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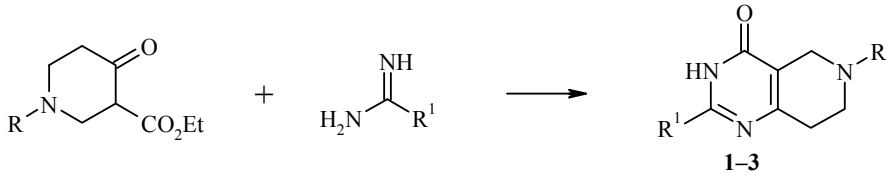
2-ALKYL-4-OXOHEXAHYDROPYRIMIDO[4,5-*d*]- AND -[5,4-*d*]AZOCINES

L. G. Voskressensky[1]*, M. V. Ovcharov[1], T. N. Borisova[1], L. N. Kulikova, A. V. Listratova[1], R. S. Borisov[1], and A. V. Varlamov[1]

It has been established that 2-R-4-oxotetrahydropyrido[4,3-d]pyrimidines, under the action of activated alkynes in methanol, form a mixture of 2-R-4-oxohexahydropyrimido[4,5-d]azocines and products of decomposition of the tetrahydropyridine ring, the 2-R-5-methoxymethyl-4-oxo-6-vinylaminoethyl-pyrimidines. Tetrahydropyrido[3,4-d]pyrimidine, isomeric at the junction of the pyrimidine and tetrahydropyridine rings, forms only the corresponding pyrimido[5,4-d]azocine, the product of expansion, under the action of methyl propiolate.

Keywords: activated alkyne, pyrimidoazocine, tandem expansion, tandem decomposition.

The synthesis of 2-methyl(phenyl)-4-oxotetrahydropyrimido[4,5-*d*]azocines were described for the first time by us in [1]. The reaction used for this was the expansion of the tetrahydropyridine ring in tetrahydropyrido[4,3-*d*]pyrimidines under the action of activated alkynes in methanol. Pyridopyrimidines with a methyl and phenyl groups in position 2 of the pyrimidine ring, and benzyl or methyl groups at the nitrogen atom of the tetrahydropyridine fragment have been studied. To determine the synthetic limits of the conversions indicated above it was necessary to establish the effect of the steric bulk of a substituent at the nitrogen atom of the hydrogenated pyridine fragment, the electronic effects of the substituents in position 2 of the pyrimidine fragment, and the order of joining the oxopyrimidine and tetrahydropyridine rings. For this purpose in the present work we have studied tandem conversions of 6-isopropyl-2-methyl- (**1**) and 6-isopropyl-2-phenyl-tetrahydropyrido[4,3-*d*] pyrimidines **2**, 6-benzyl-2-methylthiotetrahydropyrido[4,3-*d*]pyrimidine **3**, 6-benzyl-2-morpholinotetrahydropyrido[4,3-*d*]pyrimidine **4**, and 7-benzyl-2-morpholinotetrahydropyrido[3,4-*d*]pyrimidine **5**, which is isomeric at the ring junction.



1–3

1 R = *i*-Pr, R^1 = Me; **2** R = *i*-Pr, R^1 = Ph; **3** R = Bn, R^1 = SMe

Dedicated to L. I. Belen'kii on the occasion of his eightieth birthday.

* To whom correspondence should be addressed, e-mail: lvoskressensky@sci.pfu.edu.ru.

[1]Peoples' Friendship University of Russia, 6 Miklukho-Maklaya St., Moscow 117198, Russia.

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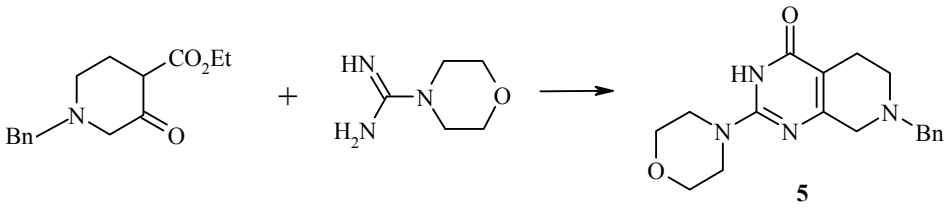
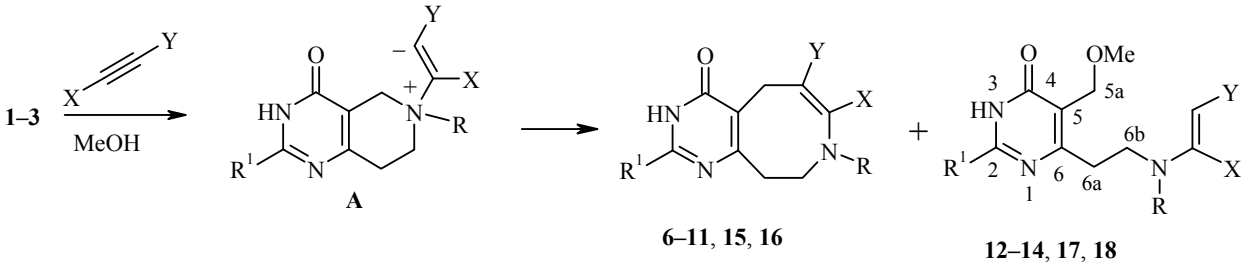


