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2,6-Diaminotoluene (**3a**) and 2,6-diamino-*p*-xylene (**3c**) led to 2-methyl (and 2,5-dimethyl)-3-acetylaminophenylhydrazines **5a,b**. Fischer indolization of their hydrazones **6a,b** and **7a,b** derived from 4-methoxycyclohexanone and 4-piperidone, and subsequent aromatization of intermediate tetrahydrocarbazole derivatives **8a,b** and **9a,b** allowed us to work out a convenient route to the title compounds.

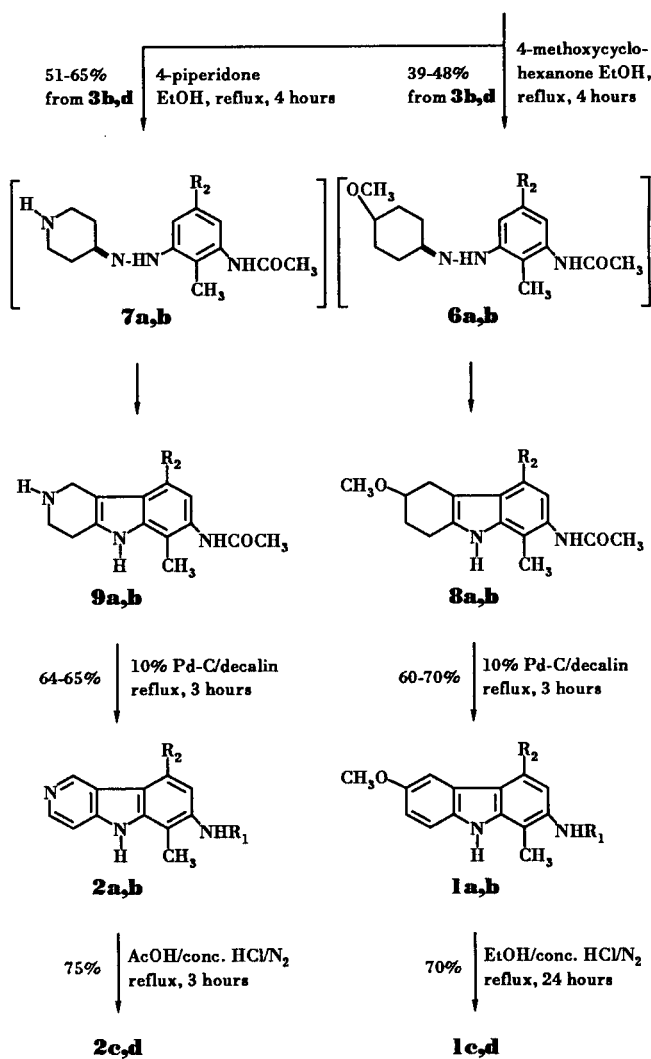
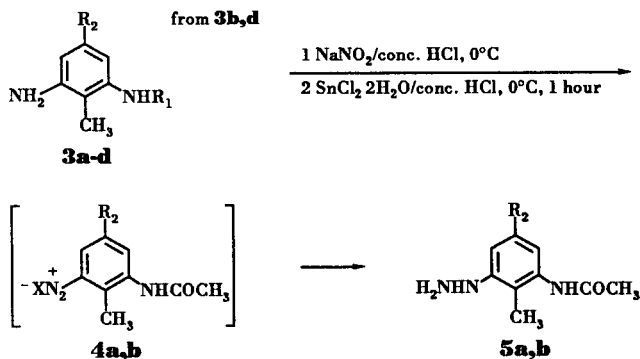
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Several aminosubstituted 9-methoxy-5-methyl (and 5,11-dimethyl)-6*H*-pyrido[4,3-*b*]carbazoles (9-methoxyellipticines) and aminosubstituted 6-methyl and (6,11-dimethyl)-5*H*-pyrido[3',4':4,5]pyrrolo[2,3-*g*]isoquinolines (9-azaellipticines) exhibit high antitumor activity [1-3].

