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SYNTHESIS OF 2,4-DISUBSTITUTED PYRIMIDO[4,5-b]-INDOLES, PYRANO[4',3':4,5]PYRROLO[2,3-d]PYRIMIDINES AND SOME CONVERSIONS OF PYRIMIDO[4,5-d]INDOLES

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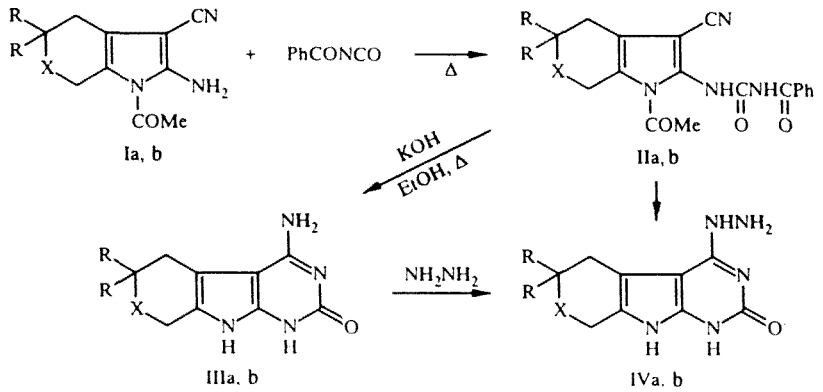
Methods have been developed for the production of 2,4-disubstituted 5,6,7,8-tetrahydro-9H-pyrimido[4,5-b]indoles and pyrano[4',3':4,5]pyrrolo[2,3-d]pyrimidines. Heterocyclization reactions were carried out on 4-hydrazinopyrimido[4,5-b]indoles.

Compounds possessing biological activity have been discovered in the series of 4-amino- and 4-oxo-derivatives of 5,6,7,8-tetrahydro-9H-pyrimido-[4,5-b]indoles [1, 2], which prompted our interest in seeking new methods for producing derivatives of pyrimido[4,5-b]indoles and their pyrano-[4',3':4,5]-pyrrolo[2,3-d]pyrimidine analogs.

We have developed a new method for producing 4-amino-2-oxo-derivatives of pyrimido[4,5-b]indoles and pyrano[4',3':4,5]pyrrolo[2,3-c]pyrimidines from 2-amino-1-acetyl-3-cyano-4,5,6,7-tetrahydroindole (Ia) [3] and 2-amino-1-acetyl-5,5-dimethyl-3-cyano-4,5-dihydro-7H-pyrrolo[2,3-c]pyran (Ib) [4]. The method consists of the reaction of aminonitriles of Ia,b with benzoyl isocyanate. The benzoylureido-derivatives (IIa,b) isolated were converted to 4-amino-2-oxopyrimidines (IIIa,b) under the action of an alcohol solution of potassium hydroxide. In the course of the reaction the acetyl and benzoyl groups are split out, and cyclization occurs. 4-Hydrazino-2-oxopyrimidines (IVa,b) were produced by the action of hydrazine on the benzoylureido-derivatives IIa,b. The hydrazinooxopyrimidines are apparently products of the transamination of compounds IIIa,b, which was demonstrated by reacting 4-amino-2-oxopyrimidines IIIa,b with hydrazine hydrate.



I–IVa R = H, X = CH_2, b R = Me, X = O

To synthesize derivatives of 2,4-dithioxopyrimido[4,5-b]indoles we reacted the aminonitrile Ia with carbon disulfide in pyridine. The reaction yielded the 2,4-dithioxopyrimidine (V). Methylation of the latter produced the dimethylthio-derivative (VI). We should mention the difference in the reactivity of dithioxo- and dimethylthio-derivatives of pyrimido[4,5-b] toward hydrazine. When a mixture of the dithioxo-derivative V was boiled with hydrazine hydrate in butanol, 2,4-dihydrazino-

