SYNTHESIS AND ANTITUMOR ACTIVITY OF 2-HYDRAZINOTHIAZOLE DERIVATIVES

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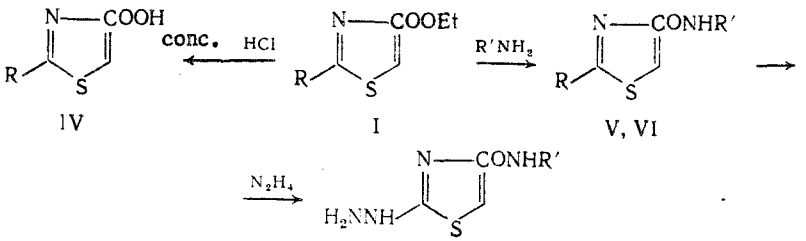
Derivatives of 2-aminothiazole display a broad spectrum of biological activities [3, 5, 6]. During the investigation of 2-ureido derivatives of thiazole it was suggested that the presence of the isothioureido structure is necessary for manifestation of antileukemic activity [7].

2-Hydrazinothiazoles, which are structural analogs of 2-aminothiazole, have not been studied in detail and may be of interest as biologically active compounds.

We have synthesized and studied the antitumor activity of 2-hydrazinothiazole derivatives that contain a carbonyl group at the 4-position of the heterocycle.

As the starting compound for the synthesis was used 2-isopropylidenehydrazino-4-carbethoxythiazole (I), prepared by reacting isopropylidenethiosemicarbazone with ethyl bromopyruvate in acetone [2]. We found earlier [2] the conditions for selective cleavage of ester I at either the azomethine bond or simultaneously at the hydrazino and the ester groups with formation of 2-hydrazino-4-carbethoxythiazole (II) and 2-hydrazino-4-carboxythiazole (III).

According to [4], 2-hydrazinothiazoles are labile compounds that can undergo intramolecular rearrangement in concentrated HCl. However, when we studied the hydrolysis of ester I in concentrated HCl we discovered the stability of the thiazole ring and the azomethine bond to hydrolytic cleavage. The hydrolysis product was 2-isopropylidenehydrazino-4-carboxythiazole (IV).



R=—NHN=CMe$_2$ (I, IV—VI); R′ = H (V, VII), Me (VI, VIII),

By reacting I with NH_3 and $MeNH_2$ we prepared the corresponding amide (V) and methylamide (VI) of 2-isopropylidenehydrazinothiazole-4-carboxylic acid. We failed to prepare pure 2-hydrazinothiazole-4-carboxamides (VII and VIII) by hydrolysis of the isopropylidene group in compounds V and VI. Therefore, we applied the transhydrazination reaction to hydrazines V and VI with an excess of hydrazine hydrate we have prepared the corresponding 2-hydrazinothiazoles VII and VIII. By reaction of ester II and amide VIII with ribose and with pyruvic acid we have prepared hydrazones (IX-XI).

For the preparation of 2-semicarbazidothiazole-4-carboxyhydrazide (XII), compound II was treated with KCNO followed by reaction of the intermediate 2-semicarbazido-4-carbethoxythiazole (XIII) with hydrazine hydrate. The structures of all the prepared compounds were proven by means of IR and PMR spectroscopy.

EXPERIMENTAL (CHEMICAL)

IR spectra were taken on a UR-20 spectrometer (GDR) from KBr disks. PMR spectra were recorded on a Perkin-Elmer R 12B spectrometer (Great Britain) operating at 60 MHz in d_6-DMSO; chemical shifts are reported in ppm relative to TMS on the δ scale. The purity of the pre-

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pared compounds was checked by TLC on Silufol UV-254 plates with the eluent propanol–ammonia (3:1). Found and calculated values of the elemental analyses correspond.

2-Isopropylidenehydrazino-4-carbethoxythiazole (I) was prepared according to [2] in the form of its hydrobromide, which was converted to the free base by alkalization of the aqueous solution with conc. NaOH to pH 8.0. The precipitate was filtered off, washed with water, and crystallized from aqueous ethanol (1:1). Yield 97%. IR spectrum, ν_{max}, cm^{-1}: 1585 (C=N), 1610 (NH), 1710 (C=O), 3305 (NH). PMR spectrum (d_6-DMSO), δ, ppm: 1.25 t (CH_3), 1.90 s (CH_3), 1.93 s (CH_3), 4.25 q (CH_2), 7.65 s (H-5).

2-Hydrazino-4-carbethoxythiazole (II) and 2-hydrazino-4-carboxythiazole (III) were prepared according to [2].