We thought it of interest to study the biological properties of their isomers: 10*H*-pyrido[2,3-*b*]carbazoles and 10*H*-pyrido[3',4':4,5]pyrrolo[3,2-*g*]quinolines derivatives. One of the two routes envisaged for the synthesis of these heterocycles required the still unknown 2-amino-6-methoxy-1-methyl (and 1,4-dimethyl)-9*H*-carbazoles **1c,d** and 7-amino-6-methyl (and 6,9-dimethyl)-5*H*-pyrido[4,3-*b*]indoles **2c,d** as key intermediates. To our knowledge, there is only one analogue of compounds **1c,d** and **2c,d** having a suitably substituted ring C reported in the literature, 2-amino-1,4-dimethyl carbazole. It was prepared by Bergman *et al.* [4] from 2-ethylindole which was condensed with 3-aminocrotonitrile followed by cyclization of 3-(2-ethylindol-3-yl)crotonitrile intermediate. This approach, however, seems less attractive for the synthesis of our target compounds **1c,d** and **2c,d** since in these cases the requisite starting materials 2-ethyl-5-methoxyindole and 6-ethylpyrrolo[3,2-*c*]pyridine are not readily available as yet.

We describe in this paper a different route to **1c,d** and **2c,d** using 2,6-diaminotoluene (**3a**) and 2,6-diamino-*p*-

Scheme 1



1,2	R ₁	R ₂	3	R ₁	R ₂	4-9	R ₂
a	COCH ₃	H	a	H	H	a	H
b	COCH ₃	CH ₃	b	COCH ₃	H	b	CH ₃
c	H	H	c	H	CH ₃		
d	H	CH ₃	d	COCH ₃	H		