5

Pyridopyrimidines **1-3, 5** were obtained by the procedure reported in [2] from 3-ethoxycarbonyl-piperidin-4-ones, 4-ethoxycarbonylpiperidin-3-ones, and the appropriate amidines. Pyridopyrimidine **4** was synthesized from 2-methylthio-substituted compound **3** by the action of morpholine.

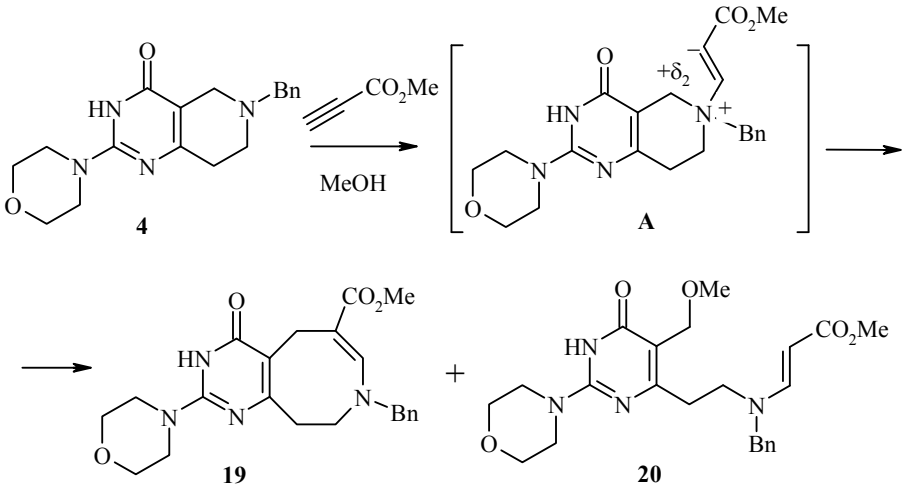
In the reaction of tetrahydropyridopyrimidines **1, 2** with methyl propiolate and acetylacetylene in methanol only the products of expanding the tetrahydropyridine ring were isolated, *viz*. hexahydropyrimido[4,5-*d*]azocines **6-9**, the yield of which when using compound **2** (65-73%) was approximately two times greater than from compound **1**. Reaction of compounds **1** and **2** with ADCE (acetylenedicarboxylic ester) was accompanied by the formation, in addition to the appropriate azocines **10** and **11**, of products of opening of the tetrahydropyridine ring, the methoxymethyl-substituted pyrimidines **12** and **13**. The yield of azocine **11** did not exceed 3%. From the reaction of 2-methylthio-substituted compound **3** with ADCE only 5-methoxymethyl-substituted pyrimidine **14** was isolated. On interacting compound **3** with methyl propiolate and acetylacetylene a mixture was formed of methoxymethyl-substituted pyrimidines **17, 18** and azocines **15, 16**, in which the latter predominated and their yields reached 65%.



A **6–11**, **15**, **16** **12–14**, **17**, **18**

6, **7** R = Pr-*i*, R^1 = Me, X = H, **6** Y = CO_2Me, **7** Y = COMe; **8**, **9** R = Pr-*i*, R^1 = Ph, X = H, **8** Y = CO_2Me, **9** Y = COMe; **10–13** R = Pr-*i*, X = Y = CO_2Me, **10**, **12** R^1 = Ph; **11, 13** R^1 = Me; **14–18** R = Bn, R^1 = SMe, **14** X = Y = CO_2Me, **15**, **17** X = H, Y = CO_2Me; **16, 18** X = H, Y = COMe

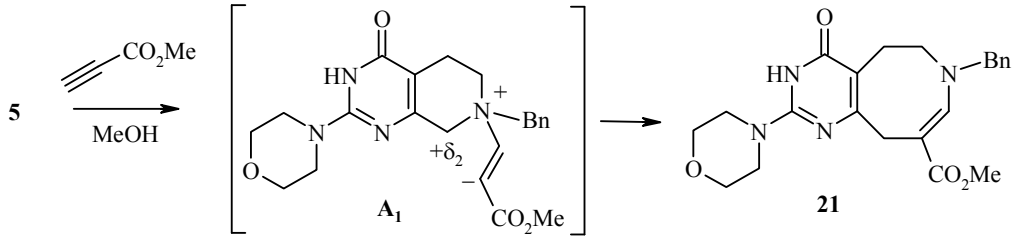
The tandem conversion reactions of tetrahydropyridopyrimidines proceed through the formation of ammonium zwitterion **A** [3].