2-Isopropylidenehydrazino-4-carboxythiazole (IV). A solution of 2 g of I in 30 ml of conc. HCl was refluxed for 30 min. The precipitate was filtered off and crystallized from i-P_2OH. Yield 70% of IV, mp 260°C, R_f 0.35. $C_7H_9N_3O_2S$. IR spectrum, ν_{max}, cm^{-1}: 1560, 1615 (C=N), 1715 (C=O), 3320 (NH). PMR spectrum (d_6-DMSO), δ, ppm: 1.90 s (CH_3), 1.95 s (CH_3), 7.60 s (H-5).

2-Isopropylidenehydrazinothiazole-4-carboxamide (V). A suspension of 1 g of 2-isopropylidenehydrazino-4-carbethoxythiazole I in 5 ml of conc. NH_3 was stirred at room temperature for 2-3 days. The precipitate was filtered off and recrystallized from water. Yield 72% of V, mp 191-193°C, R_f 0.76. $C_7H_{10}N_4OS$. IR spectrum, ν_{max}, cm^{-1}: 1590 (C=N), 1690 (C=O), 3470 (NH). PMR spectrum (d_6-DMSO), δ, ppm: 1.90 s (CH_3), 1.95 s (CH_3), 7.10 s (NH_2), 7.41 s (H-5), 10.60 s (NH).

2-Isopropylidenehydrazinothiazole-4-N-methylcarboxamide (VI). A suspension of 2 g of I in 10 ml of an aqueous $MeNH_2$ solution was stirred at room temperature for 1-2 h (till complete solution). With cooling and stirring the solution was acidified with conc. HCl. The precipitate was filtered off and recrystallized from ethanol with treatment with activated carbon. Yield 53% of VI, mp 215°C, R_f 0.85. $C_8H_{12}N_4OS \cdot HCl$. IR spectrum, ν_{max}, cm^{-1}: 1570 (NH amide II), 1600, 1680 (C=N), 3280 (NH). PMR spectrum (d_6-DMSO), δ, ppm: 1.96 s (CH_3), 1.98 s (CH_3), 2.77 s (CH_3), 7.46 s (H-5).

2-Hydrazinothiazole-4-carboxamide (VII). A suspension of 2 g of I in 15 ml of conc. NH_3 was stirred at room temperature for one day. Then 10 ml of conc. NH_3 and 10 ml of ethanol were added and stirring was continued for one day (till complete solution). The solvent was evaporated under vacuum. To the residue were added 5 ml of ethanol and 3 ml of 80% hydrazine hydrate. The reaction mixture was refluxed for 1 h and cooled. The precipitate was filtered off and recrystallized from water. Yield 47% of VII, mp 245-246°C, R_f 0.60. $C_4H_6N_4OS$. IR spectrum ν_{max}, cm^{-1}: 1555 (C=N), 1635 (C=O), 3200, 3325, 3415 (NH). PMR spectrum (d_6-DMSO), δ, ppm: 4.83 s (NH_2), 7.25 s (H-5), 7.30 (NH_2), 8.4 s (NH).

2-Hydrazinothiazole-4-N-methylcarboxamide (VIII). A suspension of 2 g of I in 10 ml of aqueous $MeNH_2$ solution was stirred at room temperature for 1-2 h. The solution was concentrated under vacuum and to the residue were added 5 ml of ethanol and 3 ml of 80% hydrazine hydrate. The reaction mixture was refluxed for 2 h. The solution was evaporated under vacuum and 10 ml of water was added to the residue. The precipitate was filtered off and washed with water. Yield 46% of VIII, mp 215-216°C, R_f 0.60. $C_5H_8N_4OS$. IR spectrum, ν_{max}, cm^{-1}: 1550 (C=N), 1620 (C=O), 3230, 3325, 3385 (NH). PMR spectrum (d_6-DMSO), δ, ppm: 2.7 d (NCH_3), 4.85 s (NH_2), 7.23 s (H-5), 7.7 q (NH), 8.43 s (NH).

2-Ribosylidenehydrazino-4-carbethoxythiazole (IX). To a suspension of 2 g (10.7 mmole) of 2-hydrazino-4-carbethoxythiazole in 10 ml of ethanol was added a solution of 1.61 g (10.7 mmole) of D-ribose in 5 ml of water. The reaction mixture was refluxed for 10 min. The precipitate was filtered off and crystallized from ethanol. Yield 59% of IX, mp 167-168°C. $C_{11}H_{17}N_3O_6S$. IR spectrum, ν_{max}, cm^{-1}: 1580 (C=N), 1710 (C=O). PMR spectrum (d_6-DMSO), δ, ppm: 1.25 t (CH_2), 4.25 q (CH_2), 3.5-5.2 (ribose, 5H), 7.28 d (=CH), 7.6 q (NH), 7.67 s (NH).

