:1) as eluent.

7a: mp 254-256° C [Lit. mp 266°C (ref. 11)]; ^{1}H NMR ($CDCl_3$), δ: 2.15 (s,3H), 2.80-3.00 (m,2H), 3.90-4.20 (m,2H), 6.95 (s,2H), 7.00-7.20 (m,2H), 7.35 (s,5H), 7.50-7.70 (m,2H); ^{13}C NMR (DMSO-d_6), δ: 21.58 (4-C), 22.42 (CH_3), 38.59 (3-C), 56.27 (1-C), 108.45, 111.29, 117.96, 118.70, 121.31, 126.31, 127.45, 127.73, 128.09, 128.48, 128.79. 132.02, 136.29, 140.69 (Ar), 168.77 (CO); MS m/z (M^+) calcd 290.4 ($C_{19}H_{18}N_2O$), obsd 290.

6a,b: 166-169°C [[b]Lit. mp 173-174°C (ref. 11)]; ^{1}H NMR ($CDCl_3$), δ: 1.95 (s,1H), 2.70-3.00 (t,2H,J=6), 3.00-3.30 (m, 2H), 5.10 (s,1H), 7.20 (s,3H), 7.30 (s,1H), 7.35 (s,4H), 7.50-7.70 (m,2H); MS m/z (M^+) calcd 248.3 ($C_{17}H_{16}N$), obsd 248.

7b: mp 184-185°C; ^{1}H NMR ($CDCl_3$), δ: 1.30 (t,3H,J=6), 2.70-3.10 (m,4H), 4.20 (q,2H, J=6), 6.60 (s,1H), 7.10-7.30 (m,2H),7.35(s,5H), 7.40-7.70 (m,2H), 8.00 (s,1H); ^{13}C NMR ($CDCl_3$), δ: 14.69 (CH_3), 21.35 (4-C), 38.13 (CH_2), 54.34 (3-C), 61.66 (1-C), 110.95, 118.28, 119.60, 122.11, 126.73, 128.16, 128.52, 131.52, 136.26 (Ar), 140.12 (CO); MS m/z (M^+) calcd 320.4 ($C_{20}H_{20}N_2O_2$), obsd 320.

7c: mp 146-148 °C; ^{1}H NMR ($CDCl_3$), δ: 2.10 (s,3H), 2.70-3.00 (m,2H), 3.90-4.20 (m,2H), 5.80 (s,1H), 6.90 (s,2H), 6.90-7.20 (m,2H), 7.30 (s,1H), 7.50 (d,2H,J=6), 8.20 (d,2H,J=8); ^{13}C NMR (DMSO-d_6), δ: 21.55 (4-C), 22.46 (CH_3), 38.93 (3-C), 50.64(1-C), 108.92, 111.46, 118.17, 118.92, 121.65, 123.74, 126.27, 128.82, 129.34, 130.87, 136.41, 147.04, 147.97 (Ar), 169.25 (CO); MS m/z (M^+) calcd 335.4 ($C_{19}H_{17}N_3O_3$), obsd 335.

6c,d: mp 171-173 °C; ^{1}H NMR ($CDCl_3$), δ: 2.90-3.10 (m,2H), 3.20-3.60 (m,2H), 5.40 (s,1H) 5.55 (s,1H), 7.20-7.50 (m,5H), 7.60 (d,2H,J=6), 8.30 (d,2H,J=6); ^{13}C NMR ($CDCl_3$), δ: 22.36 (4-C), 42.26 (3-C), 57.14 (1-C), 110.91, 118.43, 119.73 122.24, 123.93, 127.16, 129.40, 132.62, 135.99, 147.71, 149.26 (Ar); MS m/z (M^+) calcd 293.3 ($C_{17}H_{15}N_3O_2$), obsd 293.