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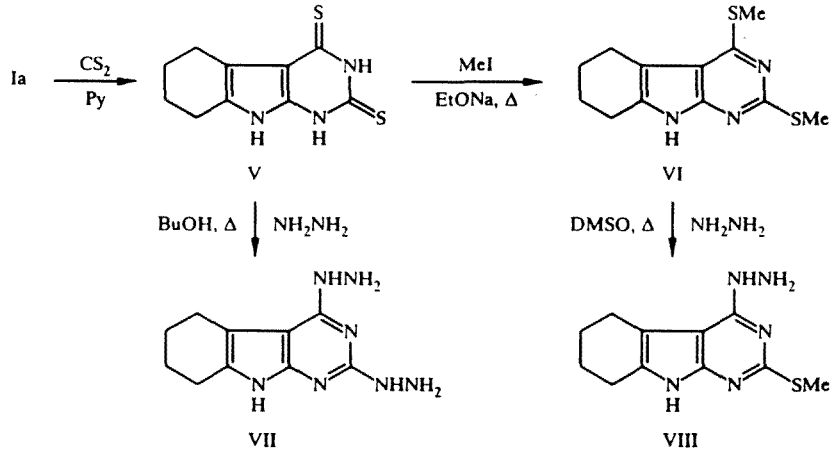
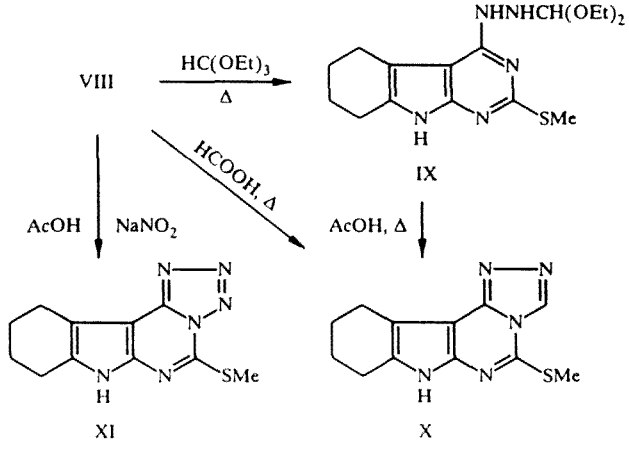
pyrimido[4,5-b]indole (VII) was obtained, whereas boiling of the dimethylthio-derivative (VI) in DMSO led only to the 4-hydrazino derivative VIII. This is explained by hindrance to nucleophilic attack in the 2-position of the pyrimidine ring [5].



In the PMR spectra of compounds IVa and VIII, the signals of the protons of the hydrazine residues take the form of broadened singlets in the region of 5.2...5.3 ppm. The singlet signals of the thiomethyl groups in the 2-position of the pyrimidine ring lie at 2.7 ppm (compounds VI and VIII), and those of the 4-SCH_3 group at 3.4 ppm (compound VI). The latter signal is absent in the spectrum of compound VIII.

The hydrazo group in the 4-position of the pyrimidine ring in compound VIII was used to produce condensed triazolo- and tetrazolopyrimidines. When the indicated compound reacted with orthoformic ester, the derivative (IX) was obtained; when boiled in acetic acid it was converted to the triazolopyrimidine (X). The latter was also produced in one step in the condensation of compound VIII with formic acid. The tetrazolo[1,5-c]pyrimidine (XI) was synthesized by the action of sodium nitrite in acetic acid on the compound VIII.



EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in liquid petrolatum. The PMR spectra were recorded on a Varian T-60 instrument in DMSO-D_6 (IIb, IVa, VI), pyridine-D_5 (IIa, V, XI), and $CDCl_3$ (IX). Internal standard TMS. The mass spectra were obtained on an MX-1303 mass spectrometer with direct introduction of the sample. The purity of the substances obtained was monitored by a TLC method on Silufol UV-254 plates using the systems: pyridine—ethanol, 1:4 (IIa,b), pyridine—ethanol, 1:3 (III, IVa,b, V, VII), butanol—acetic acid—water, 4:2:5 (IV, VIII, XI), chloroform—ether, 1:2 (IX), and methanol—chloroform, 1:1 (X).

The data of elementary analysis of the compounds synthesized for C, H, N, and S correspond to the calculated values (see below).

1-Acetyl-2-benzoylureido-3-cyano-4,5,6,7-tetrahydroindole (IIa). A mixture of 2.0 g (0.01 mole) of compound Ia, 1.5 g (0.01 mole) of benzoyl isocyanate, and 50 ml of dry benzene was boiled with a reflux condenser for 4 h. After cooling, the crystals of the product IIa were filtered off, washed with benzene, and dried. Yield 2.9 g (82.0%). Mp 229...230°C (ethanol). R_f 0.54. IR spectrum: 1680, 1705 (CO), 2230 (CN), 3290 cm^{-1} (NH). PMR spectrum: 1.38...1.73 (4H, m, $2CH_2$), 2.35...2.84 (7H, m, $2CH_2$, CH_3), 7.41...7.72 (5H, m, C_6H_5), 8.17...8.33 ppm (2H, m, 2NH). Found, %: C 65.16, H 5.20, N 15.89. $C_{19}H_{18}N_4O_3$. Calculated, %: C 65.13, H 5.18, N 15.99.