4 **A** **19** **20**

The isomeric tetrahydropyrido[4,3-*d*]- and [3,4-*d*]pyrimidines **4** and **5** react with methyl propiolate in methanol equally readily. From pyridopyrimidine **4** a mixture was formed of pyrimido[4,5-*d*]azocine **19** and methoxymethylpyrimidine **20** in the ratio ~1:2.

Pyridopyrimidine **5,** isomeric at the junction of the pyrimidine and tetrahydropyridine rings, was converted almost quantitatively under these conditions into tetrahydropyrimido[5,4-*d*]azocine **21** (89% yield).



We assume that the difference in the course of the tandem conversions is caused by the different values of δ_2^+ at the methylene group in the intermediate zwitterions **A** and $\mathbf{A_1}$ (different ability of the pyrimidine fragment to delocalize this charge). Calculations of charges according to the expanded method of Huckel in the program *Chem Office 2006*, *Chem3D Ultra 10.0* showed that in the intermediate $\mathbf{A_1}$ δ_2^+ was equal to 0.027, and in **A** 0.016. Nucleophilic assistance by the solvent is necessary for the tandem conversions in the latter case, which was also observed experimentally.

Allowing for the data of [1] it may be proposed that the steric bulk of the substituent at the nitrogen of the tetrahydropyridine ring has practically no effect on the direction of its tandem transformations. This direction is determined mainly by electronic effects of substituents in the oxopyrimidine fragment and the order of its joining with tetrahydropyridine.

Bands were observed in the IR spectra of compounds **6-21** in the 1610-1701 cm^{-1} region for the stretching vibrations of the carbonyls of ester, amide, and keto groups. In the mass spectra there were peaks for molecular ions of various intensity corresponding to their empirical formula. The ^1H NMR spectra of pyrimidoazocines **7-10, 15, 16, 19, 21,** obtained by the action on pyridopyrimidines of terminal alkynes, are characterized by the presence of a singlet signal at 7.41-7.78 ppm, caused by the H-7 or H-8 (for **21**) proton of the enamine fragment of the azocine ring. In the spectra of pyrimidines **12-14** singlet signals in the 4.36-4.95 ppm region were caused by the terminal proton of the vinyl group. In the spectra of compounds **17, 18, 20** the terminal vinyl group causes the presence of two signals, a doublet at 7.56-7.68 (J = 13.0-13.1 Hz) and a broadened singlet in the 4.36-5.30 ppm region. The value of ^3J indicates the *trans* configuration of the vinyl group.

EXPERIMENTAL

The IR spectra were obtained on a Infralyum FT 801 Fourier spectrometer in KBr disks. The ^1H NMR spectra were recorded on a Bruker WP 400 (400 MHz) in $CDCl_3$ (compounds **1-4**) and DMSO-d_6 (compounds **6-8, 19-21**) and a Jeol JNM-ECA 600 (600 MHz) in $CDCl_3$ (compounds **9-18**) (Center for Collective Use, Russian Foreign Students University RUDN), internal standard was TMS. Chromatography / mass spectrometry analysis was carried out on a system comprising an Agilent 1100 liquid chromatograph, an Agilent Technologies LC/MSD VL (electrospraying, chemical ionization at atmospheric pressure), ELSD Sedex 75. High resolution mass spectra of compounds **15** and **17** were obtained on a JEOL JMS-T100LP-DART 100 instrument (DART ionization) (Center for Collective Use, Peoples' Friendship University of Russia). Thin-

layer chromatography was carried out on Silufol UV-254 or Sorbfile plates. Acros 60 Å silica gel was used for preparative chromatography (granule size 0.04-0.06 mm).

5,6,7,8-Tetrahydropyrido[4,3-*d*]pyrimidin-4-ones 1-3 (General Method). Acetamidine (benzamidine, or S-methylisothiouronium iodide) (0.05 mol) and K_2CO_3 (0.1 mol) were added to a solution of 3-ethoxycarbonylpiperidin-4-one hydrochloride (0.05 mol) in water (100 ml). The mixture was heated for 12 h at 60°C (check by TLC, Silufol, ethyl acetate–ethanol, 5:1). The precipitated solid was filtered off and recrystallized from ethyl acetate.

