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SYNTHESIS OF 1,2,4-TRIAZOLO[4,3-*c*]-, TETRAZOLO[1,5-*c*]-, AND 1,2,4-TRIAZINO[5,6-*c*]PYRANO[4',3':4,5]PYRROLO-[3,2-*e*]PYRIMIDINE DERIVATIVES

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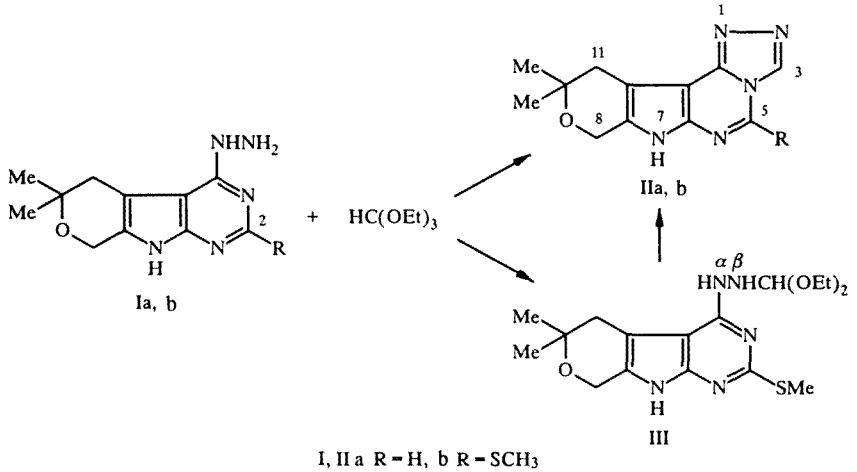
4-Hydrazinopyrano[4',3':4,5]pyrrolo[2,3-d]pyrimidines served as precursors in the synthesis of new heterocyclic systems, namely, 1,2,4-triazolo[4,3-c]-, tetrazolo[1,5-c]-, and 1,2,4-triazino[5,6-c]-pyrano[4',3':4,5]-pyrrolo[3,2-e]pyrimidines.

Condensed triazoles, tetrazoles, and triazines possess high pharmocological activity [1-3], while a derivative of pyrrolo[3,2-*e*][1.2.4]triazolo[1,5-*a*]pyrimidine, namely, bumepidil, is an agent for coronary dilation [4]. In a continuation of work on the synthesis of pyrano[4',3':4,5]pyrrolo[2,3-*d*]pyrimidine derivatives, we obtained previously unreported triazolo-[4,3-*c*]-, tetrazolo[1,5-*c*]-, and 1,2,4-triazino[5,6-*c*]pyrano[4',3':4,5]pyrrolo[3,2-*e*]pyrimidines.

4-Hydrazinopyrano[4,',3':4,5]pyrrolo[2,3-*d*]pyrimidine derivatives synthesized in our laboratory [5] proved convenient starting materials for the construction of triazole, tetrazole, and triazine rings at the [*c*] bond of the pyrimidine ring.

The reaction of 4-hydrazinopyrimidines Ia and Ib with ethyl orthoformate gave triazolo[4,3-*c*]pyrimidines IIa and IIb.



I, II a R = H, b R = SCH_3

In the case of Ia, which lacks a substituent at $C_{(2)}$, product IIa is formed in high yield by heating the reagents at reflux. Product IIb is obtained in two steps from 2-methylthiopyrimidine Ib. Derivative III is formed initially and then is converted to triazolopyrimidine IIb only upon heating at reflux in acetic acid.

The signal for 3-H in the triazole ring in the PMR spectra of IIa and IIb is found at 9.3 ppm, while the singlet for 5-H of the pyrimidine ring in IIa is found at 8.4 ppm. The rates of intermolecular or intramolecular exchange are different in different solvents and, thus, the PMR signals of the NH groups are not always clearly seen.

