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SYNTHESIS OF SUBSTITUTED 5H-1,2,3,4,6,7,8,9-OCTAHYDRODIPYRIDO-[4,3-*b*;3',4'-*d*]PYRROLES BY THE PICTET–SPENGLER CONDENSATION

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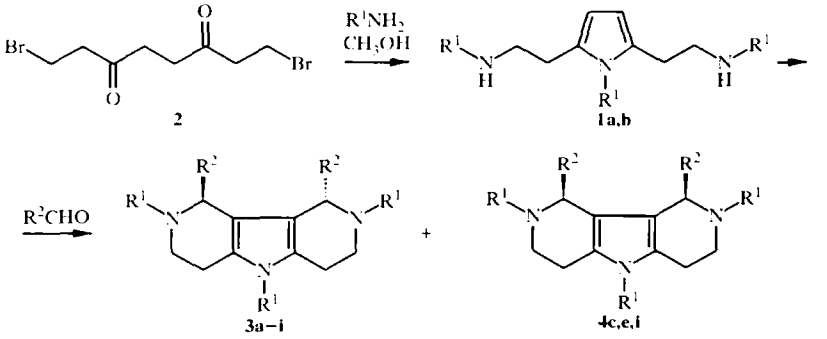
N,N',N''-Trialkyl-2,5-bis(1-aminoethyl)pyrroles, prepared by the heterocyclization of 1,8-dibromooctan-3,6-dione with aliphatic amines, underwent the Pictet–Spengler reaction with formaldehyde and aromatic aldehydes to give substituted 5H-1,2,3,4,6,7,8,9-octahydrodipyrido[4,3-b;3',4'-d]pyrroles.

Keywords: 2,5-bis(2-alkylaminoethyl)pyrroles, diazacarbazole, Pictet–Spengler reaction.

The Pictet–Spengler reaction [1] is one of the most widely used methods for the preparation of isoquinolines [2] and β-carbolines [3,4] which have a wide spectrum of biological activity. However this route has not been used, with one rare exception [5], for the synthesis of derivatives of pyrrolo[3,2-*c*]piperidines [6,7], γ-carbolines [8], and 5H-dipyrido[4,3-*b*; 3',4'-*d*]pyrroles [9, 10] which have different types of biological activity [11, 12]. As for derivatives of 5H-1,2,3,4,6,7,8,9-octahydrodipyrido[4,3-*b*;3',4'-*d*]pyrroles, there are no reports in the literature until now.

In the present work a suitable method for the synthesis of these compounds is proposed, based on the Pictet–Spengler condensation of formaldehyde and aromatic aldehydes with substituted 2,5-bis(2-aminoethyl)pyrroles (**1a,b**), prepared by heterocyclization of aliphatic amines with 1,8-dibromooctan-3,6-dione (**2**). The latter were synthesized in two steps with an overall yield of 76% by reaction of diethyl succinate with ethylmagnesium bromide in the presence a catalytic amount of tetraisopropoxytitanium [13] followed by bromination of 1,2-bis(1-hydroxycyclopropyl)ethane produced [14].



2-4 a,c-h $R^1 = CH_3$; **b,i** $R^1 = C_6H_5CH_2$; **a,b** $R^2 = H$; **c** $R^2 = p\text{-}O_2NC_6H_4$; **d** $R^2 = p\text{-}FC_6H_4$; **e** $R^2 = p\text{-}ClC_6H_4$; **f,i** $R^2 = C_6H_5$; **g** $R^2 = p\text{-}CH_3OC_6H_4$; **h** $R^2 = 3\text{-}C_5H_4N$

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Reaction of dibromo diketone **2** with a 20-fold molar excess of methyl- or benzylamine proceeded quite easily at room temperature in 1-2 h to give a high yield of the corresponding 2,5-bis(2-aminoethyl)pyrroles **1a,b** (see Experimental). Attempts to prepare 2,5-bis(2-aminoethyl)pyrrole by reaction with the considerably less basic ammonia was unsuccessful since it led to the formation of polymeric products.