6-Isopropyl-2-methyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4(3H)-one (1). Yield 35%; mp 163-165°C. IR spectrum, ν, cm^{-1}: 1658 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (6H, d, *J* = 6.5 $(C\underline{H}_3)_2CH$); 2.44 (3H, s, 2-CH_3); 2.73-2.82 (4H, m, H-7,8); 2.96 (1H, sept, *J* = 6.5, $(CH_3)_2C\underline{H}$); 3.51 (2H, s, H-5); 12.88 (1H, br. s, NH). Found, %: C 63.66; H 8.36; N 20.13. $[M+H]^+$ 208. $C_{11}H_{17}N_30$. Calculated, %: C 63.74; H 8.27; N 20.27. M 207.

6-Isopropyl-2-phenyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4(3H)-one (2). Yield 58%; mp 199-201°C. IR spectrum, ν, cm^{-1}: 1641 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.19 (6H, d, *J* = 6.5, $(C\underline{H}_3)_2CH$); 2.79-2.92 (4H, m, H-7,8); 2.99 (1H, sept, *J* = 6.5, $(CH_3)_2C\underline{H}$); 3.62 (2H, s, H-5); 7.45-7.58 (3H, m, H Ph); 8.12 (2H, d, *J* = 6.9, H Ph). Found, %: C 71.43; H 7.31; N 15.58. $[M+H]^+$ 270. $C_{16}H_{19}N_3O$. Calculated, %: C 71.35; H 7.11; N 15.60. M 269.

6-Benzyl-2-methylthio-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4(3H)one (3). Yield 59%; mp 210-213°C (decomp.). IR spectrum, ν, cm^{-1}: 1642 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.53 (3H, s, CH_3S); 2.65-2.75 (4H, m, H-7,8); 3.47 (2H, s, H-5); 3.70 (2H, s, $C\underline{H}_2Ph$); 7.25-7.45 (5H, m, H Ph). Found, %: C 62.80; H 5.84; N 14.80. $[M+H]^+$ 288. $C_{15}H_{17}N_3OS$. Calculated, %: C 62.69; H 5.96; N 14.62. M 287.

6-Benzyl-2-(4-morpholino)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4(3H)-one (4). A solution of compound **3** (0.2 g, 0.69 mmol) and morpholine (1 ml) in dioxane (5 ml) was boiled for 32 h (check by TLC, Sorbfile, ethyl acetate). The mixture was cooled, and heptane (20 ml) was added. The solid was filtered off, washed with ether, and dried. Compound **4** (0.18 g, 79%) was obtained as colorless crystals; mp 230-232°C. IR spectrum, ν, cm^{-1}: 1645 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.60 (2H, t, *J* = 5.7, H-8); 2.71 (2H, t, *J* = 5.7, H-7); 3.28 (2H, br. s, H-5); 3.59-3.62 (4H, m, CH_2–N–CH_2); 3.64-3.69 (4H, m, CH_2–O–CH_2); 3.70 (2H, s, $C\underline{H}_2Ph$); 7.25-7.37 (5H, m, H Ph). Found, %: C 66.35; H 6.90; N 17.38. $[M+H]^+$ 327. $C_{18}H_{22}N_4O_2$. Calculated, %: C 66.24; H 6.79; N 17.13. M 326.

7-Benzyl-2-(4-morpholino)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4(3H)-one (5). A sample obtained by this method was given by "ASINEKS Medkhim" [4].

5,8,9,10-Tetrahydropyrimidin[4,5-*d*]azocin-4(3H)-ones 6-11, 15, 16, and 5-Methoxymethylpyrimidin-4(3H)-ones 12-14, **17**, **18 (General Method)**. ADCE, methyl propiolate, or acetylacetylene (1.0-1.16 mmol) was added to a solution of pyridopyrimidine **1-3** (0.2 g) in methanol (20 ml) at 20°C. At the end of the reaction (check by TLC, Silufol, chloroform–methanol, 9:1) the solvent was distilled in vacuum to 2 ml. The crystals of azocine were filtered off and recrystallized from ethyl acetate. If the crystals did not form the reaction mixture was evaporated to dryness, and the residue was chromatographed on silica gel in the system hexane–ethyl acetate, 20:1 to 3:1.

