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SYNTHESIS OF BICYCLIC PYRIMIDO[2,1-*b*][1,3]THIAZINES BASED ON 3,4-DIHYDROPYRIMIDINE-(1H)-2-THIONES

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Bicyclic pyrimido[2,1-b][1,3]thiazines were produced by the acylation of 4-aryl-substituted 3,4-dihydropyrimidine(1H)-2-thiones with 3-bromopropionyl chloride, and their structures were proved by the data from X-ray crystallographic analysis.

Keywords: 3,4-dihydropyrimidine(1H)-2-thiones, pyrimidino[2,1-*b*][1,3]thiazines, 3-bromopropionyl chloride, intramolecular heterocyclization, X-ray crystallographic analysis.

Today an enormous number of derivatives of 3,4-dihydropyrimidin-2-ones(2-thiones) with various aromatic and heterocyclic functional substituents have been synthesized by the Biginelli reaction, numerous methods including microwave and solvent-free methods have been developed for their production, and highly effective catalysts leading to a significant increase in the yields and reduction of the time for the condensation have been found [1-7]. Many researches on the synthesis and subsequent modification of derivatives of 3,4-dihydropyrimidin(1H)-2-ones have continued in many countries with developed pharmaceutical industry; this is due to the fact that they display of a wide range of pharmacological activity – antihypertensive, antibacterial, antiviral, antitumor, etc. [8-10], making further searches in the 3,4-dihydro-pyrimidin-2-one-(2-thione) series extremely promising.

In [11] we proposed a convenient method for the synthesis of new derivatives of bicyclic 3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidines from 3,4-dihydropyrimidine-2-thiones, established their stereochemical structure, and studied the conditions for cyclization with various haloacetyl reagents [12]. In an attempt to produce bicyclic thiazine derivatives based on 4-aryl-substituted 3,4-dihydropyrimidine-2-thiones the acylation of 4-aryl-substituted 3,4-dihydropyrimidine-2-thiones **1a-c** with 3-bromopropionyl chlorides according to the Scheme was realized. (Compounds **1a-c** are shown in a thiol tautomer form.)

Acylation was conducted in solution of anhydrous DMF in the presence of a twofold excess of potassium carbonate with the reaction mixture heated from 25 to 120°C for 6-10 h. Here, as expected, the heterocyclization products **2a-c** in the form of slightly yellowish crystalline substances were isolated. The most

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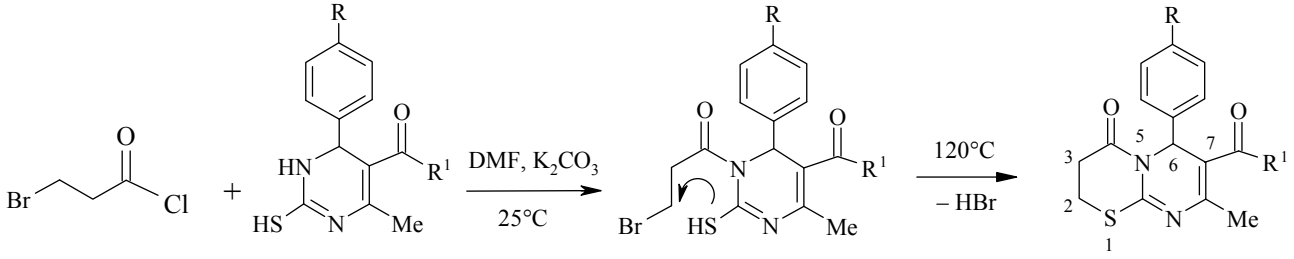
acceptable yields of compounds **2a-c** were obtained when a 1.5-fold excess of 3-bromopropionyl chloride was used. Realization of the reaction at a lower temperature (60-70°C) with an equimolar amount of the acid chloride led to isolation not of the intermediate acylation products but mainly of the original 3,4-dihydro-pyrimidine-2-thiones **1a-c**.



1 a–c **2 a–c**

a R = OMe, R^1 = OEt; **b** R = OMe, R^1 = Me; **c** R = F, R^1 = OEt

In this case the pyrimido[2,1-*b*][1,3]thiazines **2a-c** are formed, as described earlier in [12], according to the general principles of the theory of hard and soft acids and bases, with initial acylation of the N(3) atom followed by intramolecular alkylation of the thiol fragment and closure to a thiazine ring.