Table 1
Physical and Spectral Data for compounds **1a-9b**

Compound No.	Yield (%)	Mp (°C) solvent	¹ H-NMR (ppm) (DMSO-d ₆ /TMS) δ, J (Hz)	Molecular Formula	Analysis % Calcd./Found		
					C	H	N
1a	60	248-249 EtOH	2.11 (s, 3 H, COCH ₃), 2.39 (s, 3 H, CH ₃ -1), 3.87 (s, 3 H, OCH ₃), 7.01 (dd, 1 H, H-7, J _{7,8} = 8.7, J _{7,5} = 2.5), 7.10 (d, 1 H, H-3, J _{3,4} = 6.9), 7.41 (d, 1 H, H-8), 7.63 (d, 1 H, H-5), 7.89 (d, 1 H, H-4), 9.46 (s, 1 H, NHC(=O)CH ₃), 10.90 (s, 1 H, H-9)	C ₁₆ H ₁₆ N ₂ O ₂	71.62 71.90	6.01 5.87	10.44 10.23
1b	70	228-229 EtOH	2.03 (s, 3 H, COCH ₃), 2.36 (s, 3 H, CH ₃ -1), 2.76 (s, 3 H, CH ₃ -4), 3.88 (s, 3 H, OCH ₃), 6.90 (s, 1 H, H-3), 7.05 (dd, 1 H, H-7, J _{7,8} = 8.3, J _{7,5} = 2.5), 7.45 (d, 1 H, H-8), 7.58 (d, 1 H, H-5), 9.42 (s, 1 H, NHC(=O)CH ₃), 10.92 (s, 1 H, H-9)	C ₁₇ H ₁₈ N ₂ O ₂	72.32 72.48	6.43 6.57	9.92 10.22
1c	70	240-242 CH ₃ CN	2.24 (s, 3 H, CH ₃ -1), 3.82 (s, 3 H, OCH ₃), 4.86 (s, 2 H, NH ₂), 6.54 (d, 1 H, H-3, J _{3,4} = 8.4), 6.82 (dd, 1 H, H-7, J _{7,8} = 8.7, J _{7,5} = 2.5), 7.26 (d, 1 H, H-8), 7.41 (d, 1 H, H-5), 7.58 (d, 1 H, H-4), 10.39 (s, 1 H, H-9)	C ₁₄ H ₁₄ N ₂ O	74.31 74.32	6.24 6.25	12.38 12.62
1d	70	202-204 CH ₃ OH	2.22 (s, 3 H, CH ₃ -1), 2.63 (s, 3 H, CH ₃ -4), 3.84 (s, 3 H, OCH ₃), 4.81 (s, 2 H, NH ₂), 6.35 (s, 1 H, H-3), 6.85 (dd, 1 H, H-7, J _{7,8} = 8.6, J _{7,5} = 2.4), 7.29 (d, 1 H, H-8), 7.40 (d, 1 H, H-5), 10.39 (s, 1 H, H-9)	C ₁₅ H ₁₆ N ₂ O	74.97 75.15	6.71 6.59	11.66 11.76
2a	64	>310 EtOH	2.12 (s, 3 H, COCH ₃), 2.44 (s, 3 H, CH ₃ -6), 7.26 (d, 1 H, H-8, J _{7,8} = 8.3), 7.48 (dd, 1 H, H-4, J _{4,3} = 5.4, J _{4,1} = 1.1), 8.01 (d, 1 H, H-9), 8.43 (d, 1 H, H-3), 9.30 (s, 1 H, H-1), 9.57 (s, 1 H, NHC(=O)CH ₃), 11.6 (s, 1 H, H-9)	C ₁₄ H ₁₃ N ₃ O	70.28 70.36	5.48 5.56	17.56 17.81
2b	65	>310 DMF	2.11 (s, 3 H, COCH ₃), 2.49 (s, 3 H, CH ₃ -6), 2.78 (s, 3 H, CH ₃ -9), 7.08 (s, 1 H, H-8), 7.50 (dd, 1 H, H-4, J _{4,3} = 5.7, J _{4,1} = 1.1), 8.44 (d, 1 H, H-3), 9.28 (s, 1 H, H-1), 9.50 (s, 1 H, NHC(=O)CH ₃), 11.60 (s, 1 H, H-5)	C ₁₅ H ₁₅ N ₃ O 1/3 H ₂ O	69.48 69.37	6.09 6.17	16.20 16.20
2c	75	283 CH ₃ OH/H ₂ O	2.25 (s, 3 H, CH ₃ -6), 5.02 (s, 2 H, NH ₂), 6.64 (s, 1 H, H-8, J _{7,8} = 8.4), 7.30 (d, 1 H, H-4, J _{4,3} = 5.7), 7.68 (d, 1 H, H-9), 8.38 (d, 1 H, H-3), 9.02 (s, 1 H, H-1), 11.10 (s, 1 H, H-5)	C ₁₂ H ₁₁ N ₃	73.07 72.90	5.62 5.72	21.31 21.19
2d	75	280 dec CH ₃ OH	2.26 (s, 3 H, CH ₃ -6), 2.65 (s, 3 H, CH ₃ -9), 5.0 (s, 2 H, NH ₂), 6.49 (s, 1 H, H-8), 7.34 (dd, 1 H, H-4, J _{4,3} = 5.5, J _{9,1} = 0.9), 8.27 (d, 1 H, H-3), 9.05 (s, 1 H, H-1), 11.13 (s, 1 H, H-5)	C ₁₃ H ₁₃ N ₃	73.91 73.69	6.20 6.69	19.89 20.00
3b	75	145 toluene	2.05 (s, 3 H, COCH ₃), 2.18 (s, 3 H, CH ₃), 3.65 (br s, 2 H, NH ₂), 6.60 (m, 1 H, H-6), 7.11-6.90 (m, 3 H, NHC(=O)CH ₃ , H-4, H-5)	C ₉ H ₁₂ N ₂ O	65.83 66.05	7.37 7.21	17.06 16.93
3d	75	156 toluene	1.98 (s, 3 H, COCH ₃), 2.17 and 2.22 (2s, 2 x 3 H, 1-CH ₃ , 4-CH ₃), 6.41 (s, 1 H, H-6), 6.76 (s, 1 H, H-4), 6.87 (br s, 1 H, NHC(=O)CH ₃)	C ₁₀ H ₁₄ N ₂ O	67.39 67.64	7.92 7.70	15.72 15.62
8a	48	220 CH ₂ Cl ₂	1.95-2.20 (m, 2 H, 2 x H-7), 2.05 (s, 3 H, COCH ₃), 2.27 (s, 3 H, CH ₃), 2.60-2.95 (m, 3 H, 2 H-8 + 1 H-5), 3.07 (m, 1 H, H-5), 3.37 (1, 3 H, OCH ₃), 3.67 (m, 1 H, H-6), 6.93 (d, 1 H, H-2, J _{2,3} = 7), 7.12 (d, 1 H, H-4), 9.27 (s, 1 H, NHC(=O)CH ₃), 10.53 (s, 1 H, H-9)	C ₁₆ H ₂₀ N ₂ O ₂	70.56 70.46	7.40 7.63	10.29 10.39
8b	39	227 CH ₃ CN	1.89-2.03 (m, 2 H, 2 x H-7), 2.04 (s, 3 H, COCH ₃), 2.21 (s, 3 H, CH ₃ -1), 2.61 (s, 3 H, CH ₃ -4), 2.67-2.95 (m, 3 H, 2 H-8 + 1 H-5), 3.22 (m, 1 H, H-5), 3.38 (s, 3 H, OCH ₃), 3.68 (m, 1 H, H-6), 6.59 (s, 1 H, H-3), 9.18 (s, 1 H, NHC(=O)CH ₃), 10.43 (s, 1 H, H-9)	C ₁₇ H ₂₂ N ₂ O ₂	71.30 71.44	7.74 7.79	9.78 9.92
9a	65	>310 DMF	2.05 (s, 3 H, COCH ₃), 2.28 (s, 3 H, CH ₃), 2.71 (m, 2 H, CH ₂ -4), 3.06 (m, 2 H, CH ₂ -3), 3.06 (s, 2 H, CH ₂ -1), 6.84 (d, 1 H, H-8, J _{8,7} = 8.1), 7.1 (d, 1 H, H-7), 9.29 (s, NHC(=O)CH ₃), 10.5 (s, 1 H, H-9)	C ₁₄ H ₁₇ N ₃ O	69.11 69.05	7.04 6.95	17.27 17.02