The effect of the methylthio group is also seen in the reaction of 4-hydrazinopyrimidines Ia and Ib with aqueous sodium nitrite in the presence of acetic acid, leading to tetrazolo[1,5-*c*]pyrimidines IVa and IVb. Thus, product IVa is obtained from

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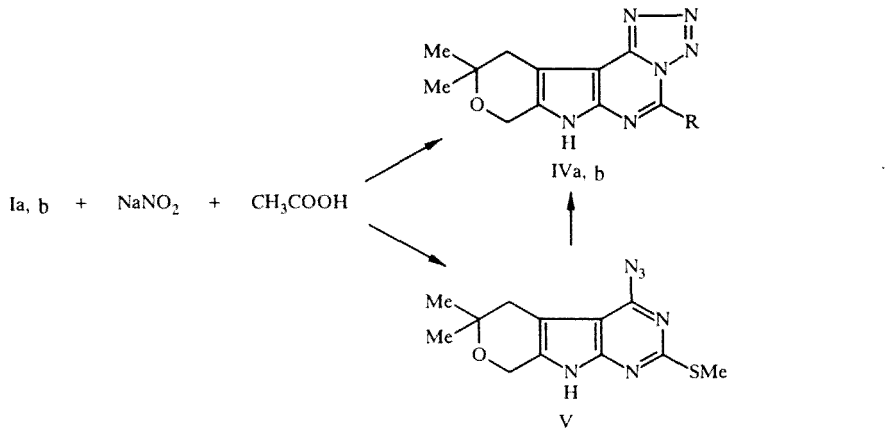
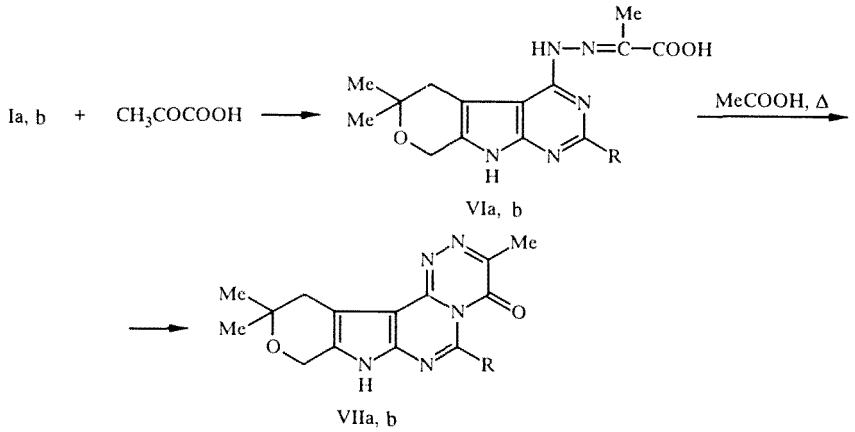
pyrimidine Ia in high yield in one step at temperatures not exceeding 40°C. On the other hand, 4-azidopyrimidine V, which is converted to IVb upon heating, is formed initially from methylthio derivative Ib.



The IR spectra of IVa and IVb display bands characteristic for the tetrazole ring in the 1070-1100 cm^{-1} region but lack the azide group band in the vicinity of 2150 cm^{-1}. The PMR singlet for the pyrimidine proton in tetrazolopyrimidine IVa is downfield (9.82 ppm) relative to the corresponding signal of triazolopyrimidine IIa (9.30 ppm).

The reaction of 4-hydrazinopyrimidines Ia and Ib with pyruvic acid gave acids VIa and VIb, which were then converted into 1,2,4-triazino[5,6-*c*]pyrimidines VIIa and VIIb upon heating in acetic acid at reflux.



EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for vaseline mulls. The PMR spectra were taken on a Varian T-60 spectrometer in DMSO-d_6 (IIa, IIb, IVa, and IVb) and $CDCl_3$ (III and IV) with TMS as the internal standard. The mass spectra were taken on an MKh-1303 mass spectrometer with direct sample inlet. The purity of the products was monitored by thin-layer chromatography on Silufol UV-254 plates using 1:2 chloroform—ether (III), 1:3 pyridine—ethanol (IIa, IIb, IVa, IVb), and 4:2:5 butanol—acetic acid—water (V, VIa, IVb, VIIa, VIIb).

The elemental analysis data for the products for C, H, N, and S corresponded to the calculated values (see below).

10,10-Dimethyl-10,11-dihydro-8H-1,2,4-triazolo[4,3-*c*]pyrano[4′,3′:4,5]pyrrolo[3,2-*e*]pyrimidine (IIa). A mixture of 2.3 g (0.01 mole) Ia and 50 ml ethyl orthoformate was heated at reflux for 10 h. The solvent was distilled off and 20 ml ethanol was added to the dry residue. The crystalline precipitate formed was filtered off, washed with ethanol, and dried to give 1.7 g (70.4%) IIa, mp 270-271°C (from 1:1 methanol—chloroform), R_f 0.63. IR spectrum: 1620 (C=N), 3130 cm^{-1} (NH). PMR spectrum: 1.20 (6H, s, $2CH_3$), 2.76 (2H, t, CH_2), 4.65 (2H, t, CH_2O), 8.40 (1H, s, 5-H), 9.30 ppm (1H, s, 3-H). Mass spectrum, *m/e* (*I*, %): M^+ 243 (100), 228 (15), 213 (10), 185 (80), 149 (25). Found: C, 59.18; H, 5.41; N, 28.83%. Calculated for $C_{12}H_{13}N_5O$: C, 59.24; H, 5.38; N, 28.85%.

