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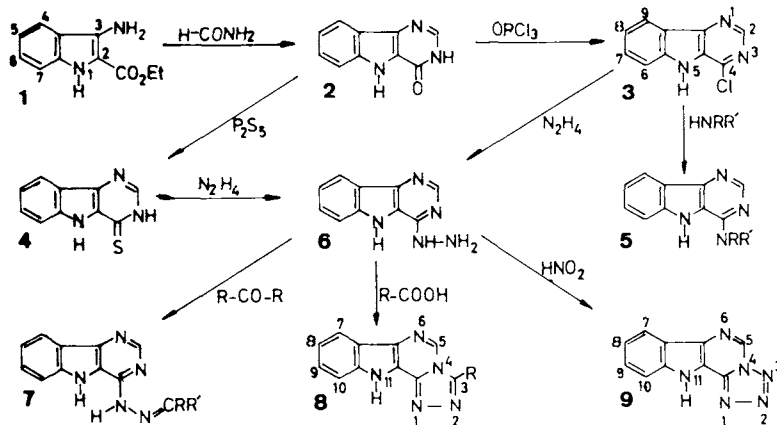
This paper describes the synthesis of two 4-amino-5*H*-pyrimido[5,4-*b*]indoles **5**, 4-hydrazino-5*H*-pyrimido[5,4-*b*]indole **6**, two 1,2,4-triazolo[4,3-*c*]pyrimido[5,4-*b*]indoles **8**, and tetrazolo[4,5-*c*]pyrimido[5,4-*b*]indole **10**. Starting with ethyl 3-aminoindole-2-carboxylate **1**, 5*H*-pyrimido[5,4-*b*]indol-4-one **2** was obtained (80%) by condensing with formamide. Reactions of **2** with phosphorus oxychloride and phosphorus pentasulfide gave respectively, 4-chloro-5*H*-pyrimido[5,4-*b*]indole **3** (70%) and 5*H*-pyrimido[5,4-*b*]indole-4-thione **4** (80%). Compound **3** reacted with amines (morpholine, piperidine) to give the respective 4-amino-5*H*-pyrimido[5,4-*b*]indoles **5**, and compound **4** reacted with hydrazine to give 4-hydrazino-5*H*-pyrimido[5,4-*b*]indole **6** (80%). Two hydrazones of **6** (benzylidene, isopropylidene) **7** were also prepared (90%). Compound **6** reacted with formic and acetic acids to give (65-75%) the respective 1,2,4-triazolo[4,3-*c*]pyrimido[5,4-*b*]indoles **8** and with nitrous acid to give tetrazolo[4,5-*c*]pyrimido[5,4-*b*]indole **9** (85%). All the new compounds **2** to **9** were characterized by elemental analysis and spectral data (ir, nmr).

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As a continuation of our previous work [1,2,3,4,5] about the synthesis [1,2,3] and properties as potential pharmacologic agents [4,5] of fused systems of indole with different nitrogenous heterocycles and, particularly, of hydrazine derivatives of these systems, as structural analogs of the well known antihypertensive agent Hydralazine (Apresoline, 1-hydrazinophthalazine) [6], we report in this paper the synthesis of 4-hydrazino-5*H*-pyrimido[5,4-*b*]indole and some related compounds, which are structural analogs of another antihypertensive agent Prazosin (4-amino-6,7-dimethoxy-2-[4-(2-furoyl)piperazino]quinazoline) [7].