Methyl 8-Isopropyl-2-methyl-4-oxo-3,4,5,8,9,10-hexahydropyrimido[4,5-*d*]azocine-6-carboxylate (6). Yield 37%, colorless crystals; mp 220-222°C. IR spectrum, ν, cm^{-1}: 1646, 1648 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.38 (6H, d, *J* = 6.8, $(C\underline{H}_3)_2CH$); 2.38 (3H, s, 2-CH_3); 3.19 (2H, t, *J* = 6.8, H-10); 3.38 (1H, sept, *J* = 6.8, $(CH_3)_2C\underline{H}$); 3.66 (3H, s, OCH_3); 3.71 (2H, t, *J* = 6.8, H-9); 3.89 (2H, s, H-5); 7.49 (1H, s, H-7). Found, %: C 61.71; H 7.38; N 14.62. $[M+H]^+$ 292. $C_{15}H_{21}N_3O_3$. Calculated, %: C 61.84; H 7.27; N 14.42. M 291.

6-Acetyl-8-isopropyl-2-methyl-5,8,9,10-tetrahydropyrimido[4,5-*d*]azocin-4(3H)-one (7). Yield 30%, colorless crystals; mp 208-210°C. IR spectrum, ν, cm^{-1}: 1610, 1655 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (6H, d, *J* = 6.7, $(C\underline{H}_3)_2CH$); 2.29 (3H, s, CH_3CO); 2.34 (3H, s, 2-CH_3); 3.18 (2H, t, *J* = 6.5, H-10); 3.40

(1H, sept, J = 6.7, $(CH_3)_2C\underline{H}$); 3.71 (2H, t, J = 6.5, H-9); 3.86 (2H, s, H-5); 7.41 (1H, s, H-7). Found, %: C 65.31; H 7.44; N 15.46. $[M+H]^+$ 276. $C_{15}H_{21}N_3O_2$. Calculated, %: C 65.43; H 7.69; N 15.26. M 275.

Methyl 8-Isopropyl-4-oxo-2-phenyl-3,4,5,8,9,10-hexahydropyrimido[4,5-*d*]azocine-6-carboxylate (8). Yield 55%, light-yellow crystals; mp 253-255°C. IR spectrum, ν, cm^{-1}: 1642, 1697 (C=O). ^1H NMR spectrum, δ, ppm (J, Hz): 1.31 (6H, d, J = 6.7, $(C\underline{H}_3)_2CH$); 3.48 (2H, t, J = 6.6, H-10); 3.54 (1H, sept, J = 6.7, $(CH_3)_2C\underline{H}$); 3.74 (3H, s, CH_3O); 3.90 (2H, t, J = 6.6, H-9); 4.15 (2H, s, H-5); 7.65-7.75 (3H, m, H Ph); 7.78 (1H, s, H-7); 8.44 (2H, d, J = 7.8, H Ph). Found, %: C 68.09; H 6.66; N 11.63. $[M+H]^+$ 354. $C_{20}H_{23}N_3O_3$. Calculated, %: C 67.97; H 6.56; N 11.89. M 353.

6-Acetyl-8-isopropyl-2-phenyl-5,8,9,10-tetrahydropyrimido[4,5-*d*]azocin-4(3H)-one (9). Yield 24%, colorless crystals, mp 255-257°C (decomp.). IR spectrum, ν, cm^{-1}: 1632, 1697 (C=O). ^1H NMR spectrum, δ, ppm (J, Hz): 1.21 (6H, d, J = 6.7 $(C\underline{H}_3)_2CH$); 2.25 (3H, s, CH_3CO); 3.37 (2H, t, J = 6.7, H-10); 3.46 (1H, sept, J = 6.7, $(CH_3)_2C\underline{H}$); 3.80 (2H, t, J = 6.7, H-9); 4.01 (2H, s, H-5); 7.45 (1H, s, H-7); 7.55 (2H, t, J = 7.7, H Ph); 7.65 (1H, m, H Ph); 8.25 (2H, d, J = 7.7, H Ph). Found, %: C 71.31; H 6.77; N 12.61. $[M+H]^+$ 338. $C_{20}H_{23}N_3O_2$. Calculated, %: C 71.19; H 6.77; N 12.45. M 337.