It should be noted that formation of the pyrrole ring in compounds **1a,b** occurs in considerably milder conditions than the classical variant of the Paal–Knorr reaction [15, 16] which may be explained by anchimeric assistance of the alkylamino group in the removal of water from the intermediate products of the addition of the amines to the carbonyl group.

The substituted 2,5-bis(2-aminoethyl)pyrroles **1a,b** obtained were converted in high yield into the hydrochlorides of 2,5,8-trialkyl-5H-1,2,3,4,6,7,8,9-octahydrodipyrido[4,3-*b*;3',4'-*d*]pyrroles (**3a,b**) on boiling with 2 equivalents of 37% formalin in the presence of concentrated hydrochloric acid in propanol-2. Under these conditions compound **1a** reacted with aromatic aldehydes with predominant formation of *anti*-1,9-diaryl-2,5,8-trimethyl-5H-1,2,3,4,6,7,8,9-octahydrodipyrido[4,3-*b*;3',4'-*d*]pyrroles (**3c-h**) (Table 1). However we were unable to condense compound **1a** with paraldehyde or *p*-dimethylaminobenzaldehyde. The quantity of hydrochloric acid used had a considerable influence on the yield of the desired products. It was determined empirically that the best yields of compounds **3a,b** were obtained with 1.8 molar equivalents of hydrochloric acid, whereas this was decreased to 1.2 molar equivalents for compounds **3c-h**.

The relative positions of the aryl substituents in compounds **3c-h** were established from their ^{1}H NMR spectra in which the signals of the protons in positions 1 and 9 were shifted by almost 1 ppm to strong field in comparison with compound **4** (Table 2). This shift is explained by shielding of the protons in positions 1 and 9 in the *anti*-isomers of **3c-h** by the ring currents of the aryl substituents at positions 9 and 1 respectively, which is impossible for the *syn* isomers for steric reasons.

The formation of the *syn*-isomers **4**, observed only on interaction of N, N', N"-trimethyl-2,5-bis(2-aminoethyl)pyrrole **1a** with *p*-nitro-, and to a lesser extent, with *p*-chlorobenzaldehyde, is probably connected with differences in solubility of the products. The less soluble hydrochlorides of the *anti*-isomers **3c,e** are precipitated during the reaction and take no part in further reactions. In fact our attempts to carry out this reaction in methanol or ethanol, in which the hydrochlorides of **3d-h** dissolve well, gave no products of the Pictet–Spengler cyclization. Moreover, when 0.1 N solutions of mixtures of the hydrochlorides of **3c-4c** in methanol were boiled for 6 h in an attempt to bring about *syn-anti* isomerization [17], only decomposition of the starting materials occurred.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	R^1	R^2	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
				C	H	N		
3a	CH_3	H	$C_{13}H_{21}N_3$	71.34 / 71.19	9.61 / 9.65	19.43 / 19.16	107-109	91
3b	$C_6H_5CH_2$	H	$C_{31}H_{33}N_3$	83.31 / 83.18	7.57 / 7.43	9.62 / 9.39	104-106	86
3c	CH_3	*p*-$O_2NC_6H_4$	$C_{25}H_{27}N_4O_4$	65.11 / 65.06	5.83 / 5.90	15.34 / 15.17	269-271	47
3d	CH_3	*p*-FC_6H_4	$C_{25}H_{27}F_2N_3$	73.81 / 73.69	6.74 / 6.68	10.68 / 10.31	196-198	45
3e	CH_3	*p*-ClC_6H_4	$C_{25}H_{27}Cl_2N_3$	68.23 / 68.18	6.11 / 6.18	9.76 / 9.54	216-217	52
3f	CH_3	C_6H_5	$C_{25}H_{29}N_3$	80.97 / 80.82	7.75 / 7.87	11.62 / 11.31	145-146	49
3g	CH_3	*p*-$CH_3OC_6H_4$	$C_{27}H_{33}N_3O_2$	75.27 / 75.14	7.83 / 7.71	10.06 / 9.74	155-156	42
3h	CH_3	3-C_5H_4N	$C_{23}H_{27}N_5$	74.05 / 73.96	7.15 / 7.29	19.04 / 18.75	174-175	32
4c	CH_3	*p*-$O_2NC_6H_4$	$C_{25}H_{27}N_4O_4$	65.11 / 65.06	5.87 / 5.90	15.34 / 15.17	195-197	30
4e	CH_3	*p*-ClC_6H_4	$C_{25}H_{27}Cl_2N_3$	68.29 / 68.18	6.21 / 6.18	9.79 / 9.54	186-187	3.5

