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SYNTHESIS AND CHEMICAL REACTIONS OF 2-RS-METHYL-7-METHYL-5-OXO-5H-1,3,4-THIADIAZOLO[3,2-*a*]PYRIMIDINES

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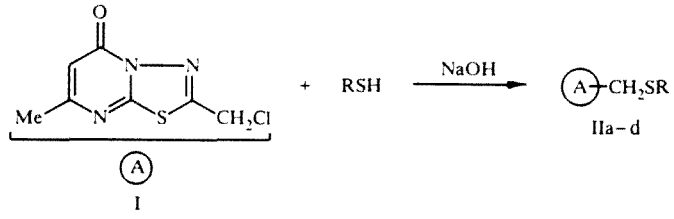
The corresponding sulfides have been synthesized starting from 2-chloromethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-a]pyrimidine and some of their reactions have been studied.

Among the derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidines are to be found substances with a wide spectrum of biological activity. In particular derivatives of the 1,3,4-thiadiazolo[3,2-*a*]pyrimidine sulfides possess antibacterial, antifungal, antineoplastic and even herbicidal activity [1-4].

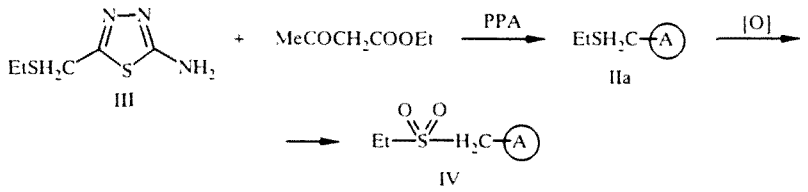
Thanks to the chlorine of the chloromethyl group, 2-chloromethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (I) is an excellent starting material for the preparation of new thio derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine. We have synthesized the 2-RS-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidines (IIa-d) by reaction of I with aliphatic, aromatic and heterocyclic thiolates.



IIa R = Et, b R = Ph, c R = 2-amino-1,3,4-thiadiazolo-5-yl, d R = 2-mercapto-1,3,4-thiadiazol-5-yl

The reaction of I with thiols was carried out in aqueous ethanol in the presence of an equimolar amount of sodium hydroxide by boiling for 2-3 h to give 80-90% yields of the sulfides IIa-d.

Compound IIa was also synthesized directly from 2-amino-5-ethylthiomethyl-1,3,4-thiadiazole (III) and ethyl acetoacetate in polyphosphoric acid and this provided additional confirmation of the structures of compounds IIa-d.



Oxidation of compound IIa in glacial acetic acid at room temperature for 20-24 h gave the sulfone IV in ~37% yield (a result of its moderate solubility under the reaction conditions).

The presence of the mercapto and amino groups in compounds IIc and IIg permits the synthesis of new derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine.

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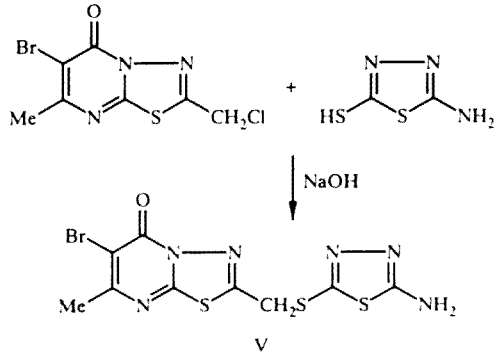
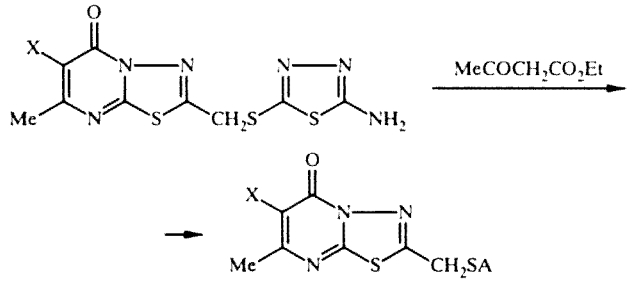
It is known [5] that the proton at position 6 of the thiadiazolopyrimidine system is readily substituted by molecular bromine. We have observed that bromination of compound IIc with an equimolar amount of molecular bromine did not go to completion but gave a mixture of IIc and the reaction product 2-(2-amino-1,3,4-thiadiazol-5-yl)-thiomethyl-6-bromo-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (V). To avoid this problem, compound V was prepared from 6-bromo-2-chloromethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine [6] and 2-amino-5-mercapto-1,3,4-thiadiazole in the presence of an equimolar amount of sodium hydroxide.



V

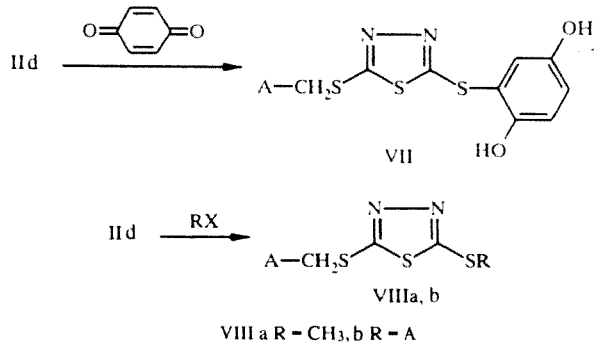
Cyclodehydration of IIc and V with ethyl acetoacetate in polyphosphoric acid gave 2-(7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)thiomethyl-6-X-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidines (VIa,b).