Dimethyl 8-Isopropyl-4-oxo-2-phenyl-3,4,5,8,9,10-hexahydropyrimido[4,5-*d*]azocine-6,7-dicarboxylate (10). Yield 15%, yellow crystals; mp 248-250°C. IR spectrum, ν, cm^{-1}: 1648, 1690 (C=O). ^1H NMR spectrum, δ, ppm (J, Hz): 1.30 (6H, d, J = 6.8, $(C\underline{H}_3)_2CH$); 3.24 (2H, m, H-10); 3.38 (1H, br. s, $(CH_3)_2C\underline{H}$); 3.74 3H, s, OCH_3); 3.85 (2H, m, H-9); 3.95 (3H, s, OCH_3); 4.45 (2H, s, H-5); 7.64-7.66 (2H, m, H Ph); 7.76 (1H, m, H Ph); 8.42 (2H, m, H Ph). Found, %: C 64.37; H 6.05; N 10.45. $[M+H]^+$ 412. $C_{22}H_{25}N_3O_5$. Calculated, %: C 64.22; H 6.12; N 10.21. M 411.

Dimethyl 8-Isopropyl-2-methyl-4-oxo-3,4,5,8,9,10-hexahydropyrimido[4,5-*d*]azocine-6,7-dicarboxylate (11). Yield 3%, yellow crystals; mp 217-220°C. IR spectrum, ν, cm^{-1}: 1643, 1692 (C=O). ^1H NMR spectrum, δ, ppm (J, Hz): 1.32 (6H, d, J = 6.8, $(C\underline{H}_3)_2CH$); 2.37 (3H, s, 2-CH_3); 3.23 (2H, t, J = 6.5, H-10); 3.38 (1H, br. s, $(CH_3)_2C\underline{H}$); 3.70 (3H, s, OCH_3); 3.72 (2H, t, J = 6.5, H-9); 3.87 (2H, s, H-5); 3.90 (3H, s, OCH_3). Found, %: C 58.29; H 6.79; N 12.23. $[M+H]^+$ 350. $C_{17}H_{23}N_3O_5$. Calculated, %: C 58.44; H 6.64; N 12.03. M 349.

Dimethyl (2*E*)-2-(Isopropyl{2-[5-(methoxymethyl)-6-oxo-2-phenyl-1,6-dihydropyrimidin-4-yl]ethyl}-amino))but-2-enedioate (12). Yield 54%, yellow crystals; mp 195-197°C. IR spectrum, ν, cm^{-1}: 1646, 1696 (C=O). ^1H NMR spectrum, δ, ppm (J, Hz): 1.19 (6H, d, J = 6.8, $(C\underline{H}_3)_2CH$); 3.05 (2H, d, J = 6.7, H-6a); 3.40 (3H, s, OCH_3); 3.45 (1H, m, $(CH_3)_2C\underline{H}$); 3.50 (2H, t, J = 6.7, H-6b); 3.62 (3H, s, CO_2CH_3); 3.95 (3H, s, CO_2CH_3); 4.50 (2H, s, $C\underline{H}_2{-}OCH_3$); 5.15 (1H, s, $C{=}\underline{H}CCO_2CH_3$); 7.50-7.61 (3H, m, H Ph); 8.31 (2H, d, J = 6.9, H Ph). Found, %: C 62.46; H 6.33; N 9.31. $[M+H]^+$ 444. $C_{23}H_{29}N_3O_6$. Calculated, %: C 62.29; H 6.59; N 9.47. M 443.

Dimethyl (2*E*)-2-(Isopropyl{2-[5-(methoxymethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-4-yl]ethyl}-amino))but-2-enedioate (13). Yield 54%, yellow crystals; mp 146-148°C. IR spectrum, ν, cm^{-1}: 1650, 1701 (C=O). ^1H NMR spectrum, δ, ppm (J, Hz): 1.19 (6H, d, J = 6.8, $(C\underline{H}_3)_2CH$); 2.44 (3H, s, 2-CH_3); 2.88 (2H, t, J = 6.7, H-6a); 3.38 (2H, t, J = 6.7, H-6b); 3.40 (3H, s, OCH_3); 3.46 (1H, m, $(CH_3)_2C\underline{H}$); 3.59 (3H, s, CO_2CH_3); 3.92 (3H, s, CO_2CH_3); 4.37 (2H, s, $C\underline{H}_2{-}OCH_3$); 4.90 (1H, s, $C{=}C\underline{H}CO_2CH_3$). Found, %: C 56.81; H 7.25; N 11.25. $[M+H]^+$ 382. $C_{18}H_{27}N_3O_6$. Calculated, %: C 56.68; H 7.13; N 11.02. M 381.