2-Ribosylidenehydrazinothiazole-4-N-methylcarboxamide (X). To a suspension of 2.58 g (1.5 mmole) of VIII in 10 ml of ethanol was added a solution of 2.25 g (1.5 mmole) of D-ribose in 7 ml of water. The reaction mixture was refluxed for 15 min and the solution obtained was cooled. The precipitate was filtered off and recrystallized from water. Yield 78% of X, mp 215-216°C, R_f 0.54. $C_{10}H_{16}N_4O_5S$. IR spectrum, ν_{max}, cm^{-1}: 1560 (NH amide II), 1625 (C=N), 1640 (C=O). PMR spectrum (d_6-DMSO), δ, ppm: 2.78 d (CH_3), 4.0-5.3 (ribose, 5H), 7.4 s (H-5), 7.43 d (=CH), 7.75 (NH), 11.53 s (NH).

2-(1-Carboxy)ethylidenehydrazino-4-carbethoxythiazole (XI). To a solution of 1 g (3.7 mmole) of the hydrobromide of II in 5 ml of distilled DMF was added 0.7 ml (9.6 mmole) of freshly distilled pyruvic acid. The reaction mixture was refluxed for 1 h, cooled, and poured out in cold water. The precipitate was filtered off and recrystallized from a DMF–water mixture. Yield 58% of XI, mp 260°C, R_f 0.31. $C_9H_{11}N_3O_4S$. IR spectrum, ν_{max}, cm^{-1}: 1590 (C=N), 1690, 1725 (C=O), 3120 (NH). PMR spectrum (d_6-DMSO), δ, ppm: 1.28 t (CH_3), 2.06 s (CH_3), 4.26 q (CH_2), 7.88 s (H-5).

2-Semicarbazido-4-carbethoxythiazole (XIII). To a solution of 1.87 g of 2-hydrazino-4-carbethoxythiazole in 10 ml of diluted HCl was added 2 g of KCNO. The precipitate was filtered off and crystallized from ethanol. Yield 54% of XIII, mp 224-225°C, R_f 0.61. $C_7H_{10}N_4O_3S$. IR spectrum, ν_{max}, cm^{-1}: 1530 (NH amide II), 1600 (C=N), 1680, 1720 (C=O), 3200, 3330, 3450 (NH). PMR spectrum (d_6-DMSO), δ, ppm: 1.2 t (CH_3), 4.22 q (CH_2=), 6.12 s (NH_2), 7.68 s (H-5), 8.4 s (NH), 9.4 s (NH).

2-Semicarbazido-4-carboxyhydrazidothiazole (XII). With cooling, 2.3 g (10 mmole) of XIII was stirred with 1.5 ml (30 mmole) of hydrazine hydrate. The precipitate was filtered off, washed with water, and purified by reprecipitation from 0.02 N HCl with an NH_3 solution. Yield 45% of XII. IR spectrum, ν_{max}, cm^{-1}: 1560, 1579 (NH amide II), 1625, 1670 (C=O), 3230, 3300, 3420 (NH). PMR spectrum (d_6-DMSO), δ, ppm: 6.10 s (NH_2), 7.35 s (H-5), 8.3 s (NH).

EXPERIMENTAL (BIOLOGICAL)

The antitumor activity of the prepared compounds was determined by the primary selection method recommended by the All-Union Oncology Research Center of the Academy of Medical Sciences of the USSR [1] with mice of the lines $C57Bl_6$, BDF, BALB, and mongrel mice weighing 18-20 g. As experimental models were used lymphocytic leukemia P388, mammary adenocarcinoma AK 755, Lewis lung epidermoid carcinoma, melanoma B16, adenocarcinoma of the large intestine, and sarcomas 37 and 180. The compounds under investigation were administered intraperitoneally, within 48 h after transplantation of solid tumors and within 24 h in case of leukemias, five times at three doses every 24 h. As solvents water and 0.001 N HCl were used. Each dose of the preparation was studied in six mice, the control group of animals consisted of 18 mice. The numbers of animals in the control and experimental groups were chosen in order to obtain statistically reliable results (the significance level is $p < 0.05$ for the biological experiment). The efficacy of the preparation was judged on the fourteenth day after transplantation by tumor growth inhibition (increase in lifespan in case of P388).

The results of the investigations have shown that compounds III, VII, and VIII at a dose of 10 mg/kg and compound XI at a dose of 50 mg/kg possess some antitumor activity (50-60% growth inhibition) with regard to adenocarcinoma AK 755; with other kinds of tumors the investigated compounds did not show antitumor activity.

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