An exhaustive search through the *Chemical Abstracts*

showed us that only a very small number of pyrimido[5,4-*b*]indole derivatives have been reported. Two Russian papers [8,9] describe three derivatives of this system by the reactions of 3-dimethylamino-2-formylindole with ammonia, hydroxylamine and benzylamine, respectively, and they are reported as mild antitumor agents; two other Russian papers [10,11] describe the photolytic cyclization of 5-azido-4-phenylpyrimidine to 5*H*-pyrimido[5,4-*b*]indole. A recent paper [12] reports the condensation of ethyl 3-aminoindole-2-carboxylate with 6-chloronicotinic acid to give 5,6-dihydro-6-oxo-pyrido[1',2':1,2]pyrimido[5,4-*b*]indole-9-carboxylic acid, which did not show antiallergic



	NRR'		R	R'		R
5	a)	7	a) H	a) C ₆ H ₅	8	a) H
	b)		b) CH ₃	b) CH ₃		b) CH ₃

properties. Finally, a recent patent [13] reports the synthesis of some 5*H*-pyrimido[5,4-*b*]indoles from 3-amino-1-tosylindole-2-cyanide. In a previous paper [14] we have reported a new synthesis of ethyl 3-aminoindole-2-carboxylate, its reactions with phenylisocyanate and phenylisothiocyanate, and the preparation of some 5*H*-pyrimido[5,4-*b*]indole derivatives.

Compound **6** and related 5*H*-pyrimido[5,4-*b*]indole derivatives reported in this paper were obtained according to the Scheme, starting with ethyl 3-aminoindole-2-carboxylate **1**. When this compound was warmed with formamide, the new pyrimidone **2** was obtained (80%). Boiling a solution of **2** in dioxane with phosphorus oxychloride gave the monohydrochloride of **3** (70%), which when treated with ammonium hydroxide yielded the free base **3**. On the other hand, the reaction of **2** with phosphorus pentasulfide in dry pyridine gave the new pyrimidothione **4** (80%).

When **3** was boiled with amines (morpholine, piperidine) the 4-amino-5*H*-pyrimido[5,4-*b*]indole derivatives **5** were obtained (85-90%). On the other hand, boiling a solution of **3** or **4** in ethanol with hydrazine, **6** was obtained (80%). By the usual methods we prepared and characterized also the monohydrochloride of **6** and the hydrazones **7a** (from benzaldehyde) and **7b** (from acetone).

When **6** was boiled with formic and acetic acids, the respective triazole derivatives **8a** (65%) and **8b** (75%) were obtained.

Finally, **6** reacted with sodium nitrite in hydrochloric acid gave the tetrazolo derivative **9**. The ir spectra of this compound does not show any characteristic band for the azido group at about 2000-2200 cm⁻¹; thus, it seems that in the solid state **9** has essentially the tetrazole structure represented without any demonstrable contribution of the possible azido form.

All the new compounds **2** to **9** were suitably characterized by elemental analysis and spectral data (ir, nmr), which were satisfactory for the expected data.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and they are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over phosphorus pentoxide at 3-4 mm Hg, 2-3 hours, at about 60-70°). The ir spectra were recorded on a Perkin-Elmer 681 apparatus, using potassium bromide tablets for solid products and placing the products between crystals of sodium chloride; the frequencies were expressed in cm⁻¹. The ¹H-nmr spectra were obtained on a Perkin-Elmer R-32 (90MHz) instrument, with TMS as the internal reference, at a concentration of about 0.1 g/ml and solvent as indicated; the chemical shifts are reported in ppm from TMS and are given in δ units. Thin-layer chromatography (tlc) was carried out on silicagel (DSF-5, Cammaga 0.3 mm. thickness) with benzene:dioxane:acetic acid (90:25:4) as solvent and the plates were scanned under ultraviolet light, λ = 254 and 366 nm.

Compound **1** (mp 150-152°) was prepared by reported methods from 2-aminobenzonitrile [12] or ethyl indole-2-carboxylate [14].

5*H*-Pyrimido[5,4-*b*]indole-4-one (**2**).

A mixture of 6.50 g (32 mmoles) of **1** in 35 ml of formamide was warmed with stirring under a steam of nitrogen at about 220° for 2 hours. On cooling the reaction mixture crystallized. The product was collected and washed with *N,N*-dimethylformamide, ethanol and ether, giving 4.5 g (80%) of **2**, mp > 250° as a light gray powder. An analytical sample was obtained by recrystallization from *N,N*-dimethylformamide; ir: 3050, 3150, (NH), 1700 (C=O); 735 (1,2-aromatic disubst); nmr (DMSO-*d*₆): 3.5° 7.15-7.80 (m, 3H, H-6, H-7, H-8), 7.95-8.10 (m, 1H, H-9), 8.06 (s, 1H, H-2), 12.30 (bs, 1H, NH-indole).