Dimethyl (2*E*)-2-(Benzyl{2-[5-(methoxymethyl)-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-4-yl]-ethyl}amino))but-2-enedioate (14). Yield 91%, colorless crystals; mp 170-171°C. IR spectrum, ν, cm^{-1}: 1651, 1695 (C=O). ^1H NMR spectrum, δ, ppm (J, Hz): 2.45 (3H, s, SCH_3); 2.71 (2H, m, H-6a); 3.09 (3H, s, OCH_3); 3.18 (3H, s, CO_2CH_3); (2H, t, J = 7.4, H-6b); 3.80 (3H, s, CO_2CH_3); 4.16 (2H, s, $C\underline{H}_2Ph$); 4.36 (2H, s, $C\underline{H}_2{-}OCH_3$); 4.86 (1H, br. s, $C{=}C\underline{H}CO_2CH_3$); 7.26 (2H, d, J = 7.0, H Ph); 7.30 (1H, d, J = 7.3, H Ph); 7.37 (2H, t, J = 7.3, H Ph). Found, %: C 57.41; H 5.73; N 9.19. $[M+H]^+$ 462. $C_{22}H_{27}N_3O_6S$. Calculated, %: C 57.25; H 5.90; N 9.10. M 461.

Methyl 8-Benzyl-2-(methylthio)-4-oxo-3,4,5,8,9,10-hexahydropyrimido[4,5-*d*]azocine-6-carboxylate (15). Yield 65%, yellow crystals; mp 224-226°C. IR spectrum, ν, cm^{-1}: 1677 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (3H, s, SCH_3); 3.34 (2H, m, H-10); 3.55 (3H, s, CO_2CH_3); 3.75 (2H, m, H-9); 4.25 (2H, s, C$\underline{H}_2$Ph); 4.41 (2H, s, H-5); 7.12-7.13 (2H, m, H Ph); 7.28-7.29 (3H, m, H Ph); 7.35 (1H, s, H-7). Found, %: C 61.68; H 5.82; N 11.39. $[M+H]^+$ 372.1383. $C_{19}H_{21}N_3O_3S$. Calculated, %: C 61.44; H 5.70; N 11.31. $[M+H]^+$ 372.1376.

6-Acetyl-8-benzyl-2-(methylthio)-5,8,9,10-tetrahydropyrimido[4,5-*d*]azocin-4(3H)-one (16). Yield 58%, yellow crystals; mp 248-250°C. IR spectrum, ν, cm^{-1}: 1613, 1656 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.14 (3H, s, SCH_3); 2.34 (3H, s, $COCH_3$); 2.94 (2H, t, *J* = 6.3, 10-CH_2); 3.73-3.76 (4H, m, 5,9-CH_2); 4.46 (2H, s, C$\underline{H}_2$Ph); 7.15-7.17 (2H, m, H Ph); 7.25-7.32 (3H, m, H Ph); 7.60 (1H, s, H-7); 12.31 (1H, br. s, NH). Found, %: C 64.11; H 6.09; N 11.61. $[M+H]^+$ 356. $C_{19}H_{21}N_3O_2S$. Calculated, %: C 64.20; H 5.95; N 11.82. M 355.

Methyl (2*E*)-3-((Benzyl{2-[5-(methoxymethyl)-2-(methylthio)-6-oxo-1,6-dihydropyrimidin-4-yl]ethyl}-amino))acrylate (17). Yield 15%, yellow crystals; mp 169-171°C. IR spectrum, ν, cm^{-1}: 1651, 1670 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.48 (3H, s, SCH_3); 2.75 (2H, t, *J* = 7.4, H-6a); 3.27 (3H, s, OCH_3); 3.40-3.49 (2H, m, H-6b); 3.60 (3H, s, CO_2CH_3); 4.22 (2H, s, C$\underline{H}_2$Ph); 4.26 (2H, s, C$\underline{H}_2$OCH$_3$); 4.77 (1H, m, CH=C$\underline{H}$CO$_2$CH$_3$); 7.10-7.25 (2H, m, H Ph); 7.26-7.30 (3H, m, H Ph); 7.56 (1H, d, *J* = 13.0, C$\underline{H}$=CHCO$_2$CH$_3$). Found, %: C 59.75; H 6.30; N 10.28. $[M+H]^+$ 404.1646. $C_{20}H_{25}N_3O_4S$. Calculated, %: C 59.53; H 6.25; N 10.41. M 404.1648.