VIa, b

VI a X = H, b X = Br

We used the mercapto group in compound IId to synthesize new sulfides. Compound IId was readily alkylated in the presence of an equimolar amount of sodium hydroxide to give the corresponding 2-RS-5-(7-Methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl-methylthio)-1,3,4-thiadiazoles (VIIIa,b). Quinone was observed to add to IId at room temperature to give 2-(2,5-dihydroxyphenylthio)-5-(7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl-methylthio)-1,3,4-thiadiazole (VII).



VII

VIIIa, b

VIII a R = CH3, b R = A

The structures of the compounds synthesized were confirmed by ^{1}H NMR and IR spectroscopy and elemental analysis. In all cases the IR spectra of the new compounds contained carbonyl absorption bands in the 1690-1710 cm^{-1} range and the spectra of compounds IIc, V, and VII contained bands in the 3200-3400 cm^{-1} region corresponding to NH_2 and OH stretching vibrations.

EXPERIMENTAL

IR spectra of KBr disks were recorded with a UR-20 spectrometer while ^{1}H NMR spectra of DMSO-D_6 solutions with HMDS as internal standard were recorded with a Tesla 5873 C (80 MHz) machine. Melting points were determined with a Boetius microheating block.

Elemental analyses for C and H corresponded to calculated values.

General Method for the Synthesis of 2-RS-Methyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidines IIa-d, V, VIIIa,b. Sodium hydroxide (0.01 mole) in water (5 cm^3) was added to an alcohol solution (20 cm^3) of a mercaptan (0.01 mole), the mixture was stirred for 10-20 min and 2-chloromethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine [7] (0.01 mole) was added. The mixture was boiled for 2 h, the reaction mixture was cooled, diluted with water (50 cm^3), and the precipitate of IIa-d was filtered off an dried in the air.

Compound V was made analogously from 2-chloromethyl-6-bromo-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine and 2-mercapto-5-amino-1,3,4-thiadiazole.

Compounds VIIIa,b were made analogously from compound IId, methyl iodide, and 2-bromo-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine [6].

2-Ethylthiomethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (IIa). Yield 78.8 %. mp 93-97°C (5:1 dioxane–water). IR spectrum: 1700 (C=O), 1570 cm^{-1} (C=N). ^{1}H NMR spectrum: 6.18 (H, s, CH), 4.08 (2H, s, CH_2), 3.70 (2H, q, CH_2), 2.16 (3H, s, Me), 1.08 ppm (3H, t, Me). Found, %: C 44.17, H 4.22. Calculated, $C_9H_{11}N_3OS_2$, %: C 44.81, H 4.56.

Compound IIa was obtained by direct synthesis from III (mp 178-180°C, yield 67%, made from ethylthioglycollic acid and thiosemicarbazide [8]) and ethyl acetoacetate in polyphosphoric acid (see method of synthesis of VIa,b). Yield 75%.

2-Phenylthiomethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (IIb). Yield 91%. mp 126-127°C (5:1 dioxane–water). IR spectrum: 1734 (C=O), 1590 cm^{-1} (C=N). ^{1}H NMR spectrum: 7.2 (5H, m, Ar), 6.10 (H, s, CH), 4.20 (2H, s, CH_2), 2.22 ppm (3H, s, Me). Found, %: C 53.44, H 4.10. Calculated, $C_{13}H_{11}N_3OS_2$: C 53.95, H 3.83.

2-(2-Amino-1,3,4-thiadiazol-5-yl)thiomethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (IIc). Yield 95.5%. mp 330-334°C (dioxane). IR spectrum: 3150 (NH), 1710 (C=O), 1590 cm^{-1} (C=N). ^{1}H NMR spectrum: 7.32 (2H, s, NH_2), 6.20 (H, s, CH), 4.62 (2H, s, CH_2), 2.21 ppm (3H, s, Me). Found, %: C 34.36, H 2.35. Calculated, $C_9H_8N_6OS_3$, %: C 34.60, H 2.58.

2-(2-Mercapto-1,3,4-thiadiazol-5-yl)thiomethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine(IId). Yield 39.8%. mp 170-174°C (4:1 dioxane–water). IR spectrum: 1710 (C=O), 1585 cm^{-1} (C=N). ^{1}H NMR spectrum: 6.23 (H, s, CH), 4.50 (2H, s, CH_2), 2.20 ppm (3H, s, Me). Found, %: C 32.51, H 2.18. Calculated, $C_9H_{11}N_5OS_4$, %: C 32.81, H 2.14.