7d: mp 152-153 °C; ^{1}H NMR ($CDCl_3$), δ: 1.40 (t,3H,J=6), 2.70-3.10 (m,4H), 4.20 (q,2H, J=6), 6.55 (s,1H), 7.10-7.30 (m,4H), 7.40 (s,1H), 7.60 (d,2H,J=4), 8.20 (d,2H,J=6); ^{13}C NMR ($CDCl_3$), δ: 14.60 (CH_3),21.21 (4-C), 38.31(CH_2), 53.69 (3-C), 62.07 (1-C), 105.80, 111.14, 118.45, 119.82, 122.54, 123.10, 126.54, 129.46, 129.77, 134.28, 136.45, 142.26, 148.31 (Ar), 155.82 (CO); MS m/z (M^+) calcd 365.4 ($C_{20}H_{20}N_3O_4$), obsd 365.

7e: mp 258-259 °C; ^{1}H NMR ($CDCl_3$), δ: 2.20 (s,3H), 2.80-3.00 (m,2H), 3.30-3.60 (m,2H), 6.90 (s,1H), 7.00-7.20 (m,3H), 7.30-7.70 (m,4H), 7.50-7.70 (m,1H), 8.25 (s,1H); ^{13}C NMR (DMSO-d_6), δ: 21.58 (4-C); 22.22 (CH_3), 38.94 (3-C), 50.34 (1-C), 108.58, 111.35, 115.08, 115.42, 118.03, 118.77, 121.42, 126.31, 129.68, 130.06, 130.19, 131.85, 136.34, 136.96 (Ar), 168.85 (CO); MS m/z (M^+) calcd 308.4 ($C_{19}H_{17}FN_2O$), obsd 308.

6e: mp 68-70; ^{1}H NMR ($CDCl_3$), δ: 1.95 (s,1H), 2.70-3.00 (m,2H), 3.10-3.40 (m,2H), 5.00 (s,1H), 7.10-7.40 (m,6H), 7.50-7.80 (m,2H); ^{13}C NMR ($CDCl_3$), δ: 22.42 (4-C), 42.64 (3-C), 57.25 (1-C), 110.30, 110.79, 115.42, 115.76, 118.23, 119.42, 121.80, 127.28, 130.03, 130.16, 134.08, 135.83, 137.56, 164.46 (Ar); MS m/z (M^+) calcd 266.3 ($C_{17}H_{15}FN_2$), obsd 266.

7f: mp 224-225 °C; ^{1}H NMR ($CDCl_3$), δ: 2.20 (s,3H), 2.80-3.00 (m,2H), 3.40-3.90 (m,2H), 7.05(s,1H), 7.10-7.40 (m,7H), 7.50-7.70 (m,1H), 8.55(s,1H); ^{13}C NMR ($CDCl_3$), δ: 21.45 (4-C), 22.44 (CH_3), 40.22 (3-C), 52.36 (1-C), 109.36, 112.48, 118.10, 119.17, 120.46, 121.24, 126.86, 129.28, 130.17, 130.42, 132.86, 136.82, 138.85 (Ar), 166.35 (CO); MS m/z (M^+) calcd 324.8 ($C_{19}H_{17}ClN_2O$), obsd 266.

7g: mp 211-212 °C; ^{1}H NMR ($CDCl_3$), δ: 2.20 (s,3H), 2.70-3.00 (m,2H), 3.10-3.30 (m,2H), 6.90 (s,1H), 7.10-7.40 (m,5H), 7.30 (d,2H,J=8), 7.70 (d,2H,J=8); ^{13}C NMR (DMSO-d_6), δ: 21.55 (4-C), 22.46 (CH_3), 39.26 (3-C), 50.44 (1-C), 108.65, 111.34, 118.03, 118.77, 120.96, 121.44, 126.26, 129.70, 130.27, 131.40, 131.66, 136.31, 140.05 (Ar), 168.90 (CO); MS m/z (M^+) calcd 369.3 ($C_{19}H_{17}BrN_2O$), obsd 369.