1-Acetyl-2-benzoylureido-5,5-dimethyl-3-cyano-4,5-dihydro-7H-pyrrolo[2,3-c]pyran (IIb). The product IIb was produced under the conditions described above from compound Ib. Yield 75.4%. Mp 247...248°C (ethanol). R_f 0.65. IR spectrum: 1680, 1710 (CO), 2235 (CN), 3270 cm^{-1} (NH). PMR spectrum: 1.21 (6H, s, $2CH_3$), 2.52 (2H, t, CH_2), 2.63 (3H, s, CH_3), 4.45 (2H, t, CH_2O), 7.43...8.21 (5H, m, C_6H_5), 10.77...11.3 ppm (2H, m, 2NH). Found, %: C 63.17, H 5.27, N 14.70. $C_{20}H_{20}N_4O_4$. Calculated, %: C 63.14, H 5.29, N 14.73.

4-Amino-2-oxo-5,6,7,8-tetrahydro-1H,9H-pyrimido[4,5-b]indole (IIIa). To a solution of 0.56 g (0.01 mole) of potassium hydroxide in 30 ml of ethanol we added 1.75 g (0.005 mole) of compound IIa. The mixture was boiled with a reflux condenser for 3 h. After cooling, 50 ml of water was added, and the precipitated crystals of product IIIa were filtered off, washed with water, and dried. Yield 0.75 g (73.5%). Mp > 360°C (DMFA). R_f 0.62. IR spectrum: 1660 (CO), 3180-3470 cm^{-1} (NH_2, NH). Found, %: C 58.76, H 5.94, N 27.55. $C_{10}H_{12}N_4O$. Calculated, %: C 58.81, H 5.92, N 27.43.

4-Amino-6,6-dimethyl-2-oxo-5,6,7,8-tetrahydro-1H,9H-pyrano[4',3':4,5]pyrrolo[2,3-d]pyrimidine (IIIb). The product IIIb was produced from compound IIb under the conditions described above. Yield 74.6%. Mp > 360°C (DMFA). R_f 0.59. IR spectrum: 1650 (CO), 3170-3400 cm^{-1} (NH_2, NH). Mass spectrum, m/e (I, %): M^+ 234 (100), 219 (10), 177 (17), 176 (78), 148 (43). Found, %: C 56.32, H 6.08, N 23.87. $C_{11}H_{14}N_4O_2$. Calculated, %: C 56.36, H 6.02, N 23.91.

4-Hydrazino-2-oxo-5,6,7,8-tetrahydro-1H,9H-pyrimido[4,5-b]indole (IVa). A. A mixture of 1.75 g (0.005 mole) of compound IIa, 3 ml of hydrazine hydrate, and 20 ml of butanol was boiled with a reflux condenser for 10 h. After cooling, the crystals of the product IVa that precipitated were filtered off, washed with water, and dried. Yield 1.0 g (91.3%). Mp 309...310°C (DMSO). R_f 0.61. IR spectrum: 1650 (CO), 3200-3400 cm^{-1} (NH_2, NH). PMR spectrum: 1.5...1.95 (4H, m, $2CH_2$), 2.18...2.83 (4H, m, $2CH_2$), 5.3 (2H, br. s, NH_2), 6.77...7.24 (2H, m, 2NH), 11.3 ppm (1H, s, NH). Mass spectrum, m/e (I, %): M^+ 219 (100), 218 (5), 203 (19), 160 (17). Found, %: C 54.75, H 5.96, N 32.01. $C_{10}H_{13}N_5O$. Calculated, %: C 54.80, H 5.93, N 31.94. B. A mixture of 2.05 g (0.01 mole) of compound IIIa, 5 ml of hydrazine hydrate, and 3 ml of butanol was boiled with a reflux condenser for 10 h. After cooling, the precipitated crystals of compound IVa were filtered off, washed with water, and dried. Yield 1.9 g (92.6%).