6,6-Dimethyl-4-(β-diethoxymethylhydrazino)-2-methylthio-5,6-dihydro-8H-pyrano-[4′,3′:4,5]pyrrolo[2,3-*d*]pyrimidine (III). Product III was obtained in 80.0% yield from Ib under the conditions described above, mp 150-151°C (ethanol), R_f 0.69. IR spectrum: 1630 (C=N), 3140-3200 cm^{-1} (NH). PMR spectrum: 1.15-1.50 (12H, m, $2CH_2CH_3$, 2 *gem*-CH_3), 286 (3H, s, SCH_3), 3.10 (2H, t, ring CH_2), 3.68 (4H, q, $2C\underline{H}_2CH_3$, J = 6 Hz), 5.03 (2H, t, ring CH_2O), 6.80 (1H, s, CH), 8.85 ppm (1H, s, NH). Found: C, 53.47; H, 7.15; N, 18.42; S, 8.31%. Calculated for $C_{17}H_{27}N_5O_3S$: C, 53.52; H, 7.13; N, 18.35; S, 8.40%.

10,10-Dimethyl-5-methylthio-10,11-dihydro-8H-1,2,4-triazolo[4,3-*c*]pyrano[4′,3′:4,5]pyrrolo[3,2-*e*]pyrimidine (IIb). A solution of 1.9 g (0.005 mole) III in 15 ml glacial acetic acid was heated at reflux for 2 h. After cooling, crystalline IIb was filtered off, washed with water, and dried to give 1.2 g (82.5%) IIb, mp 300-301°C (1:1 methanol—chloroform), R_f 0.57. IR spectrum: 1620 (C=N), 3120 cm^{-1} (NH). PMR spectrum: 1.32 (6H, s, $2CH_3$), 2.62 (s, SCH_3), 2.70 (2H, t, CH_2), 4.75 (2H, t, CH_2O), 9.30 (1H, s, 3-H), 12.10 ppm (1H, s, NH). Found: C, 53.88; H, 5.30; N, 23.93; S, 11.28%. Calculated for $C_{13}H_{15}N_5OS$: C, 53.95; H, 5.22; N, 24.20; S, 11.08%.

10,10-Dimethyl-10,11-dihydro-8H-tetrazolo[1,5-*c*]pyrano[4′,3′:4,5]pyrrolo[3,2-*e*]pyrimidine (IVa). A solution of 1.6 g (0.025 mole) sodium nitrite in 10 ml water was added dropwise with stirring to a solution of 1.2 g (0.005 mole) Ia in 12 ml 2 N aqueous acetic acid and stirred for 1 h at 40°C. After cooling, crystalline IVa was filtered off, washed with water, and dried to give 1.1 g (87.5%) IVa, mp 239-240°C (1:1 DMSO—ethanol), R_f 0.72. IR spectrum: 1100 (tetrazole), 1620 (C=C, C=N), 3200 cm^{-1} (NH). PMR spectrum: 1.4 (6H, s, $2HC_3$), 2.92 (2H, t, CH_2), 4.86 (2H, t, CH_2O), 9.82 (1H, s, 5-H), 12.7 ppm (1H, s, NH). Found: C, 54.17; H, 5.02; N, 34.28%. Calculated for $C_{11}H_{12}N_6O$: C, 54.08; H, 4.95; N, 34.40%.

4-Azido-6,6-dimethyl-2-methylthio-5,6-dihydro-8H-pyrano[4′,3′:4,5]pyrrolo[2,3-*d*]pyrimidine (V). Product V was synthesized from Ib in 90.4% yield under the conditions described above, mp 190-192°C (dec., ethanol), R_f 0.68. IR spectrum: 1620 (C=C, C=N), 2150 (N_3), 3140 cm^{-1} (NH). PMR spectrum: 1.35 (6H, s, $2HC_3$), 2.8 (3H, s, SCH_3), 2.95 (2H, t, CH_2), 4.86 ppm (2H, t, CH_2O). Found: C, 49.66; H, 4.89; N, 28.85; S, 10.99%. Calculated for $C_{12}H_{14}N_6OS$: C, 49.63; H, 4.86; N, 28.94; S, 11.04%.

