Chemistry of Heterocyclic Compounds, Vol. 34, No. 8, 1998

NOVEL POLYCYCLIC PYRIMIDINES

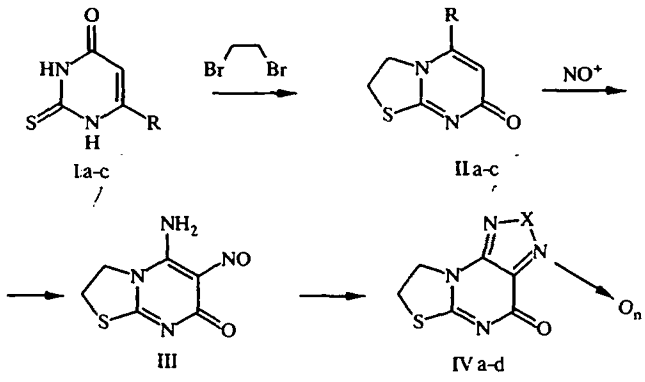
A. A. Yavolovskii, O. S. Timofeev, and É. I. Ivanov

Methods are reported for preparing the novel pyrimidines 7,8-dihydro-9H-1,2,5-chalcodiazolo[3,4-d]thiazole[2,3-b]pyrimidin-4-ones and their N-oxides.

Interest in the chemistry of polycyclic pyrimidines is due to the broad spectrum of their biological activity. Pyrimidine derivatives, annelated with oxazolidine and thiazolidine heterocycles, show gastric antisecretory properties [1] and have a diuretic action [2]. Prolonged, selective, antiarrythmic activity has been found in a series of 1,2,5-thiadiazoles and their N-oxides [3].

The aim of this work was to develop convenient methods of synthesis of polycyclic pyrimidines which have thiazolidine and chalcodiazole structural elements and also of their N-oxides.

We chose as starting materials the available 2-thiouracils (Ia-c). Reaction of these with 1,2-dibromoethane in DMF with heating but without the use of base gives products of regioselective annelation, i.e., 2,3-dihydro-4H-thiazole[2,3-*a*]pyrimidin-7-ones II. In conditions suitable for 6-aminouracils [4], compound IIa is converted to the 5-amino-6-nitrouracil III.



I, II a $R = NH_2$; b $R = H$; c $R = CH_3$; IV a $X = S$, $n = 0$; b $X = S$, $n = 1$;
c $X = Se$, $n = 0$; d $X = Se$, $n = 1$

The thiazolidine fragment of compound III appears to be quite stable to acid catalyzed hydrolysis which allows the preparation of 7,8-dihydro-9H-1,2,5-thiadiazolo[3,4-d]thiazole[2,3-b]pyrimidin-4-one (IVa) in the presence of excess hydrochloric acid. The 1,2,5-selenadiazole IVc was prepared by the reaction of selenious acid on the sodium hydrosulfite reduction without separation of the diamino aminouracil III. The 1,2,5-chalcodiazolo[3,4-d]thiazole[2,3-b]pyrimidin-4-one N-oxides IVb, d were prepared by the method proposed by us earlier [5] via treatment of the orthonitrosoamine III with sulfur or selenium monochloride in DMF.

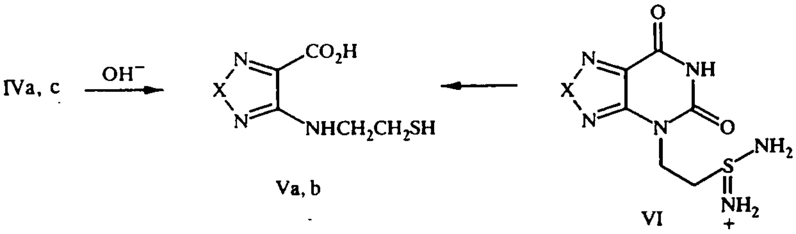
There is direct evidence for the angular structure of compound IV since the products of basic hydrolysis IVa, c are the 3-(β-mercaptoethylamino)-1,2,5-chalcodiazole-4-carboxylic acids Va, b whereas, for a linear structure, the unsubstituted 3-amino-1,2,5-chalcodiazole-4-carboxylic acids would be obtained.