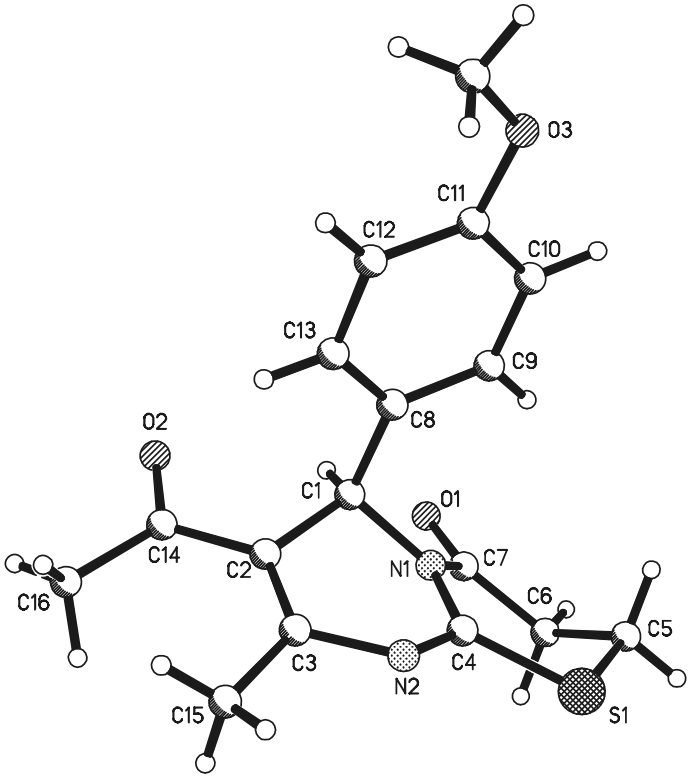


Fig. 1. The spatial structure of the molecule of 7-acetyl-6-(4-methoxyphenyl)-8-methyl-2,3-dihydropyrimido[2,1-*b*][1,3]thiazin-4(6H)-one (**2b**).

The formation of the pyrimido[2,1-*b*][1,3]thiazines **2a-c** was proved by the absence of the stretching vibrations of the amino group in the IR spectra and also by the absence in the ^{1}H NMR spectra of signals for the N(3)–H protons, which appear in the initial compounds in the form of doublets at 9.2 ppm. The signals for the methylene protons of the thiazine ring are complex multiplets centered in the region of 3.04 ppm.

In order to establish the three-dimensional structure of the synthesized bicyclic pyrimido[2,1-*b*][1,3]thiazines and their possible differences from our previously synthesized structurally similar bicyclic 3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidines we undertook an X-ray structural investigation of compound **2b** (Fig. 1).

The bond lengths and valence angles in structure **2b** are close to the standard values [13]. The thiazine ring N(1)C(4)S(1)C(5)C(6)C(7) assumes a distorted 5,6-*half-chair* conformation with $\Delta C_2^{5,6}$ = 6.55 Å. In our opinion the distortion occurs on account of the presence of the heavier sulfur atom in the ring, and the carbonyl O(1) atom is in the equatorial position and lies in the C(4)N(1)C(7)C(6) plane. The pyrimidine ring assumes the conformation of a strongly distorted *boat half-chair* with $\Delta C_2^{C(1)N(1)}$ = 19.57, as also in the structure of 5-nitro-4-(2-nitrophenyl)-6-phenyl-3,4-dihydro(1H)-pyrimidin-2-one [14], although in our previously studied molecule of ethyl 5-(2,4-dimethoxyphenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidine-6-carboxylate [11] the ring is in a *flattened sofa* conformation. Such a difference in our opinion depends on the presence and position of the bulky substituent at the C(1) atom, which in the first case is turned through 24.3°, while the rotation of the 2,4-dimethoxyphenyl substituent in the second case amounted to 68.6° in relation to the main framework.

The 4-methoxyphenyl group is in the axial orientation to the main skeleton of the molecule (torsional angle C(7)N(1)C(1)C(8) -106.31°). The methoxy group lies in the plane of the benzene ring. The methyl group and aceto group are in the equatorial orientation in relation to the pyrimidine ring.

EXPERIMENTAL

The IR spectra (KBr) were recorded on an AVATAR-320 Fourier spectrometer. The ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker DRX500 instrument (500 MHz) with TMS as internal standard. The mass spectra were obtained on a Finnigan MAT Incos 50 instrument with direct injection into the ion source and ionization energy 70 eV. The reactions and the purity of the obtained compounds were monitored by TLC on Sorbfil plates. The 3-bromopropionyl chloride was the commercial product from Aldrich and was used without further purification. The initial 3,4-dihydropyrimidine(1H)-2-thiones **1a-c** were prepared by the three-component condensation of the respective aldehydes, acetoacetic ester (for compounds **1a**,**b**), acetylacetone (for compound **1c**), and thiourea by boiling in DMF according to the procedure described in [15].

X-Ray Crystallographic Experiment. The cell parameters and the intensities of 3715 unique reflections of compound **2b** were measured at -100°C on a Bruker APEX-II CCD automatic four-circle diffractometer with a graphite monochromator using MoKα radiation (θ/2θ scan, 2θ < 56°). Yellow crystals (0.15×0.40×0.60 mm), monoclinic, a = 8.572(2), b = 9.919(3), c = 18.399(6), V = 1557.4(8) Å^3, d_{calc} = 1.409 g/cm^3, Z = 4 ($C_{17}H_{18}N_20_30_3S$). Space group $P2(1)/n$.