7h: mp 237-238 °C; ^{1}H NMR ($CDCl_3$), δ:2.15 (s,3H), 2.30 (s,3H), 2.80-3.00 (m,2H), 3.40-3.90 (m,2H), 7.05 (s,1H), 7.10-7.40 (m,7H), 7.50-7.70 (m,1H), 8.35

(s,1H); ^{13}C NMR ($CDCl_3$), δ: 20.98 (4'-CH_3), 21.65 (4-C), 21.90(CH_3), 40.43 (3-C), 51.40 (1-C), 109.24, 111.10, 117.89, 119.28, 121.79, 126.47, 127.24, 128.51, 128.97, 129.43, 131.86, 136,24, 136.97, 137.59 (Ar), 169.03 (CO); MS m/z (M^+) calcd 304.4 ($C_{20}H_{20}N_2O$), obsd 304

7i: mp 216-217 °C; ^{1}H NMR ($CDCl_3$), δ:2.15 (s,3H), 2.70-3.00 (m,2H), 3.70 (s,3H), 3.80 (s,3H), 3.70-4.00 (m,2H), 6.70 (s,2H), 6.90 (d,1H, J=8), 7.10-7.30 (m,4H), 7.40-7.60 (m,1H), 8.75(s,1H); ^{13}C NMR ($CDCl_3$), δ: 21.83 (4-C), 22.04 (CH_3) 40.49 (3-C), 51.47 (1-C), 55.75 (2OCH_3), 109.53, 110.32, 111.10, 112.05, 117.98, 119.37, 120.80, 121.93, 126.48, 131.79, 132.67, 136.30, 148.64, 148.86 (Ar), 169.03 (CO); MS m/z (M^+) calcd 350.4 ($C_{21}H_{22}N_2O_3$), obsd 350

7j: mp 186-187 °C; ^{1}H NMR ($CDCl_3$), δ:2.20 (s,3H), 2.70-2.90 (m,4H), 3.30-3.70 (m,2H), 3.90-4.20 (m,2H), 6.00 (t,1H,J=6),7.10-7.60 (m,4H), 7.20 (s,5H), 8.45 (s,1H); ^{13}C NMR ($CDCl_3$), δ: 20.85 (4-C), 21.87 (CH_3), 32.43 (CH_2), 35.95 (CH_2), 48.94 (1-C), 107.27, 110.99, 117.80, 119.32, 121.63, 122.00, 125.82, 126.52, 128.21, 128.31, 128.67, 134.32, 135.99, 141.48 (Ar), 169.85 (CO); MS m/z (M^+) calcd 318.4 ($C_{21}H_{22}N_2O$), obsd 318

7k: mp 201-202 °C; ^{1}H NMR ($CDCl_3$), δ:2.20 (s,3H), 2.70-2.90 (m,4H), 3.50-3.70 (m,1H), 3.90-4.20 (m,1H), 6.50 (s,1H), 7.10-7.70 (m,4H), 7.30 (s,5H), 8.55 (s,1H); ^{13}C NMR ($CDCl_3$), δ: 21.77 (4-C), 22.00 (CH_3), 40.95 (3-C), 50.47 (1-C), 108.75, 111.20, 118.00, 119.38, 121.89, 126.13, 126.55, 127.87, 128.49, 128.68, 131.45, 133.19, 136.07, 136.28 (Ar), 169.29 (CO); MS m/z (M^+) calcd 316.4 ($C_{21}H_{20}N_2O$), obsd 316

7l: mp 190-191 °C; ^{1}H NMR ($CDCl_3$), δ:1.35 (t,3H,J=6), 2.70-2.90 (m,2H), 3.00-3.40 (m,2H), 4.30 (q,2H,J=6), 6.00-6.10 (m,1H), 6.60 (d,1H,J=4), 7.10-7.30 (m,2H), 7.35 (s,5H), 7.40-7.70 (m,3H), 8.30 (s,1H); ^{13}C NMR ($CDCl_3$), δ: 14.69 (CH_3), 21.43 (4-C), 38.51 (CH_2) 52.95(3-C), 61.68(1-C), 109.64, 110.99, 118.24, 119.48, 121.97, 126.35, 126.60, 126.81, 127.98, 128.56, 131.36, 132.87, 136.12, 136.23 (Ar), 155.64 (CO); MS m/z (M^+) calcd 330.4 ($C_{22}H_{22}N_2O$), obsd 330

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