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CONDENSED PYRIDOPYRIMIDINES.
1. SYNTHESIS OF NEW DERIVATIVES OF PYRANO[3',4':5,6]PYRIDO[2,3-*d*]PYRIMIDINES

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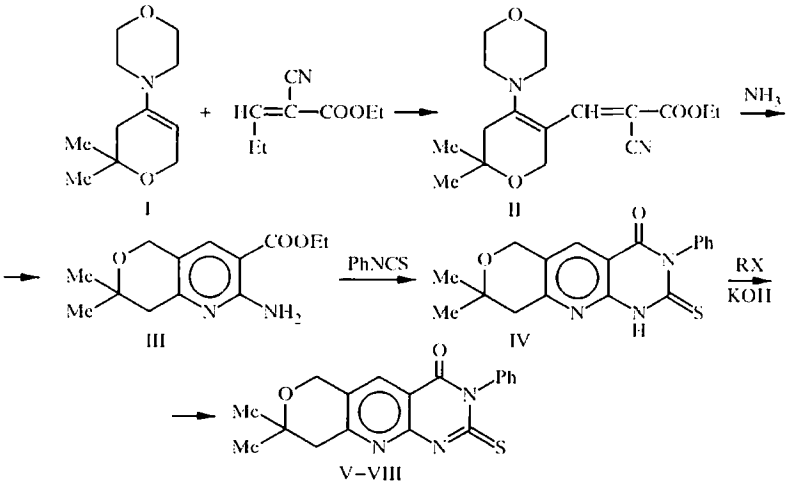
New derivatives of pyrano[3',4':5,6]pyrido[2,3-d]pyrimidines were synthesized from ethyl 2-amino-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carboxylate.

The condensed system of pyran and pyridine can be regarded as an analog of naphthyridine, the structure of which forms the basis of many substances with strong biological activity [1, 2]. In the course of investigations in the present work we synthesized new representatives of the pyranopyridine system containing tetrahydropyran ring. The aim was achieved by the reaction of enamine obtained from 2,2-dimethyltetrahydropyran-4-one and morpholine [3] with ethyl ethoxymethylenecyanoacetate, resulting in formation of ethyl 2-cyano-3-(2,2-dimethyl-4-morpholino-3,6-dihydro-2H-pyran-5-yl)acrylate (II). The latter undergoes cyclization under the influence of an aqueous solution of ammonia to ethyl ester of the corresponding 2-aminopyrano[4,3-*b*]pyridine-3-carboxylic acid (III). When heated with phenyl isothiocyanate at 130°C the ester III gave the desired product – 8,8-dimethyl-4-oxo-3-phenyl-2-thioxo-2,3,4,6,8,9-hexahydro-1H-pyrano[3',4':5,6]pyrido[3,2-*d*]pyrimidine (IV). The reaction of the latter with various alkylating reagents in the presence of potassium hydroxide gave the corresponding S-alkyl derivatives V-VIII.



V R = Me; VI R = CH_2COOEt; VII R = CH_2–COPh; VIII R = CH_2CO–C₆H₄–Br

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EXPERIMENTAL

The IR spectra were recorded in vaseline oil on a UR-20 instrument, and the PMR spectra were obtained on a Varian T-60 instrument. Thin-layer chromatography was carried out on Silufol UV-254 plates with iodine vapor as developer.

Ethyl 2-cyano-3-(2,2-Dimethyl-4-morpholino-3,6-dihydro-2H-pyran-5-yl)acrylate (II). To solution of the enamine I [3] (19.8 g, 0.1 mol) in THF (40 ml) at room temperature with stirring we added in portions solution of ethyl ethoxymethylenecyanoacetate (16.9 g, 0.1 mol) in THF (60 ml). The mixture was left overnight. After distillation of the solvent 20 ml of cold absolute ethanol were added to the viscous mass. The precipitated crystals were filtered off, recrystallized from absolute ethanol, and dried. Yield of compound II 24.0 g (75%); mp 135-136°C; R_f 0.60 (1:1:1 benzene–ether–methanol). IR spectrum, cm^{-1}: 2210 (C≡N); 1700 (C=O); 1620 (C=C). PMR spectrum, $CDCl_3$ (δ, ppm): 7.96 (1H, s, =CH); 4.73 (2H, s, 6-CH_2); 4.22 (2H, t, J = 7 Hz, COO$\underline{CH_2}CH_3$); 3.80 (4H, m, –CH_2–O–CH_2–); 3.33 (4H, m, –CH_2–N–CH_2–); 2.50 (2H, s, 3-CH_2); 1.33 (3H, t, J = 7 Hz, COO$\underline{CH_2}CH_3$); 1.26 (6H, s, 2-$(CH_3)_2$). Found, %: C 63.50; H 7.19; N 8.45. $C_{17}H_{24}N_2O_4$. Calculated, %: C 63.75; H 7.50; N 8.75.