TABLE 2. Spectroscopic Characteristics of 5H-1,2,3,4,6,7,8,9-Octahydrodipyrido[4,3-*b*;3',4'-*d*]pyrroles **3a-h, 4c,e**

Compound	^{1}H NMR spectrum, δ, ppm ($CDCl_3$)					IR spectrum, ν, cm^{-1} ($CHCl_3$)
	N^2,N^5-CH_2R*	N^5-CH_2R*^{2}	3-H, 4-H 6-H, 7-H (8H, m)	1-H, 9-H (2H, s)	H_{arom}	
3a	2.43	3.28	2.53-2.77	3.28	—	1128, 1139, 1251, 1405, 1464, 1543, 2792, 2847, 2944, 2967
3b	3.66	4.84	2.39-2.82	3.38	7.17-7.42 (15H)	700, 1120, 1183, 1546, 1600, 1657, 1708, 1741, 1803, 863, 1943, 2843, 2907, 3034, 3067, 3088
3c	2.06	3.43	2.40-2.98	3.32	6.56 (4H); 8.61 (4H) (J_{AB} = 8.7 Hz)	1266, 1354, 1528, 1602, 1717, 1800, 1935, 2808, 2861, 2964, 3043, 3090
3d	2.05	3.39	2.42-2.99	3.23	6.74-7.02 (8H)	1170, 1266, 1470, 510, 1548, 1613, 1783, 1900, 1949, 2017, 2804, 2860, 2960, 3043, 3080
3e	2.05	3.39	2.42-2.99	3.25	6.63 (4H); 7.35 (4H) (J_{AB} = 8.4 Hz)	659, 1260, 1400, 1493, 1550, 1600, 1730, 1790, 1910, 2804, 2857, 2963, 3020
3f	2.05	3.39	2.43-3.02	3.26	6.80-6.93 (4H); 7.12-7.26 (6H)	1264, 1404, 1550, 1588, 1604, 1729, 1765, 1816, 1890, 1903, 1953, 2804, 2857, 2963, 3073, 3092
3g^{*3}	2.04	3.38	2.47-2.96	3.26	6.76 (8H, s)	1044, 1244, 1443, 1511, 1587, 1612, 1880, 2007, 2057, 2785, 2840, 2904, 2940, 3000
3h	2.05	3.41	2.43-3.00	3.25	7.10-7.34 (4H, m); 8.01 (2H, br. s); 8.46-8.55 (2H, m)	1036, 1192, 1500, 1583, 1597, 1886, 1918, 1940, 1974, 2807, 2860, 2970, 3050, 3073, 3100
4c	2.15	3.43	2.40-2.98	4.20	6.53 (4H); 8.00 (4H) (J_{AB} = 8.7 Hz)	1266, 1354, 1528, 1602, 1717, 1800, 1935, 2808, 2861, 2964, 3043, 3090
4e	2.11	3.39	2.45-2.90	4.05	6.52; 6.91 (J_{AB} = 8.6 Hz)	659, 1260, 1400, 1493, 1550, 1600, 1730, 1790, 1910, 2804, 2857, 2963, 3020

* **2a, 3a,c-h, 4c,e** R = H (6H); **2b, 3b, 4i** R = C_6H_5 (4H).
*^{2} **2a, 3a,c-h, 4c,e** R = H (3H); **2b, 3b, 4i** R = C_6H_5 (2H).
*^{3} 3.79 (6H, s, OCH_3).