10,10-Dimethyl-5-methylthio-10,11-dihydro-8H-tetrazolo[1,5-*c*]pyrano[4′,3′:4,5]pyrrolo[3,2-*e*]pyrimidine(IVb). A mixture of 0.9 g (0.003 mole) V and 3 ml DMSO was heated to 180°C over 10 min. After cooling, 20 ml water was added to the mixture and crystalline IVb was filtered off, washed with water, and dried to give 0.7 g (77.7%) IVb, mp 202-203°C (1:1 DMSO—ethanol), R_f 0.59. IR spectrum: 1070 (tetrazole), 1630 (C=N), 3200 cm^{-1} (NH). PMR spectrum: 1.28 (6H, s, $2CH_3$), 2.80 (3H, s, SCH_3), 3.42 (3H, t, CH_2), 4.80 (2H, t, CH_2O), 12.6 ppm (1H, s, NH). Found: C, 49.58; H, 4.88; N, 28.86; S, 10.95%. Calculated for $C_{12}H_{14}N_6OS$: C, 49.63; H, 4.86; N, 28.94; S, 11.04%.

6, 6-Dimethyl-4-(2-N-methylcarboximino)amino-5, 6-dihydro-8H-pyrano [4′, 3′ : 4, 5]pyrrolo[2, 3-*d*] pyrimidine (VIa). A mixture of 2.3 g (0.01 mole) Ia, 0.9 g (0.01 mole) pyruvic acid, and 50 ml ethanol was heated at reflux for 4 h. After cooling, crystalline VIa was filtered off, washed with ethanol, and dried to give 3.7 g (90.0%) VIa, mp 313-315°C (propanol), R_f 0.58. IR spectrum: 1600 (C=C), 1670 (C=N), 1740 (C=O), 3230-3420 cm^{-1} (NH, OH). Found: C, 55.47; H, 5.59; N, 23.12%. Calculated for $C_{14}H_{17}N_5O_3$: C, 55.45; H, 5.64; N, 23.09%.

6,6-Dimethyl-2-methylthio-4-(2-N-methylcarboxyimino)amino-5,6-dihydro-8H-pyrano-[4′,3′:4,5]pyrrolo[2,3-*d*]pyrimidine (VIb). Product VIb was obtained in 85.4% yield from Ib under the conditions described above, mp 273-274°C (propanol), R_f 0.69. IR spectrum: 1610 (C=O), 1660 (C=N), 1740 (C=O), 3230-3400 cm^{-1} (NH, OH). Found: C, 51.49; H, 5.51; N, 19.96; S, 9.21%. Calculated for $C_{15}H_{19}N_5O_3S$: C, 51.56; H, 5.48; N, 20.04; S, 9.17%.

4-Oxo-3,11,11-trimethyl-11,12-dihydro-9H-1,2,4-triazino[5,6-*c*]pyrano [4′,3′:4,5] pyrrolo [3,2-*e*] pyrimidine (VIIa). A mixture of 1.0 g (0.0033 mole) VI and 10 ml glacial acetic acid was heated at reflux for 6 h. After cooling, crystalline VIIa was filtered off, washed with water, and dried to give 0.7 g (75.3%) VIIa, mp >360°C (DMSO), R_f 0.62. IR spectrum: 1590 (C=C), 1650 (C=O, C=N), 3150 cm^{-1}(NH). Mass spectrum, *m/e* (*I*, %): M^+ 285 (100), 270 (30), 255 (5), 243 (20), 227 (12), 226 (23). Found: C, 58.87; H, 5.41; N, 24.77%. Calculated for $C_{14}H_{15}N_5O_2$: C, 58.93; H, 5.29; N, 24.54%.

6-Methylthio-4-oxo-3,11,11-trimethyl-11,12-dihydro-9H-1,2,4-triazino[5,6-*c*]pyrano[4′,3′:4,5]-pyrrolo[3,2-*e*]pyrimidine (VIIb). Product VIIb was obtained in 76.7% yield from VIb under the conditions described above, mp >360°C (DMSO), R_f 0.61. IR spectrum: 1600 (C=C), 1650 (C=O, C=N), 3140 cm^{-1} (NH). Found: C, 54.41; H, 5.08; N, 20.98; S, 9.59%. Calculated for $C_{15}H_{17}N_5O_2S$: C, 54.36; H, 5.17; N, 21.13; S, 9.67%.

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