A. V. Bogatskii Physicochemical Institute, National Academy of Sciences of Ukraine, Odessa, 270080. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1130-1132, August, 1998. Original article submitted October 20, 1997.

0009-3122/98/3408-0976$20.00

The β-mercaptoethyl substituted acid Va is identical to that obtained from the isothiouronate salt of 4-(β-toluenesulfoethyl)-1,2,5-thiadiazole[3,4-d]pyrimidine-5,7-(4H, 6H)-dione VI [6].

The polycyclic pyrimidines IVa-d are high melting substances, poorly soluble in water and organic solvents.



The mass spectra of the thia- and selenadiazoles IVa, c show intense molecular ion peaks (60-75% of the base peak). The molecular ion peaks for the N-oxides IVb, d are of lower intensity and decompose with elimination of the oxygen atom.

The stretching vibrations of the carbonyl group and the skeletal vibrations of the conjugated heterocyclic system of compounds IVa, c are seen as a series of strong bands in the region 1650-1500 cm^{-1}. The N-oxides are characterized by two absorption bands in the higher frequency region at 1740, 1700 cm^{-1} for compound IVb and at 1730, 1710 cm^{-1} for IVd.

EXPERIMENTAL

Monitoring of the purity of the materials was carried out by TLC on Silufol UV-Vis 254 plates. Mass spectra were recorded on a Varian MAT-112 instrument with direct introduction of the sample into the ion source. The ionization energy was 70 V and the ionization chamber temperature 220°C. IR Spectra were taken for thin films with Vaseline oil on a Specord-80 instrument and UV spectra on a Perkin-Elmer Lambda-9 instrument using ethanol solvent.

General Method for Preparing 6-R-2,3-Dihydro-4H-thiazole[2,3-*a*]pyrimidin-7-ones (IIa-c). Dibromoethane (1.3 ml, 18 mmole) was added with stirring to a solution of the 6-R-2-thiouracil (Ia-c, 10 mmole) in DMF (15 ml) at a temperature of 140°C and the heating and stirring was continued for a further 45 min. The precipitated hydrobromide II was separated by filtration, put into chloroform (50 ml), and triethylamine was added to pH 10. The precipitate was stirred for 2 h and then filtered and recrystallized from ethanol to give IIa (0.8 g, 48%) with mp 258°C and M^+ 169. IR Spectrum: 3500-3000, 1680, 1675, 1610, 1500 cm^{-1}. Found, %: C 42.56; H 4.20; N 24.87. $C_6H_7N_3OS$. Calculated, %: C 42.60; H 4.14; N 24.85.

Compound IIb: 0.7 g (46%), mp 222°C, M^+ 154. IR Spectrum: 1660, 1625, 1620, 1580, 1550, 1540 cm^{-1}. Found, %: C 46.70; H 3.92; N 18.20. $C_6H_6N_2OS$. Calculated, %: C 46.75; H 3.90; N 18.18.

Compound IIc: 0.75 g (45%), mp 220°C, M^+ 168. IR Spectrum: 1660, 1630, 1580, 1560, 1550 cm^{-1}. Found, %: C 50.03; H 4.73; N 16.65. $C_7H_8N_2OS$. Calculated, %: C 50.00; H 4.76; N 16.67.

6-Nitroso-2,3-dihydro-4H-5-aminothiazole[2,3-a]pyrimidin-7-one (III). Sodium nitrite (1.0 g, 20 mmole) in acetic acid (1.6 ml) was added with stirring to compound IIa (1.7 g, 10 mmole) in water (10 ml). The mixture was cooled and the precipitate was separated by filtration, washed with water, and dried in air to give III (1.4 g, 70%) with mp >300°C and M^+ 198. IR Spectrum: 3100-3000, 1760, 1610, 1560, 1540 cm^{-1}. Found, %: C 36.33; H 3.05; N 28.30. $C_6H_6N_4O_2S$. Calculated, %: C 36.36; H 3.03; N 28.28.