6-(2-{Benzyl[(1E)-3-oxobut-1-en-1-yl]amino}ethyl)-5-(methoxymethyl)-2-(methylthio)pyrimidin-4(3H)-one (18). Yield 13%, yellow crystals; mp 172-174°C. IR spectrum, ν, cm^{-1}: 1611, 1650 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.11 (3H, s, $COCH_3$); 2.54 (3H, s, SCH_3); 2.79-2.85 (2H, m, H-6a); 3.34 (3H, s, OCH_3); 3.44-3.62 (2H, m, H-6b); 4.31 (2H, s, C$\underline{H}_2$Ph); 4.37 (2H, s, C$\underline{H}_2$OCH$_3$); 5.24-5.41 (1H, br. s, CH=C$\underline{H}$CO$_2$CH$_3$); 7.19 (2H, d, *J* = 7.3, H Ph); 7.28-7.36 (3H, m, H Ph); 7.68 (1H, d, *J* = 13.0, C$\underline{H}$=CHCO$_2$CH$_3$). Found, %: C 61.84; H 6.43; N 10.64. $[M+H]^+$ 388. $C_{20}H_{25}N_3O_3S$. Calculated, %: C 61.99; H 6.50; N 10.84. M 387.

Methyl 8-Benzyl-2-morpholino-4-oxo-3,4,5,8,9,10-hexahydropyrimido[4,5-*d*]azocine-6-carboxylate (19) and Methyl (2*E*)-3-(Benzyl{2-[5-(methoxymethyl)-2-morpholino-6-oxo-1,6-dihydropyrimidin-4-yl]ethyl}-amino)acrylate (20). A suspension of pyridopyrimidine **4** (0.15 g, 0.46 mmol) and methyl propiolate (0.048 ml, 0.55 mmol) in methanol (10 ml) was boiled for 2 h (check by TLC, Silufol, methanol–chloroform, 9:1). The precipitated crystals (0.065 g) of azocine **19** were filtered off, yield was 35%; mp 290-295°C. IR spectrum, ν, cm^{-1}: 1645, 1687 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.23-3.32 (2H, m, H-10); 3.42-3.48 (4H, m, CH_2NCH_2); 3.54 (3H, s, CO_2CH_3); 3.59-3.69 (4H, m, CH_2OCH_2); 3.68-3.75 (4H, m, H-5,9); 4.39 (2H, s, C$\underline{H}_2$Ph); 7.12-7.18 (2H, m, H Ph); 7.24-7.32 (3H, m, H Ph); 7.50 (1H, s, H-7); Found, %: C 64.48; H 6.22; N 13.25. $[M+H]^+$ 411. $C_{22}H_{26}N_4O_4$. Calculated, %: C 64.37; H 6.38; N 13.65. M 410.

The filtrate was evaporated to dryness and the crystals were washed with ether. Pyrimidine **20** (0.12 g, 60%) was obtained; mp 208-210°C. IR spectrum, ν, cm^{-1}: 1640, 1683 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.74 (2H, t, *J* = 7.3, H-6a); 3.29 (3H, s, OCH_3); 3.47 (2H, m, H-6b); 3.66 (3H, s, CO_2CH_3); 3.70 (4H, m, CH_2NCH_2); 3.76 (4H, m, CH_2OCH_2); 4.21 (2H, s, C$\underline{H}_2$Ph); 4.34 (2H, s, C$\underline{H}_2$OCH$_3$); 4.81 (1H, br. s, CH=C$\underline{H}$CO$_2$CH$_3$); 7.17-7.21 (2H, m, H Ph); 7.27-7.35 (3H, m, H Ph); 7.50 (1H, s, H-7); 7.62 (1H, d, *J* = 13.1, C$\underline{H}$=CHCO$_2$CH$_3$). Found, %: C 62.29; H 6.71; N 12.72. $[M+H]^+$ 443. $C_{23}H_{30}N_4O_5$. Calculated, %: C 62.43; H 6.83; N 12.66. M 442.

Methyl 7-Benzyl-2-morpholino-4-oxo-3,4,5,6,7,10-hexahydropyrimido[5,4-*d*]azocine-9-carboxylate (21) was obtained analogously to azocine **19** on boiling pyridopyrimidine **5** (0.2 g, 0.61 mmol) and methyl propiolate (0.065 ml, 0.74 mmol) in methanol (10 ml). Yield 0.22 g (89%), colorless crystals; mp 292-294°C (decomp.). IR spectrum, ν, cm^{-1}: 1642, 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.87 (2H, m, 10-CH_2);

3.40-3.60 (8H, m, $4CH_2$ morpholine); 3.62 (3H, s, CO_2CH_3); 3.65-3.80 (4H, m, H-5,6); 4.39 (2H, s, $\underline{CH_2}$Ph; 7.09-7.22 (2H, m, H Ph); 7.27-7.42 (3H, m, H Ph); 7.50 (1H, br. s, H-8). Found, %: C 64.20; H 6.19; N 13.53. $[M+H]^+$ 411. $C_{22}H_{26}N_4O_4$. Calculated, %: C 64.37; H 6.38; N 13.65. M 410.

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