Anal. Calcd. for C₁₀H₇N₃O: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.45; H, 3.91; N, 22.63.

4-Chloro-5*H*-pyrimido[5,4-*b*]indole (**3**).

A mixture of 1.0 g (6 mmoles) of **2**, 25 ml of dried dioxane and 10 ml of recently distilled phosphorus oxychloride, protected with a tube of anhydrous calcium chloride, was refluxed for 8 hours. Solvent was removed in vacuum and the residual oil treated with ethanol. The monohydrochloride of **3** crystallized, mp 244-247° dec (ethanol), yield about 70%; ir: 3100 (NH), 2300-2700 (NH⁺), 1630 (C=N), 730 (1,2-aromatic disubst); nmr (DMSO-*d*₆): 6.0° 5.00 (bs, 1H, NH⁺), 7.20-7.70 (m, 3H, H-6, H-7, H-8), 8.20 (d, 1H, H-9), 8.70 (s, 1H, H-2), 12.2 (bs, 1H, NH-indole).

Anal. Calcd. for C₁₀H₆ClN₃.HCl: C, 50.00; H, 2.91; N, 17.50. Found: C, 50.30; H, 2.89; N, 17.18.

The free base **3** was obtained treating with 30 ml of ammonium hydroxide, a warmed solution of 0.5 g of the monohydrochloride **3** in 20 ml of ethanol. Solvent was removed in vacuum. The solid residue washed with water and recrystallized, mp 231-233° (ethanol/water); ir: 3100, 3200 (NH), 1630 (C=N), 750 (1,2-aromatic disubst); nmr (DMSO-*d*₆): 6.0° 7.15-7.80 (m, 3H, H-6, H-7, H-8), 8.80 (d, 1H, H-9), 12.10 (s, 1H, NH-indole).

Anal. Calcd. for C₁₀H₆ClN₃: C, 58.97; H, 2.95; N, 20.64. Found: C, 58.59; H, 2.76; N, 20.47.

5*H*-Pyrimido[5,4-*b*]indole-4-thione (**4**).

A mixture of 5.0 g (17.5 mmoles) of **2**, 8 g of phosphorus pentasulfide and 50 ml of dried pyridine was boiled for 6 hours. The hot reaction mixture was filtered, the solvent removed in vacuum and the residual material extracted with boiling dioxane (4 x 50 ml). Solvent was removed in vacuum again and the solid residue washed with 5% ammonium hydroxide and recrystallized to give **4** (yield 80%), mp > 250°; ir: 3110 (NH), 1600, 1620 (C=N), 1380 (N-C=S), 725 (1,2-aromatic disubst); nmr (DMSO-*d*₆): 3.5° 7.15-7.80 (m, 3H, H-6, H-7, H-8), 8.10 (d, 1H, H-9), 8.25 (s, 1H, H-2), 12.30 (bs, 1H, NH-indole).

Anal. Calcd. for C₁₀H₆N₃S: C, 59.70; H, 3.48; N, 20.89. Found: C, 58.39; H, 3.39; N, 21.13.

4-Alkylamino-5*H*-pyrimido[5,4-*b*]indoles (**5**).

A mixture of **3** (free base or monohydrochloride) and 15 ml of the respective amine (morpholine, piperidine) was boiled for 4 hours. Solvent was removed in vacuum and the residual solid washed with water and recrystallized. In this way, the following compounds were prepared:

4-(4-Morpholinyl)-5*H*-pyrimido[5,4-*b*]indole (**5a**).