2-Ethylsulfonomethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (IV). Compound IIa (0.02 mole) was dissolved in glacial acetic acid (20 cm^3), 30% hydrogen peroxide (6 g) was added and the mixture kept for 16-20 h. The precipitate was filtered off, washed with water and dried in the air. Yield 37.5%. mp 212-214°C (5:1 dioxane–DMF). IR spectrum: 1716 (C=O), 1590 cm^{-1} (C=N). ^{1}H NMR spectrum: 6.76 (H, s, CH), 5.06 (2H, s, CH_2), 3.24 (2H, q, CH_2), 2.36 (3H, s, Me), 1.12 ppm (3H, t, Me). Found, %: C 38.99, H 3.88. Calculated, $C_9H_{11}N_3O_3S_2$, %: C 39.66, H 4.02.

2-(2-Amino-1,3,4-thiadiazol-5-yl)thiomethyl-6-bromo-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine(V). Yield 90%. mp 208-210°C (dioxane). IR spectrum: 3310 (NH), 1720 (C=O), 1648 cm^{-1} (C=N). ^{1}H NMR spectrum: 4.68 (2H, s, CH_2), 2.35 ppm (3H, s, Me). Found, %: C 27.30, H 1.66. Calculated, $C_9H_7N_6OS_3$, %: C 27.61, H 1.80.

2-(7-Methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)thiomethyl-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (VIa). Ethyl acetoacetate (5.5 mmole) was added with stirring to a solution of IIc (5 mmole) in polyphosphoric acid (10 g) and the mixture was heated on a boiling water bath for 6 h. The reaction mixture was diluted with water (50 cm^3) and neutralized with 10% sodium hydroxide solution. The precipitate was filtered off, washed with water, dried in air and recrystallized from 2:1 dioxane–water. Yield 84.1%, mp 248-250°C. IR spectrum: 1730 (C=O), 1598 cm^{-1} (C=N). ^{1}H NMR spectrum: 6.20 (H, s, CH), 4.35 (2H, s, CH_2), 2.44 ppm (3H, s, Me). Found, %: C 41.45, H 2.70. Calculated, $C_{13}H_{10}N_6O_2S_3$, %: C 41.25, H 2.66.

2-(7-Methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)thiomethyl-6-bromo-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (VIb) was obtained analogously to V. Yield 93.8%. mp 239-241°C (dioxane). IR spectrum:

1740 (C=O), 1729 (C=O), 1680 (C=N), 1595 cm^{-1} (C=N). ^1H NMR spectrum: 5.92 (H, s, CH), 3.46 (2H, s, CH_2) 2.32 (3H, s, Me), 2.12 ppm (3H, s, Me). Found, %: C 34.00, H 1.77. Calculated, $C_{13}H_9BrN_6O_2S_3$, %: C 34.12, H 1.98.

2-(2,5-Dihydroxyphenyl)-5-(7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidinemethyl-2-)-1,3,4-thiadiazole Disulphide (VII). 2,5-Dimercapto-1,3,4-thiadiazole (0.01 mole) was dissolved in ethanol (25 cm^3), NaOH (0.01 mole) in water (5 cm^3) was added, the mixture was stirred for 20 min and then compound I (0.01 mole) was added and the mixture was boiled for 2 h. Quinone (0.01 mole) was added to the cooled reaction mixture which was stirred for 30 min and boiled for 20-30 min. The mixture was cooled, the precipitate was filtered off and washed with water. Yield 78%. mp 238-239°C (1:4 water–dioxane). IR spectrum: 3480 (OH), 1700 (C=O), 1590 cm^{-1} (C=N). ^1H NMR spectrum: 9.72 (H, s, OH), 9.12 (H, s, OH), 6.80 (3H, s Ar), 6.22 (H, s, CH), 4.90 (2H, s, CH_2), 2.22 ppm (3H, s Me). Found, %: C 41.03, H 2.32. Calculated, $C_{15}H_{11}N_5O_3S_4$, %: C 41.17, H 2.53.

Compounds VIIIa,b were prepared by the method described for the synthesis of IIa-d.

2-Methyl-5-(7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidinemethyl-2)-1,3,4-thiadiazole Disulfide (VIIIa). Yield 87.5%. mp 194-196°C. IR spectrum: 1720 (C=O), 1600 cm^{-1} (C=N). ^1H NMR spectrum: 6.22 (H, s, CH), 4.70 (2H, s, CH_2), 2.67 (3H, s, Me), 2.20 ppm (3H, s, Me). Found, %: C 34.51, H, 2.17. Calculated, $C_{10}H_9N_5OS_4$, %: C 34.96, H 2.64.

2-(7-Methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)-5-(7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-*a*]pyrimidinemethyl-2)-1,3,4-thiadiazole Disulfide (VIIIb). Yield 69%. mp 240°C (dioxane). IR spectrum: 1729 (C=O), 1680, 1595 cm^{-1} (C=N). ^1H NMR spectrum: 5.92 (H, s, CH), 3.46 (2H, s, CH_2), 2.32 (3H, s, Me), 2.12 ppm (3H, s, Me). Found, %: C 35.99, H, 1.88. Calculated, $C_{15}H_{10}N_8O_2S_5$, %: C 36.42, H 2.03.

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