4-Hydrazino-6,6-dimethyl-2-oxo-5,6,7,8-tetrahydro-1H,9H-pyrano[4',3':4,5]pyrrolo[2,3-d]pyrimidine(IVb). The product IVb was produced from compound IIb (method A) and from IIIb (method B) under the conditions described above. Yield 88.5% (A) and 90.4% (B). Mp 326...327°C (DMSO). R_f 0.63. IR spectrum: 1650 (CO), 3200-3400 cm^{-1} (NH_2, NH). Found, %: C 53.05, H 6.14, N 27.83. $C_{11}H_{15}N_5O_2$. Calculated, %: C 52.99, H 6.06, N 28.09.

5,6,7,8-Tetrahydro-9H-pyrimido[4,5-b]indole-2,4(1H,3H)-dithione (V). A mixture of 2.0 g (0.01 mole) of compound Ia, 7 ml of carbon disulfide, and 30 ml of pyridine was boiled with a reflux condenser for 12 h. The excess carbon disulfide and pyridine were distilled off; a solution of 1.4 g (0.025 mole) potassium hydroxide in 30 ml of water was added to the residue. The mixture was kept on a boiling water bath for 30 min. After cooling it was filtered off, and the filtrate was acidified with 20% hydrochloric acid. The crystals of product V that precipitated were filtered off, washed with water, and dried. Yield 1.8 g (75.9%). Mp 323...324°C (DMSO). R_f 0.58. IR spectrum: 1180 (C=S), 3180-3320 cm^{-1} (NH). PMR spectrum: 1.28...1.57 (4H, m, $2CH_2$), 2.05...2.25 (2H, m, CH_2), 2.87...3.1 (2H, m, CH_5), 5.96...6.23 (2H, br.s, 2NH), 10.6 ppm (1H, s, NH). Found, %: C 50.59, H 4.69, N 17.63, S 26.98. $C_{10}H_{11}N_3S_2$. Calculated, %: C 50.61, N 17.70, S 27.02.

2,4-Di(methylthio)-5,6,7,8-tetrahydro-9H-pyrimido[4,5-b]indole (VI). To a solution of sodium ethylate, obtained from 0.46 g (0.02 mole) of sodium and 40 ml of ethanol, we added 2.4 g (0.01 mole) of compound V. The mixture was mixed for 10 min, 2.9 g (0.02 mole) of methyl iodide was added, and it was boiled with mixing for 1 h. After cooling, 60 ml of water was added; the crystals of product VI that formed were filtered off, washed with water, and dried. Yield 2.3 g (86.8%). Mp 263...264°C (ethanol). R_f 0.62. PMR spectrum: 1.61...2.0 (4H, m, 2 CH_2), 2.43...2.62 (4H, m, $2CH_2$), 2.7 (3H, s, SCH_3), 3.4 (3H, s, SCH_3), 11.42 ppm (1H, s, NH). Found, %: C 54.28, H 5.73, N 15.79, S 24.06. $C_{12}H_{15}N_3S_2$. Calculated, %: C 54.30, H 5.69, N 15.83, S 24.18.

2,4-Dihydrazino-5,6,7,8-tetrahydro-9H-pyrimido[4,5-b]indole (VII). A mixture of 1.2 g (0.005 mole) of compound V, 3 ml of hydrazine hydrate, and 10 ml of butanol was boiled with a reflux condenser for 10 h. After cooling, the precipitated crystals of product VII were filtered off, washed with water and with methanol, and dried. Yield 0.5 g (44.6%). Mp 320...

322°C with dec. (DMSO). R_f 0.70. IR spectrum: 1610 (C=C, C=N), 3100-3340 cm^{-1} (NH_2, NH). Found, %: C 51.42, H 6.51, N 42.01. $C_{10}H_{15}N_7$. Calculated, %: C 51.45, H 6.48, N 42.07.

4-Hydrazino-2-methylthio-5,6,7,8-tetrahydro-9H-pyrimido[4,5-b]indole (VIII). A mixture of 2.65 g (0.01 mole) of compound VI, 15 ml of hydrazine hydrate, and 30 ml of DMSO was boiled with a reflux condenser for 20 h. After cooling, the crystals of product VIII that precipitated were filtered off, washed with ethanol, with water, and dried. Yield 2.2 g (84.5%). Mp 292...293°C (DMSO). R_f 0.67. IR spectrum: 1620 (C=C, C=N), 3050-3290 cm^{-1} (NH_2, NH). PMR spectrum: 1.6...1.95 (4H, m, $2CH_2$), 2.38...2.96 (7H, m, $2CH_2$, SCH_3), 5.3 (3H, br.s, $NHNH_2$), 11.3 ppm (1H, s, NH). Found, %: C 53.04, H 6.01, N 29.98, S 12.74. $C_{11}H_{15}N_5S$. Calculated, %: C 52.99, H 6.06, N 28.09, S 12.86.