This compound was obtained from morpholine, mp > 250° (ethanol); yield about 85%; ir: 3315 (NH), 1625 (C=N); nmr (DMSO-*d*₆): 6.0° 3.05 (s, 4H, -CH₂-N-CH₂), 3.70 (s, 4H, -CH₂-O-CH₂), 7.10-7.80 (m, 3H, H-6, H-7, H-8), 8.05 (d, 1H, H-9), 8.35 (s, 1H, H-2), 11.20 (bs, 1H, NH-indole).

Anal. Calcd. for C₁₄H₁₄N₄O: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.19; H, 5.49; N, 21.86.

4-(1-Piperidinyl)-5*H*-pyrimido[5,4-*b*]indole (**5b**).

This compound was obtained from piperidine, mp > 250° (ethanol/water); yield about 90%; ir: 3100 (NH), 1610 (C=N), 735 (aromatic 1,2-disubst); nmr (deuteriochloroform): 1.80 (s, 6H, -(CH₂)₄-), 3.90 (s, 4H, -CH₂-N-CH₂), 7.10-7.80 (m, 3H, H-6, H-7, H-8), 8.30 (d, 1H, H-9), 8.65 (bs, 1H, NH-indole), 8.70 (s, 1H, H-2).

Anal. Calcd. for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.20. Found: C, 71.60; H, 6.46; N, 21.98.

4-Hydrazino-5H-pyrimido[5,4-b]indole (**6**).

A mixture of 25 mmoles of **4** or **3**, 10 ml of hydrazine (100%) and 100 ml of ethanol, was boiled for 5 hours. Solvent was removed in vacuum, the residual material suspended in 100 ml of water and the yellow solid material collected by filtration and recrystallized, mp 227-229° (ethanol), yield about 80%; ir: 3170, 3340, 3400 (NH), 1630 (C=N), 730 (aromatic 1,2-disubst); nmr (DMSO- d_6): 3.5° 4.80 (bs, $NH-NH_2 + H_2O$), 7.05-7.80 (m, 3H, H-6, H-7, H-8), 8.05 (d, 1H, H-9), 8.30 (s, 1H, H-2), 12.30 (bs, 1H, NH-indole).

Anal. Calcd. for $C_{10}H_9N_5$: C, 60.29; H, 4.55; N, 35.15. Found: C, 60.36; H, 4.69; N, 34.86.

The monohydrochloride of **6** was prepared by the addition of 10 ml of a solution 10M of hydrogen chloride in ethanol, to a hot solution of 1 g of **6** in absolute ethanol. Solvent was removed in vacuum and the solid residue recrystallized, mp 237-240° dec (ethanol); ir: 3150, 3220 (NH), 3000-2500 (NH^+), 1670 (C=N), 730 (aromatic 1,2-disubst); nmr (DMSO- d_6): 60° 5.80 (bs, $(NH-NH_2)H^+ + H_2O$), 7.15-7.80 (m, 3H, H-6, H-7, H-8), 8.30 (d, 1H, H-9), 8.65 (s, 1H, H-2), 12.40 (bs, 1H, NH-indole).

Anal. Calcd. for $C_{10}H_9N_5 \cdot HCl$: C, 50.95; H, 4.25; N, 29.72. Found: C, 50.61; H, 4.11; N, 29.67.

Hydrazone of 4-Hydrazino-5H-pyrimido[5,4-b]indole (**7**).

A mixture of 1.0 g (5 mmoles) of **6**, 25 ml of ethanol and the respective aldehyde (benzaldehyde, 1.0 g) or ketone (acetone, 5 ml) was boiled for 1 hour. Solvent was removed in vacuum and solid residue recrystallized. In this way the following compounds were obtained:

Benzylhydrazone (**7a**).

This compound was prepared from benzaldehyde, mp >250° (ethanol); yield about 90%; ir: 3180, 3430 (NH), 1600, 1620 (C=N), 685, 730, 750 (aromatic mono and 1,2-disubst); nmr (DMSO- d_6): 7.05-8.00 (m, 8H, H-6, H-7, H-8, C_6H_5), 8.15 (d, 1H, H-9), 8.25 (s, 1H, =CH-Ph), 8.40 (s, 1H, H-2), 10.60 (s, 1H, NH-N), 11.60 (bs, 1H, NH-indole).

