SYNTHESIS OF 11-BROMO-9-METHYL-6-METHYLENE-3-METHYLTHIO-5,6,9,10-TETRAHYDRO-8H-[1,2,4]TRIAZOLO[3',4':3,4]-PYRAZINO[1,2-*c*]PYRIMIDINE-8,10-DIONE FROM 4-ALLYL-1-(3-METHYL-2,4-DIOXO-1,2,3,4-TETRAHYDRO-6-PYRIMIDINYLCARBONYL)THIOSEMICARBAZIDE

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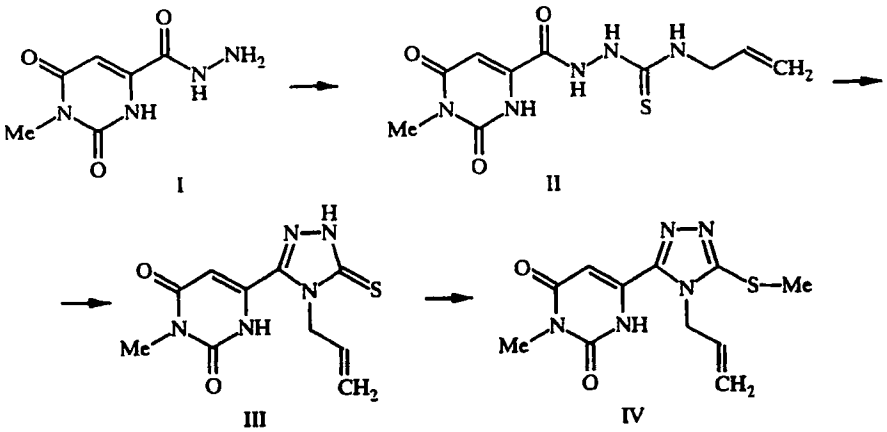
4-Allyl-1-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-6-pyrimidinylcarbonyl)thiosemicarbazide is cyclized in alkaline medium into 4-allyl-3-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-6-pyrimidinyl)-1,2,4-triazoline-3-thione, which is converted on alkylation with iodomethane into the methylthio derivative. Reaction of the latter with bromine occurs with formation of 3-(5-bromo-3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-6-pyrimidinyl)-4-(2,3-dibromopropyl)-5-methylthio-1,2,4-triazole, dehydrobromination of which with potassium carbonate leads to formation of the first representative of a new heterocyclic system, viz. 11-bromo-9-methyl-6-methylene-3-methylthio-5,6,9,10-tetrahydro-8H-[1,2,4]triazolo[3',4':3,4]pyrazino[1,2-c]pyrimidine-8,10-dione.

Azoles and azines containing allyl group and a nucleophilic grouping (OH, SH, NH_2) located ortho to it, are converted under the action of halogen (Br_2 or I_2) into condensed bicyclic systems [1-5]. It seemed expedient to us to test this method to construct tricyclic condensed systems based on pyrimidine, representatives of which may be of interest for biological testing. For this it is necessary to have an uncondensed bicyclic compound one ring of which should contain allyl grouping and the other - a nucleophilic atom. We selected 4-allyl-3-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-6-pyrimidinyl)-5-methylthio-1,2,4-triazole (IV) as such an intermediate compound. It was obtained from the hydrazide of 1-methylorotic acid (I) [6].



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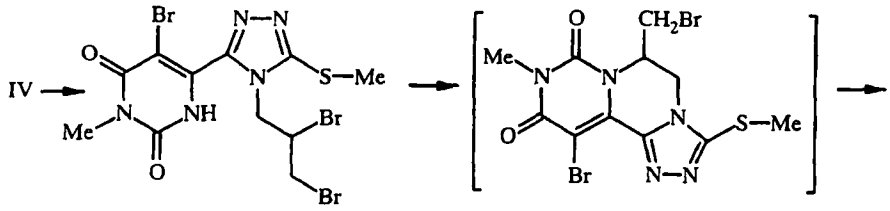
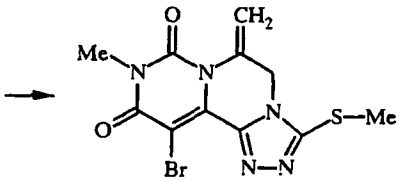
Thiosemicarbazide II was obtained by heating the hydrazide I with allyl isothiocyanate in absolute dimethylformamide and was converted by cyclization with alkali into 4-allyl-3-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-6-pyrimidinyl)-1,2,4-triazoline-3-thione (III). Compound III has two nucleophilic centers theoretically able to react with halogenated allyl group, viz. the sulfur atom on position 5 of the triazole ring and the nitrogen atom at position 1 of the pyrimidine ring. Compound II was converted into the methyl derivative IV by the action of iodomethane in the presence of sodium methoxide in order to prevent undesired reaction at the sulfur atom. The bromination of compound IV was studied in various solvents (chloroform, methanol, acetic acid) and under various conditions (reactant ratio, temperature, duration). The best yields were obtained on carrying out the bromination in acetic acid at 18-20°C and using a double quantity of bromine. In all cases electrophilic substitution at position 5 of the pyrimidine ring occurred together with addition of bromine to the double bond of the allyl group.