Bearing in mind the above observations, it may be proposed that the yield of products in this reaction depends to an important extent on the choice of solvent which to dissolve the reactants even if only partially while the products should be practically completely insoluble. N,N',N"-Benzyl-2,5-bis(2-aminoethyl)pyrrole **1b**

underwent the Pictet–Spengler reaction in an aprotic medium without an acid catalyst [18, 19] to give a mixture of the corresponding 2,5,8-tribenzyl-1,9-diphenyldipyrido[4,3-*b*;3',4''-*d*]pyrroles **3i-4i** with an overall yield of 93% (see Experimental).

EXPERIMENTAL

^{1}H NMR spectra of $CDCl_3$ solutions of the compounds synthesized with HMDS as internal standard were recorded with a Tesla BS-567A instrument with a working frequency of 100 MHz. IR spectra of chloroform solutions were recorded with a Specord 75 IR spectrophotometer. Spectroscopic characteristics of the compounds synthesized for the first time are given in Table 2.

N, N',N''-Trimethyl-2,5-bis(2-aminoethyl)pyrrole (1a). A solution of 1,8-dibromooctan-3,6-dione (12 g, 0.04 mol) in methanol (300 ml) was added dropwise to a vigorously stirred 40% aqueous solution of methylamine (125 ml, 0.8 mol) at room temperature. The mixture was stirred at this temperature for 1 h, then NaOH (4 g) was added, the solvent was removed in vacuum (T < 60°C/10 mm Hg), the residue was diluted with ether and dried over granulated KOH. Crude product (7.8 g, 93 % yield) obtained by removal of the solvent was used without further purification. IR spectrum: 1120, 1500, 1514, 2812, 2960, 3007, 3113, 3332 cm^{-1}. ^{1}H NMR spectrum: 1.81 (2H, s, 2NH); 2.43 (6H, s, $2CH_3$); 2.67-2.82 (8H, m, $2CH_2CH_2$); 3.41 (3H, s, CH_3); 5.82 ppm (2H, s, H_{pyrr}). Found, %: C 67.87; H 10.91; N 21.79. $C_{11}H_{21}N_3$. Calculated, %: C 67.64; H 10.84; N 21.52.

N, N',N''-Tribenzyl-2,5-bis(2-aminoethyl)pyrrole (1b). A solution of 1,8-dibromooctan-3,6-dione (18 g, 0.06 mol) in methanol (400 ml) was added dropwise during 2 h to a vigorously stirred solution of benzylamine (128 ml, 1.2 mol) in methanol (200 ml) at room temperature. The reaction mixture was stirred at the same temperature for 30 min, NaOH (5.5 g) was added, the solvent and the excess of benzylamine were removed on a rotary evaporator (T 70°C/1 mm Hg), the residue was dissolved in a 3:1 benzene–hexane mixture and washed with water until neutral (5 × 500 ml), and then dried over granulated KOH. After removal of the solvent on a rotary evaporator slightly colored oil was obtained which was used without further purification. Yield 24 g (91%); mp 52-53°C. IR spectrum: 1193, 1461, 1500, 1605, 1800, 1853, 1944, 2824, 3032, 3067, 3090, 3307 cm^{-1}. ^{1}H NMR spectrum: 1.44 (2H, s, 2NH); 2.53-2.88 (8H, m, $2CH_2CH_2$); 3.68 (4H, s, $2CH_2$); 5.01 (2H, s, CH_2); 5.90 (2H, s, H_{pyrr}); 7.15-7.32 ppm (15H, m, H_{arom}). Found, %: C 82.31; H 7.89; N 10.31. $C_{29}H_{33}N_3$. Calculated, %: C 82.23; H 7.85; N 9.92.