Anal. Calcd. for $C_{17}H_{13}N_5$: C, 71.07; H, 4.56; N, 24.37. Found: C, 70.68; H, 4.84; N, 24.44.

Isopropylhydrazone (**7b**).

This compound was prepared from acetone, mp 200-202° (ethanol), yield about 90%; ir: 3180, 3400 (NH), 1590, 1610 (C=N), 725 (aromatic 1,2-disubst); nmr (DMSO- d_6): 2.05 (s, 3H) and 2.20 (s, 3H) for two CH_3 ; 7.10-7.90 (m, 3H, H-6, H-7, H-8), 8.10 (d, 1H, H-9), 8.50 (s, 1H, H-2), 10.1 (bs, 1H, NH), 10.70 (bs, 1H, NH-indole).

Anal. Calcd. for $C_{13}H_{13}N_5$: C, 65.26; H, 5.48; N, 29.27. Found: C, 65.33; H, 5.48; N, 29.21.

1,2,4-Triazolo[4,3-c]pyrimido[5,4-b]indoles (**8**)

A mixture of 0.87 g (4.3 mmoles) of **6** and 30 ml of the respective acid (formic or acetic acids) was boiled for 5 hours. Solvent was removed in vacuum, the residual material suspended in water and the solid collected by filtration and recrystallized. In this way the following compounds were obtained:

1,2,4-Triazolo[4,3-c]pyrimido[5,4-b]indole (**8a**).

This compound was obtained from formic acid, mp >250° (DMF/ethanol), yield about 65%; ir: 3100 (NH), 1640 (C=N), 725

(aromatic 1,2-disubst); nmr (DMSO- d_6): 60° 7.25-7.90 (m, 3H, H-8, H-9, H-10), 8.20 (dd, 1H, H-7), 8.70 (s, 1H, H-3), 9.60 (s, 1H, H-5), 12.80 (bs, 1H, NH-indole).

Anal. Calcd. for $C_{11}H_7N_5$: C, 63.15; H, 3.37; N, 33.47. Found: C, 62.70; H, 3.26; N, 33.16.

3-Methyl-1,2,4-Triazolo[4,3-c]pyrimido[5,4-b]indole (**8b**).

This compound was obtained from acetic acid, mp >300° (DMF/ethanol), yield about 75%; ir: 3120 (NH), 1650 (C=N), 720 (aromatic 1,2-disubst); nmr (DMSO- d_6): 60° 2.60 (s, 3H, CH_3), 7.10-7.80 (m, 3H, H-8, H-9, H-10), 8.10 (dd, 1H, H-7), 9.40 (s, 1H, H-5), 12.80 (bs, 1H, NH-indole).

Anal. Calcd. for $C_{12}H_9N_5$: C, 64.56; H, 4.06; N, 31.37. Found: C, 64.29; H, 4.23; N, 31.57.

Tetrazolo[4,5-c]pyrimido[5,4-b]indole (**9**).

Into a stirred mixture of 1.0 g (5 mmoles) of **6** and 1.7 g (24 mmoles) of powdered sodium nitrite, 30 ml of hydrochloric acid (1.5N) was dropped and the mixture stirred for 24 hours at room temperature. The precipitate was collected by filtration, washed with water and recrystallized, mp >245°, yield about 85%; ir: 3100 (NH), 1640 (C=N), 730 (aromatic 1,2-disubst); nmr (DMSO- d_6): 60° 7.10-7.85 (m, 3H, H-8, H-9, H-10), 8.15 (m, 1H, H-7), 9.80 (s, 1H, H-5), 13.2 (bs, 1H, NH-indole).

Anal. Calcd. for $C_{10}H_6N_6$: C, 57.14; H, 2.86; N, 40.00. Found: C, 56.96; H, 2.92; N, 39.83.

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