V

VI



VII

Dehydrobromination of compound V was accomplished using potassium carbonate in absolute dimethylformamide or absolute ethanol. It was not possible to isolate the intermediate bromomethyl derivative VI, since after ring closure elimination of second HBr molecule probably occurs with the formation of methylene derivative VII. Higher yields of compound VII were achieved on using the protic solvent ethanol. The IR spectra of compounds II-V and VII contained strong bands assigned to the stretching vibrations of lactams $C_{(2)}$=O and $C_{(4)}$=O of the pyrimidine ring at 1710-1728 and 1640-1672 cm^{-1} respectively. Absorption bands were observed in the IR spectrum of acylthiosemicarbazide II for amide C=O at 1700 cm^{-1} and for C=S at 1340 and 1544 cm^{-1}. In the spectrum of 1,2,4-triazolin-5-thione III the first band was absent and the second was observed at 1330 and 1528 cm^{-1}. The IR spectra of compounds IV, V, and VII contained absorption bands for C-S-C at 1280-1300 cm^{-1} characteristic of alkylated 1,2,4-triazolin-5-thiones [7]. Absorption bands in the IR spectra of compounds II-V at 3175-3325 cm^{-1} were assigned to the stretching vibrations of the N—H bond. There were no vibrations of this bond in the spectrum of compound VII.

In the PMR spectra of compounds II-IV signals for the protons of the main groups (3-CH_3, 5-CH, allyl fragment, SCH_3) were observed. On going to the bromo derivative V the pyrimidine $H_{(5)}$ proton signal disappeared. In the spectrum of compound VII the methylene group protons gave two signals due to the anisotropic effect of the oxo group double bond.

A peak was observed in the mass spectrum of compound VII for the molecular ion, the *m/z* value of which corresponded with the calculated value.

EXPERIMENTAL

The IR spectra were drawn on a Specord M 80 spectrometer (in Nujol), and the PMR spectra were taken on a Tesla BS 487 C (80 MHz) instrument, internal standard was HMDSO. The mass spectrum was taken on a

Varian MAT 112 spectrometer over the range of 35-400 *m/z*, ionization was accomplished by electron impact of 80 eV, and the heating temperature was up to 150°C.

A check on the progress of reactions and the purity of compounds was carried out on Silufol UV 254 plates.

1-Methylorotic Acid Hydrazide (I) was synthesized according to [6]. PMR spectrum (CF_3COOH): 3.0 (3H, s, CH_3); 6.35 ppm (1H, s, 5-H).

4-Allyl-1-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-6-pyrimidinylcarbonyl)thiosemicarbazide (II). Hydrazide I (1.84 g, 0.01 mole) was dissolved in absolute dimethyl-formamide (100 ml); freshly distilled allyl isothio-cyanate (1.98 g, 0.02 mole) was added, and the mixture was heated on an oil bath at 85-90°C for 1 h. Dimethylformamide was distilled off in vacuum. The residue was washed with ether, and dried. Thiosemicarbazide II (2.7 g, 95%) was obtained. Mp 202-204°C (from DMF/H_2O), R_f 0.46 (ethyl acetate – methanol, 5:1). IR spectrum: 3175-3325 (NH), 1720, 1700, 1648 (C=O), 1544, 1340 cm^{-1} (C=S). PMR spectrum (CF_3COOH): 3.0 (3H, s, CH_3); 3.8 (4H, m, NCH_2, $=CH_2$); 5.0 (1H, m, CH); 6.35 ppm (1H, s, 5-H). Found, %: C 42.34; H 4.49; N 24.53. $C_{10}H_{13}N_5O_3S$. Calculated, %: C 42.39; H 4.62; N 24.71.

4-Allyl-3-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-6-pyrimidinyl)-1,2,4-triazoline-3-thione (III). Thiosemicarbazide II (5.6 g, 0.019 mole) was dissolved in 10% potassium hydroxide solution (20 ml) and the mixture boiled for 4 h. Water (150 ml) was added to the solution, which was then acidified to pH 6 with dilute hydrochloric acid. The solid was filtered off, washed with water, and with ethanol, and dried. Compound III (4.7 g, 90%) was obtained. Mp 227.5-228.5°C (from ethanol), R_f 0.57 (ethyl acetate - ether, 1:1). IR spectrum: 3175 (NH), 1712, 1648 (C=O), 1528, 1330 cm^{-1} (C=S). PMR spectrum (CF_3COOH): 3.05 (3H, s, CH_3); 4.53 (2H, s, NCH_2); 4.9 (2H, m, $=CH_2$); 5.5 (1H, m, CH); 6.2 ppm (1H, s, 5-H). Found, %: C 45.19; H 4.26; N 26.12. $C_{10}H_{11}N_5O_2S$. Calculated, %: C 45.27; H 4.18; N 26.39.