Ethyl 2-Amino-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine-3-carboxylate (III). To solution of the ester II (3.2 g, 0.01 mol) in THF (15 ml) we added 25% aqueous solution of ammonia (10 ml). The mixture was heated in closed round-bottomed flask at 50-55°C for 6 h. After distillation of THF the crystals that separated were filtered off, washed with water, and recrystallized from ethanol. Yield of compound III 1.8 g (75%); mp 132-133°C (ethanol); R_f 0.56 (1:1 benzene–ether). IR spectrum, cm^{-1}: 3430, 3280, 3140 (NH_2); 1690 (C=O); 1600 (arom.). PMR spectrum, $CDCl_3$ (δ, ppm): 7.80 (1H, s, 4-CH); 6.53 (2H, bs, NH_2); 4.71 (2H, s, 5-CH_2); 4.42 (2H, t, J = 7 Hz, COO$\underline{CH_2}CH_3$); 2.85 (2H, s, 8-CH_2); 1.30 (3H, t, J = 7 Hz, COO$CH_2\underline{CH_3}$); 1.26 (6H, s, 7-$(CH_3)_2$). Found, %: C 62.12; H 6.93; N 11.45. $C_{13}H_{18}N_2O_3$. Calculated, %: C 62.40; H 7.24; N 11.19.

8,8-Dimethyl-4-oxo-3-phenyl-2-thioxo-2,3,4,6,8,9-hexahydro-1H-pyrano[3',4':5,6]pyrido[2,3-*d*]-pyrimidine (IV). Mixture of compound III (2.5 g, 0.01 mol) and phenyl isothiocyanate (4 ml) was kept at 130°C for 7 h. After cooling 5 ml of ethanol were added to the viscous mass. The precipitated crystals were filtered off, washed with ether, recrystallized from ethanol, and dried. Yield of compound IV 2.9 g (85.5%); mp 290-292°C; R_f 0.58 (1:2 pyridine–ether). IR spectrum, cm^{-1}: 1680 (C=O); 3200-3400 (NH). PMR spectrum, pyridine-d_5 (δ, ppm): 8.20 (1H, s, 5-CH); 7.22-7.70 (5H, m, C_6H_5); 5.0 (2H, s, S-CH_2); 3.10 (2H, s, 9-CH_2); 1.32 (6H, s, 8-$(CH_3)_2$). Found, %: C 62.80; H 5.09; N 11.96; S 9.32. $C_{18}H_{17}N_3O_2S$. Calculated, %: C 63.70; H 5.01; N 12.39; S 9.44.

8,8-Dimethyl-2-methylthio-4-oxo-3-phenyl-4,6,8,9-tetrahydro-3H-pyrano[3',4':5,6]pyrido[2,3-*d*]-pyrimidine (V). To solution of compound IV (3.39 g, 0.01 mol) and potassium hydroxide (0.56 g, 0.01 mol) in 90% ethanol (20 ml), heated to 40°C, we added dropwise with stirring methyl iodide (1.42 g, 0.01 mol) in ethanol (5 ml). The precipitated crystals were filtered off, washed with water and with ether, and recrystallized from ethanol. Yield of compound V 3.0 g (87%); mp 215-217°C (ethanol); R_f 0.54 (1:3 methanol–ether). PMR spectrum, pyridine-d_5 (δ, ppm): 8.02 (1H, s, 5-CH); 7.25-7.60 (5H, m, C_6H_5); 4.82 (2H, s, 6-CH_2); 3.04 (2H, s, 9-CH_2); 2.50 (3H, s, S-CH_3); 1.32 (6H, s, 8-$(CH_3)_2$). Found, %: C 64.41; H 5.61; N 11.56; S 9.42. $C_{19}H_{19}N_3O_2S$. Calculated, %: C 64.58; H 5.38; N 11.89; S 9.06.