7,8-Dihydro-9H-1,2,5-thiadiazolo[3,4-d]thiazole[2,3-b]pyrimidin-4-one (IVa). A mixture of nitrosouracil III (2.0 g, 10 mmole) and sodium hyposulfite (16 ml, 0.83 mole) was heated to 60°C. Concentrated hydrochloric acid (1.9 ml) was added and the product was refluxed for 2 h with stirring. The solution was cooled and the precipitate separated by filtration and recrystallization from DMF to give IVa (1.3 g, 61%) with mp 234°C and M^+ 212. IR Spectrum: 1665, 1545, 1500 cm^{-1}. UV Spectrum (ethanol), λ_{max}, nm (log ε): 215 (4.05), 240 (1.75), 290 (3.20), 330 (3.60). Found, %: C 33.95; H 1.90; N 26.45. $C_6H_4N_4OS_2$. Calculated, %: C 33.96; H 1.89; N 26.42.

7,8-Dihydro-9H-1,2,5-selenadiazolo[3,4-d]thiazole[2.3-b]pyrimidin-4-one (IVc). A solution of sodium hydrosulfite was added with stirring to the nitrosouracil III (2.0 g, 10 mmole) in water (20 ml) until a colorless solution was obtained. Stirring was continued for 30 min and there was added a saturated aqueous solution of selenious acid (3.2 g, 15 mmole). The precipitate was separated by filtration, dried in air, and recrystallized from DMF to give IVc (1.8 g, 69%) with mp >300°C and M^+ 260. IR Spectrum: 1650, 1545, 1500 cm^{-1}. UV Spectrum (ethanol), λ_{max}, nm (log ε): 210 (3.40), 235 (1.50), 240 (1.75), 290 (0.70), 358 (4.00). Found, %: C 27.70; H 1.55; N 21.56. $C_6H_4N_4OSSe$. Calculated, %: C 27.69; H 1.54; N 21.54.

7,8-Dihydro-9H-1,2,5-thiadiazolo[3,4-d]thiazole[2,3-b]pyrimidin-4-one N-Oxide (IVb). Sulfur monochloride (10 ml, 12.5 mmole) was added with vigorous stirring to the nitrosouracil III (2.0 g, 10 mmole) in dry DMF (25 ml) at such a rate that the reaction medium temperature did not exceed 60°C. The precipitate was filtered, washed with carbon disulfide, and dried in air to give oxide IVb (1.0 g, 44%) with mp >300°C and M^+ 228. IR Spectrum: 1740, 1700, 1550, 1530, 1500 cm^{-1}. UV Spectrum (ethanol), λ_{max}, nm (log ε): 213 (4.25), 250 (3.05), 320 (2.75), 357 (0.80). Found, %: C 31.60; H 1.77; N 24.60. $C_6H_4N_4O_2S_2$. Calculated, %: C 31.58; H 1.75; N 24.56.

7,8-Dihydro-9H-1,2,5-selenadiazolo[3,4-d]thiazole[2,3-b]pyrimidin-4-one N-Oxide (Vd). Selenium monochloride (10 ml, 12.5 mmole) was added with vigorous stirring to a solution of nitrosouracil III (2.0 g, 10 mmole) in dry DMF (25 ml) at such a rate that the reaction medium temperature did not exceed 40°C. The precipitate was filtered to give oxide IVd (1.2 g, 42%) with mp >300°C and M^+ 276. IR Spectrum: 1730, 1710, 1555, 1520 cm^{-1}. UV Spectrum (ethanol), λ_{max}, nm (log ε): 210 (3.50), 230 (3.30), 273 (1.75), 327 (3.95), 390 (1.45). Found, %: C 26.10; H 1.46; N 20.30. $C_6H_4N_4O_2SSe$. Calculated, %: C 26.09; H 1.45; N 20.29.

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