4-Allyl-3-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-6-pyrimidinyl)-5-methylthio-1,2,4-triazole (IV). Compound III (6.72 g, 0.025 mole) was dissolved in sodium methoxide prepared from sodium (0.58 g, 0.025 mole) in absolute methanol (60 ml). Freshly distilled iodomethane (3.55 g, 1.57 ml, 0.025 mole) was added and the solution boiled for 9 h. Methanol was distilled off on a rotary evaporator. Ether (80 ml) was added to the residue. The solid was filtered off, dried, and crystallized from absolute ethanol. Yield was 5.16 g (73%). Mp 162-164°C, R_f 0.48 (ethyl acetate – methanol, 5:1). IR spectrum: 3175 (NH), 1710, 1640 (C=O), 1300 cm^{-1} (C-S-C). PMR spectrum (CF_3COOH): 2.55 (3H, s, SCH_3); 3.05 (3H, s, CH_3); 4.55 (2H, s, NCH_2); 5.03 (2H, m, $=CH_2$); 5.5 (1H, m, CH); 6.28 ppm (1H, s, 5-H). Found, %: C 47.44; H 4.71; N 24.67. $C_{11}H_{13}N_5O_2S$. Calculated, %: C 47.30; H 4.69; N 25.07.

3-(5-Bromo-3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-6-pyrimidinyl)-4-(2,3-dibromopropyl)-5-methylthio-1,2,4-triazole (V). Acetic acid (5 ml) containing bromine (1.44 g, 0.36 ml, 0.0072 mole) was added during 15 min to a solution of triazole IV (1.0 g, 0.0036 mole) in acetic acid (3 ml) at room temperature. The oily product solidified at the end of the reaction (15 min). Acetic acid was decanted into water (10 ml), and ethanol (10 ml) was added to the residue. The separated crystals were filtered, combined with the first crop, washed with ether, and triazole V (1.13 g, 61%) was obtained. Mp 216.5-218.5°C (from ethanol), R_f 0.75 (ethyl acetate – methanol, 5:1). IR spectrum: 3175 (NH), 1720, 1647 (C=O), 1280 cm^{-1} (C-S-C). PMR spectrum ($DMSO-d_6$): 2.63 (3H, s, SCH_3); 3.15 (3H, s, CH_3); 3.95 (2H, m, CH_2Br); 4.4 (3H, m, NCH_2CH); 12.1 ppm (1H, s, NH). Found, %: C 25.02; H 2.39; N 13.78. $C_{11}H_{12}Br_3N_5O_2S$. Calculated, %: C 25.50; H 2.34; N 13.52.

11-Bromo-9-methyl-6-methylene-3-methylthio-5,6,9,10-tetrahydro-8H-[1,2,4]triazolo[3',4':3,4]-pyrazino[1,2-c]pyrimidine-8,10-dione (VII). A. A mixture consisting of triazole V (0.52 g, 0.001 mole), freshly calcined potassium carbonate (0.14 g, 0.001 mole), and absolute dimethylformamide (2 ml) was heated in an oil bath at 80°C for 3 h. Dimethylformamide was distilled off in vacuum, and ethanol (5 ml) added to the dry residue. The crystalline solid was filtered off, washed with ether, and crystallized from ethanol. The yield of compound VII was 0.1 g (29.4%).

B. Triazole V (1.04 g, 0.002 mole) was dissolved in absolute ethanol (340 ml) and freshly calcined potassium carbonate (0.27 g, 0.002 mole) was added. The mixture was boiled for 14 h. The solution was filtered hot and left at +5°C for 15 h. The crystals were filtered off and compound VII (0.4 g, 56%) was obtained. Mp 259-260°C (from ethanol), R_f 0.35 (ethyl acetate). IR spectrum: 1728, 1672 (C=O), 1280 cm^{-1} (C-S-C). PMR spectrum

(DMSO-d_6): 2.65 (3H, s, SCH_3); 3.22 (3H, s, CH_3); 4.75 (2H, s, CH_2); 5.6 (1H, s, CH); 5.86 (1H, s, CH). Mass spectrum, *m/z* (*I*, %): 355 (46) [M]+. Found, %: C 36.96; H 2.96; N 19.53. $C_{11}H_{10}BrN_5O_2S$. Calculated, %: C 37.09; H 2.83; N 19.66.

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