9b	51	>310 DMF	1.99 (s, 3 H, COCH ₃), 2.18 (s, 3 H, CH ₃ -6),	C ₁₅ H ₁₉ N ₃ O	68.81	7.51	16.05
			2.40 (s, 3 H, CH ₃ -9), 2.96 (m, x 2 H, CH ₂ -3), 2.65 (m x 2 H, CH ₂ -4), 4.07 (s, 2 H, CH ₂ -1), 6.45 (s, 1 H, H-8), 9.16 (s, 1 H, NHCOCH ₃), 10.43 (s, 1 H, H-5)				
				1/4 H ₂ O	68.74	7.42	16.34

xylene (**3c**) as precursors and a Fischer-indole reaction as a key step (Scheme 1).

Diazotization of amines **3b,d** and subsequent reduction of the resulting diazonium salts **4a,b** afforded hydrazine hydrochlorides **5a,b**. Crude hydrazine hydrochlorides **5a,b** were condensed with 4-methoxycyclohexanone or 4-piperidone to give tetrahydrocarbazoles **8a,b** and tetrahydropyridoindoles **9a,b** respectively. Dehydrogenation of compounds **8a,b** and **9a,b** over 10% palladium on charcoal afforded 2-acetylaminocarbazoles **1a,b** and 7-acetylaminopyridoindoles **2a,b** which were hydrolyzed to give the desired compounds **1c,d** (19-20%) and **2c,d** (25-29%) (overall yields from amines **3b,d**).

EXPERIMENTAL

All melting points were determined with a Reichert hot-stage microscope and are uncorrected. The ¹H nmr spectra were recorded on a Varian XL 100 spectrometer. Elemental analyses were performed at the ICSN, CNRS 91190 Gif-sur-Yvette. The yields, melting points, elemental analysis and ¹H nmr spectra for compounds **1a-9b** are presented in Table 1.

2,6-Diamino-*p*-xylene (**3c**).

A solution of 1-chloro-2,5-dimethyl-4,6-dinitrobenzene [5] (15 g, 0.065 mmole) in ethanol (200 ml) was hydrogenated at 60° and 50 bars in a steel vessel with stirring, in the presence of 10% palladium on charcoal (2.2 g). After 2 hours the catalyst was removed by filtration and the filtrate evaporated. The residue was taken up in water and made basic with concentrated ammonium hydroxide. The precipitate was filtered off, washed with water, dried and recrystallized from toluene to afford **3c** (5.23 g, 59%), mp 104-105° (lit [6] 102-103°).

3-Acetyl-amino-2-methyl (and 2,5-dimethyl)anilines **3b,d**.

General Procedure.

Acetic anhydride (5 ml, 52.94 mmole) was added dropwise to a cooled and vigorously stirred solution of 1,3-diamino-2-methyl (or 2,5-dimethyl)benzene **3a,c** (52.58 mmole) in toluene (315 ml). The resulting precipitate was filtered off. The solid was extracted with boiling toluene and filtered while hot. The combined filtrates were concentrated and allowed to cool giving crystals, which were collected and dried to afford **3b,d** (Table 1).