2,5,8-Trialkyl-5H-1,2,3,4,6,7,8,9-octahydrodipyrido[4,3-*b*; 3',4'-*d*]pyrroles (3a,b). Hydrochloric acid (35%, 1.6 ml, 180 mol. %) and 37% formalin (1.5 ml, 0.02 mol) were added with stirring to a solution of N,N',N''-trialkyl-2,5-bis(2-aminoethyl)pyrrole **1a,b** (0.01 mol) in propanol-2 (40 ml). The reaction mixture was slowly heated to boiling (~30 min), boiled for 15 min, and then cooled to room temperature. The fine crystalline powder of hydrochloride of **3a,b** was filtered off, washed with propanol-2 (2 × 10 ml) and ether (20 ml), and dried in vacuum. Hydrochloride of **3a** was recrystallized from a mixture of methanol and ether.

To obtain the free base hydrochlorides of **3a-g** were dissolved in the minimum amount of methanol, a two-fold molar excess of NaOH was added, and the mixture was boiled until alkali had dissolved completely, methanol was removed on a rotary evaporator, the residue was suspended in anhydrous diethyl ether, filtered and evaporated to dryness. The compounds **3a-g** obtained required no further purification (Table 1).

To obtain the free bases hydrochlorides of **3b,h** without preliminary recrystallization were dissolved in minimum of water, a two-fold molar excess of NaOH was added and the product was extracted with methylene chloride. The combined organic extracts were dried exhaustively over K_2CO_3. The residue after removing the solvent was recrystallized from nitromethane (Table 1).

1,9-Diaryl-2,5,8-trimethyl-5H-1,2,3,4,6,7,8,9-octahydrodipyrido[4,3-*b*;3',4'-*d*]pyrroles (3c-h). Hydrochloric acid (35%, 1.1 ml, 120 mol. %) and aromatic aldehyde (0.02 mol) were added to a solution of N,N',N''-trimethyl-2,5-bis(2-aminoethyl)pyrrole **1a** (1.96 g, 0.01 mol) in propanol-2 (40 ml) and the mixture was boiled with stirring for 3 h until the starting compound **2a** had completely dissolved (beginning of the precipitation of hydrochloride product may occur in parallel), after which the reaction mixture was left overnight. The fine

crystalline powder of hydrochloride of **3c-h** was filtered off, washed with propanol-2 (2 × 10 ml) and ether (20 ml), and dried in vacuum. Hydrochloride of compound **3g** was recrystallized from a mixture of methanol and ether.

To obtain the free bases hydrochlorides of **3c-f** were dissolved in the minimum amount of water, made basic with an excess of NaOH, the product was filtered off, washed with water, and dried for 3 h over granulated KOH in a vacuum desiccator at 1 mm Hg, and recrystallized from propanol-2 (**3c,e, 4c,e**) or nitromethane (**3d,f**) (Table 1).

2,5,8-Tribenzyl-5H-1,9-diphenyl-1,2,3,4,6,7,8,9-octahydrodipyrido[4,3-*b*;3',4'-*d*]pyrrole (Mixture of Isomers 3i,4i). A solution of N,N',N"-tribenzyl-2,5-bis(2-aminoethyl)pyrrole **1b** (4.47 g, 0.01 mol) and benzaldehyde (2.1 ml, 0.02 mol) in benzene (50 ml) was boiled with a water separator for 48 h. The residue, after removal of benzene on a rotary evaporator, was recrystallized from nitromethane. Yield 93%; mp 160-165°C. IR spectrum: 700, 1192, 1263, 1453, 1493, 1539, 1600, 1733, 1800, 1860, 1939, 2796, 2834, 2928, 3026, 3062, 3081 cm^{-1}. ^1H NMR spectrum: 2.32-2.95 (8H, m, $2CH_2CH_2$), 3.14, 3.58 (1.86 H, AB, J_{AB} =13.4 Hz, $2CH_2$); 3.45 (2.19 H, s, $2CH_2$); 3.73 (0.91 H, s, 2CH); 4.40 (1.12 H, s, 2CH); 5.01 (2H, s, CH_2); 6.75 (5.54 H, s, H_{arom}); 6.86-7.48 ppm (19.32 H, m, H_{arom}). Found, %: C 86.33; H 6.95; N 7.24. $C_{43}H_{41}N_3$. Calculated, %: C 86.10; H 6.89; N 7.01.

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