4-(β-Diethoxymethylhydrazino)-2-methylthio-5,6,7,8-tetrahydro-9H-pyrimido[4,5-b]indole (IX). A mixture of 1.25 g (0.005 mole) of compound VIII and 30 ml of orthoformic ester was boiled with a reflux condenser for 10 h. The solvent was distilled off to dryness; 20 ml of ethanol was added to the residue; the crystals of product IX that formed were filtered off, washed with ethanol, and dried. Yield 1.4 g (80.0%). Mp 182...183 °C (ethanol). R_f 0.64. PMR spectrum: 1.24 (6H, t, J = 6 Hz, $2CH_2\underline{CH_3}$), 1.78...2.08 (4H, m, $2CH_2$), 2.82 (3H, s, SCH_3), 2.91...3.18 (4H, m, $2CH_2$), 3.63 (4H, q, J = 6 Hz, $2\underline{CH_2}CH_3$), 6.87 (1H, s, CH), 8.71 (1H, s, NH), 11.3 ppm (1H, s, NH). Found, %: C 54.71, H 7.12, N 19.93, S 9.15. $C_{16}H_{25}N_5O_2S$. Calculated, %: C 54.67, H 7.16, N 19.92, S 9.12.

5-Methylthio-8,9,10,11-tetrahydro-7H-1,2,4-triazolo[4,3-c]pyrimido[4,5-b]indole (X). A. A solution of 1.75 g (0.005 mole) of compound IX in 10 ml of glacial acetic acid was boiled with a reflux condenser for 2 h. After cooling, the crystals of product X that formed were filtered off, washed with water, and dried. Yield 1.0 g (77.6%). Mp 272...273°C (methanol—chloroform, 1:1). R_f 0.69. IR spectrum: 1630 (C=N), 3140 cm^{-1} (NH). PMR spectrum: 1.62...1.96 (4H, m, $2CH_2$), 2.5...2.96 (7H, m, $2CH_2$, SCH_3), 8.95 (1H, s, CH), 11.63 ppm (1H, s, NH). Found, %: C 55.62, H 4.98, N 27.04, S 12.31. $C_{12}H_{13}N_5S$. Calculated, %: C 55.58, H 5.05, N 27.00, S 12.37.

B. A solution of 1.0 g (0.004 mole) of compound VIII in 10 ml of formic acid was boiled for 2 h. The excess formic acid was distilled off to dryness. Then 30 ml of water was added to the residue, and it was alkalinized with 10% sodium hydroxide to a neutral pH. The crystals of product X that formed were filtered off, washed with water, and dried. Yield 0.9 g (85.7%).

5-Methylthio-8,9,10,11-tetrahydro-7H-tetrazolo[1,5-c]pyrimido[4,5-b]indole (XI). To a solution of 1.25 g (0.005 mole) of compound VIII in 12 ml of 2 N aqueous acetic acid, a solution of 1.6 g (0.025 mole) of sodium nitrite in 10 ml of water was added dropwise with mixing. The mixture was mixed for 1 h at 25°C. The precipitated crystals were filtered off, dissolved in 5 ml of DMSO, and heated to 180°C for 5 min. After cooling, 20 ml of water was added to the mixture, and the crystals of product XI that formed were filtered off, washed with water, and dried. Yield 1.1 g (84.6%). Mp 211...212°C (DMSO). R_f 0.59. IR spectrum: 1170 (tetrazole), 1640 (C=N), 3240 cm^{-1} (NH). PMR spectrum: 1.7...2.05 (4H, m, $2CH_2$), 2.78 (3H, s, SCH_3), 2.9...3.12 (4H, m, $2CH_2$), 11.54 ppm (1H, s, NH). Found, %: C 50.81, H 4.61, N 32.24, S 12.29. $C_{11}H_{12}N_6S$. Calculated, %: C 50.75, H 4.61, N 32.28, S 12.33.

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