Ethyl (8,8-Dimethyl-4-oxo-3-phenyl-4,6,8,9-tetrahydro-3H-pyrano[3',4':5,6]pyrido[2,3-*d*]pyrimidin-2-ylthio)acetate (VI). Compound VI was obtained from a mixture of the thione IV (0.01 mol) and ethyl chloroacetate (1.23 g, 0.01 mol) by the method described above. Yield 3.2 g (75%); mp 235-238°C (ethanol); R_f 0.62 (2:1 chloroform–benzene). IR spectrum, cm^{-1}: 1690 (C=O); 1720 (C=O). PMR spectrum, pyridine-d_5 (δ, ppm): 8.15 (1H, s, 5-CH); 7.20-7.70 (5H, m, C_6H_5); 4.82 (2H, s, 6-CH_2); 4.35 (2H, s, S-CH_2); 4.15 (2H, t, J = 7 Hz, O$\underline{CH_2}CH_3$); 3.0 (2H, s, 9-CH_2); 1.25 (6H, s, 8-$(CH_3)_2$); 1.12 (3H, t, J = 7 Hz, OCH_2CH_3). Found, %: C 62.44; H 5.08; N 10.20; S 7.64. $C_{22}H_{23}N_3O_4S$. Calculated, %: C 62.11; H 5.41; N 9.88; S 7.52.

2-Benzoylmethylthio-8,8-dimethyl-4-oxo-3-phenyl-4,6,8,9-tetrahydro-3H-pyrano[3',4':5,6]pyrido-[2,3-*d*]pyridine (VII). Compound VII was obtained from a mixture of the thione IV (0.01 mol) and phenacyl bromide (2.0 g, 0.01 mol) by the method described above. Yield 3.8 g (83.5%); mp 251-252°C (ethanol); R_f 0.56 (1:1:1 pyridine–benzene–ether). IR spectrum, cm^{-1}: 1680 (amide C=O); 1700 (C=O). PMR spectrum, pyridine-d_5

(δ, ppm): 8.12 (1H, s, 5-CH); 7.20-7.65 (5H, m, C_6H_5); 5.08 (2H, s, S-CH_2); 4.80 (2H, s, 6-CH_2); 2.98 (2H, s, 9-CH_2); 1.27 (6H, s, 8-$(CH_3)_2$). Found, %: C 68.42; H 4.98; N 9.42; S 7.15. $C_{26}H_{23}N_3O_3S$. Calculated, %: C 68.27; H 5.02; N 9.19; S 7.00.

2-(4-Bromobenzoylmethylthio)-8,8-dimethyl-4-oxo-3-phenyl-4,6,8,9-tetrahydro-3H-pyrano[3',4':5,6]-pyrido[2,3-*d*]pyrimidine (VIII). Compound VIII was obtained from a mixture of the thione IV (0.01 mol) and *para*-bromophenacyl bromide (2.78 g, 0.01 mol) by the method described above. Yield 4.6 g (88%); mp 245-247°C (ethanol); R_f 0.58 (1:1 pyridine–benzene). IR spectrum, cm^{-1}: 1680 (amide C=O); 1700 (C=O). PMR spectrum, $CDCl_3$ (δ, ppm): 8.10 (1H, s, 5-OH); 7.20-8.00 (9H, m, C_6H_5, C_6H_4); 4.82 (2H, s, 6-CH_2); 4.78 (2H, s, S-CH_2); 2.95 (2H, s, 9-CH_2); 1.30 (6H, s, 8-$(CH_3)_2$). Found, %: C 58.43; H 4.40; N 7.53; S 6.14. $C_{26}H_{22}BrN_3O_3S$. Calculated, %: C 58.20; H 4.10; N 7.83; 2 5.97.

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