2-Acetyl-amino-6-methoxy-1-methyl (and 1,4-dimethyl-5,6,7,8-tetrahydrocarbazoles **8a,b**).

General Procedure.

A solution of sodium nitrite (4.20 g, 60.8 mmole) in water (16 ml) was added dropwise to a stirred suspension of amines **3b,d** (53.5 mmole) in concentrated hydrochloric acid (65 ml) at 0° over 30 minutes. Then a solution of stannous chloride dihydrate (25.6 g, 113.4 mmole) in concentrated hydrochloric acid (33 ml)

was added dropwise to the mixture, the temperature being maintained at 0°. After 1 hour the solid containing stannous salts and hydrazine hydrochlorides **5a,b** were collected and dried. The crude product was used in the next step without further purification.

A mixture of the above solids **5a,b** (from 40 mmole of amines **3b,d**), ethanol (100 ml), concentrated hydrochloric acid (5 ml), 4-methoxycyclohexanone (5.8 g, 45.3 mmole) was heated under reflux for 4 hours. After cooling the precipitate of ammonium chloride was filtered off and washed with ethanol. The filtrate was evaporated and the residue dissolved in dichloromethane. The solution was washed with 1*N* sodium hydroxide and the solvent evaporated to give a residue which was recrystallized to afford tetrahydrocarbazoles **8a,b**. Chromatography of the mother liquor on silica gel column (dichloromethane/ethanol 98:2) gave an additional amount of compounds **8a,b** (Table 1).

7-Acetyl-amino-6-methyl (and 6,9-dimethyl)-1,2,3,4-tetrahydro-5*H*-pyrido[4,3-*b*]indoles **9a,b**.

General Procedure.

A mixture of crude hydrazine hydrochlorides **5a,b** (from 60 mmole of amines **3b,d**) ethanol (140 ml), concentrated hydrochloric acid (8.5 ml) and 4-piperidone monohydrate hydrochloride (11.7 g, 76.16 mmole) was heated under reflux for 4 hours. After cooling the precipitate was filtered off, washed with ethanol and taken-up in a minimum amount of water. The suspension was basified with ammonium hydroxide. The resulting precipitate was collected by filtration, washed with water, dried and recrystallized to afford **9a,b** (Table 1).

2-Acetyl-amino-6-methoxy-1-methyl (and 1,4-dimethyl)-9*H*-carbazoles **1a,b**.

General Procedure.

A suspension of tetrahydrocarbazole **8a,b** (9.92 mmole), 10% palladium on charcoal (2.4 g) in decalin (110 ml) was heated under reflux with stirring. After 3 hours the mixture was allowed to cool, diluted with hexane. The solid was collected and thoroughly extracted with hot ethanol. The combined extracts were filtered and the filtrate evaporated to give a residue which was recrystallized to afford carbazole **1a,b** (Table 1).

7-Acetyl-amino-6-methyl (and 6,9-dimethyl)-5*H*-pyrido[4,3-*b*]indoles **2a,b**.

General Procedure.

These compounds were prepared from **9a,b** in a similar way to that described for **1a,b**. Compound **2b** was extracted with hot DMF instead of ethanol (Table 1).

2-Amino-1-methyl (and 1,4-dimethyl)-6-methoxy-9*H*-carbazoles **1c,d**.

General Procedure.

A suspension of 2-acetylaminocarbazoles **1a,b** (12.94 mmole) in ethanol (70 ml) and concentrated hydrochloric acid (14 ml) was refluxed under nitrogen for 24 hours then cooled. The resulting

precipitate was filtered off, taken up in water, basified with ammonium hydroxide and extracted with ethyl acetate. The combined dried extracts were evaporated to dryness, and the residue was recrystallized to afford **1c,d** (Table 1).

7-Amino-6-methyl (and 6,9-dimethyl)-5*H*-pyrido[4,3-*b*]indoles **2c,d**.

General Procedure.

A suspension of 7-acetylamino-5-pyridoindole **2a,b** (10.6 mmoles) in acetic acid (55 ml) and concentrated hydrochloric acid (30 ml) was refluxed under nitrogen. After 4 hours the mixture was allowed to cool. The precipitate was filtered off and taken-up in water. The stirred mixture was basified with ammonium hydrox-

ide. The resulting precipitate was filtered off, washed with water, dried and recrystallized to afford **2c,d** (Table 1).

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