In the calculations we used 3283 reflections with intensity $I > 2\sigma$. The structure was interpreted by the direct method with SHELXS-97 software [16] and was refined by full-matrix least-squares treatment in anisotropic approximation for the non-hydrogen atoms. The H atoms were revealed from an electron density difference synthesis. The final divergence factors were R = 0.0315, wR_2 = 0.0829. The geometry was refined with SHELXL-97 software [16]. The structural data have been deposited at the Cambridge structural data bank (CCDC 752521).

Ethyl 6-(4-Methoxyphenyl)-8-methyl-4-oxo-2,3,4,6-tetrahydropyrimido[2,1-*b*][1,3]thiazine-7-carboxylate (2a). To a solution of 4-(4-methoxyphenyl)-3,4-dihydropyrimidine(1H)-2-thione (**1a**) (1.53 g, 5.0 mmol) in DMF (3 ml) we added K_2CO_3 (1.38 g, 10.0 mmol). With vigorous stirring at room temperature over 30 min we added dropwise 3-bromopropionyl chloride (1.28 g, 7.5 mmol). The mixture was stirred for a further 6-8 h while the temperature was gradually increased to 120°C. The mixture was cooled, 100 ml of iced water was added to the suspension, and the light-pink precipitate was filtered off, washed several times with water, and

dried. We obtained 1.26 g (70%) of compound **2a**, which after threefold recrystallization from a 1:1 mixture of 2-propanol and hexane formed transparent light-yellow crystals, mp 147-148°C. IR spectrum, ν, cm^{-1}: 1705 (C=O), 1612 (C=O), 1503 (C=N), 1240 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.29 (3H, s, CH_3); 3.72 (3H, s, OCH_3); 3.05 (4H, m, $2CH_2$); 4.09 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 6.56 (H, s, H-6); 6.88 and 7.11 (4H, two d, *J* = 8.7, H arom). Found, %: C 60.39; H 5.17; N 8.14. $C_{18}H_{20}N_2O_4S$. Calculated, %: C 59.98; H 5.59; N 7.77.

7-Acetyl-6-(4-methoxyphenyl)-8-methyl--2,3-dihydropyrimido[2,1-*b*][1,3]thiazin-4(6H)-one (2b). This compound was obtained similarly to compound **2a** from 4-(4-methoxyphenyl)-3,4-dihydropyrimidine(1H)-2-thione (**1b**) (2.76 g, 10.0 mmol), K_2CO_3 (2.76 g, 20 mmol), and 3-bromopropionyl chloride (2.57 g, 15.0 mmol). The yield of compound **2b** was 2.08 g (63%); after twofold recrystallization from a 5:1:1 mixture of 2-propanol, benzene, and hexane it formed light-yellow rhombic crystals, mp 155-156°C. IR spectrum, ν, cm^{-1}: 1706 (C=0), 1632 (C=0), 1509 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.27 (3H, s, CH_3); 2.31 (3H, s, $C(O)CH_3$); 3.04 (4H, m, $2CH_2$); 3.71 (3H, s, OCH_3); 6.67 (H, s, H-6); 6.88 and 7.10 (4H, two d, *J* = 8.7, H arom.). Mass spectrum, *m/z* (I_{rel}, %): 330 $[M]^+$ (8.3), 287 (15.5), 233 (41.7), 169 (15.1), 55 (56), 43 (100). Found, %: C 62.19; H 5.17; N 8.83. $C_{17}H_{18}N_2O_3S$. Calculated, %: C 61.80; H 5.49; N 8.48.

Ethyl 6-(4-Fluorophenyl)-8-methyl-4-oxo-2,3,4,6-tetrahydropyrimido[2,1-*b*][1,3]thiazine-7-carboxylate (2c). This compound was obtained similarly to compound **2a** from 4-(4-fluorophenyl)-3,4-dihydropyrimidine(1H)-2-thione (**1c**) (1.47 g, 5.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and 3-bromopropionyl chloride (1.28 g, 7.5 mmol). The yield of compound **2c** was 1.01 g (58%); after twofold recrystallization from a 1:1 mixture of 2-propanol and hexane it formed yellow-green crystals, mp 175-177°C. IR spectrum, ν, cm^{-1}: 1703 (C=O), 1610 (C=O), 1512 (C=N), 1233 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.30 (3H, s, CH_3); 3.06 (4H, m, $2CH_2$); 4.10 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 6.60 (1H, s, H-6); 7.17 (2H, t, *J* = 8.8, H arom.); 7.24 (2H, q, *J* = 5.5, H arom.). Mass spectrum, *m/z* (I_{rel}, %): 348 $[M]^+$ (2.1), 253 (15.2), 221 (17.5), 199 (30.6), 95 (17.4), 86 (18.1), 67 (42.4), 60 (17.6), 55 (100), 42 (19.3). Found, %: C 58.94; H 5.17; N 8.37. $C_{17}H_{17}FN_2O_3S$. Calculated, %: C 58.61; H 4.92; N 8.04.

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