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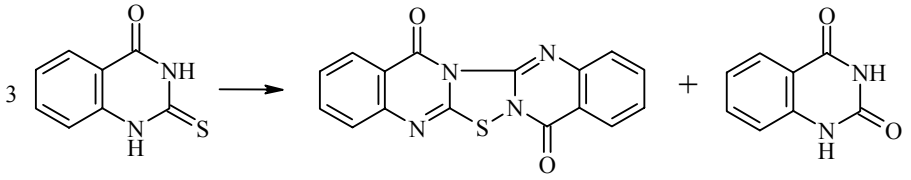
OXIDATIVE CYCLOCONDENSATION OF CYCLIC THIO- AND SELENOUREAS. 5.* 2-THIOXOTHIENO- AND 2-THIOXOPYRIDO[2,3-*d*]PYRIMIDIN-4-ONES

N. I. Mukarramov, B. A. Urakov, and Kh. M. Shakhidoyatov

A study was carried out on the oxidative cyclocondensation of 2-thioxothieno- and 2-thioxopyrido[2,3-d]pyrimidin-4-ones. The thiophene ring with excess π-electron density facilitates the reaction, while the pyridine ring with diminished π-electron density hinders it. 2-Thioxothieno-[2,3-d]pyridimin-4-ones were converted into previously unreported 7H,13H-[1,2,4]thiadiazolo-[3,2-b:5,4-b']bis(thieno[2,3-d]pyridimine-7,13-diones).

Keywords: pyrido[2,3-*d*]pyrimidine-2,4-diones, 7H,13H-[1,2,4]thiadiazolo[3,2-*b*:5,4-*b*']bis(thieno-[2,3-*d*]pyrimidine-7,13-diones), 2-thioxopyrido[2,3-*d*]pyrimidin-4-ones, 2-thioxothieno[2,3-*d*]pyrimidin-4-ones, oxidative cyclocondensation.

We have already discovered that 2-thioxo-4-quinazolinone (**1**) undergoes cyclocondensation to give derivative of 8H,15H-[1,2,4]thiadiazolo[3,2-*b*:5,4-*b'*]diquinazoline-8,15-dione **2** at room temperature either in DMSO solution in the presence of P_2O_5 or concentrated sulfuric acid [1, 2] or upon heating at reflux in methanol solution of iodine [1]. In all cases, pentacyclic product **2** is formed in 45-60% yield along with 5-8% 2,4-quinazolinedione (**3**).



1 **2** **3**

We also found that the cyclocondensation is facilitated when there are electron-donor alkyl groups in the benzene ring of 4-quinazolinone, while substituents with a *–I*-effect and electron-withdrawing groups such as Br and NO_2 hinder this reaction, leading only to the corresponding substituted 2,4-quinazolinediones [1].

*Communication 4, see ref. [1].

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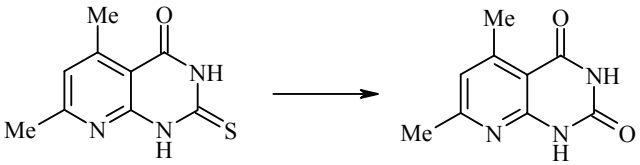
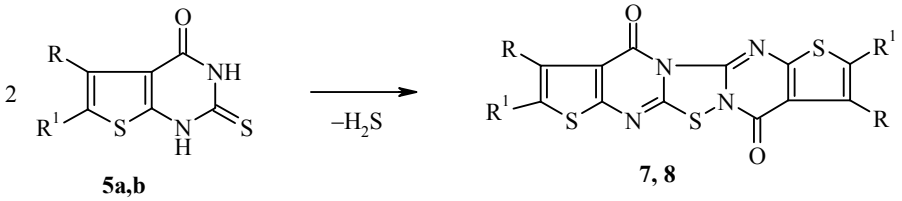
In a study of the scope of this reaction, we investigated the capacity of heteroanalogs of 2-thioxo-4-quinazolinones containing an electron-deficient pyridine ring or electron-rich thiophene heterocycle to undergo oxidative cyclocondensation. For this purpose, we synthesized 5,7-dimethyl-2-thioxopyrido-[2,3-*d*]pyrimidin-4-one (**4**), 5,6-dimethyl- (**5a**) and 5,6-tetramethylene-2-thioxothieno[2,3-*d*]pyrimidin-4-ones (**5b**) and studied their transformations under oxidative cyclocondensation conditions.

The reaction was carried out in methanol in the presence of molecular iodine upon heating at reflux or in DMSO in the presence of P_2O_5 at room temperature. Under both conditions, 5,7-dimethylpyrido-[2,3-*d*]pyrimidine-2,4-dione (**6**) was formed instead of the expected 1,2,4-thiadiazole derivative.



4 **6**

In DMSO in the presence of P_2O_5, **5a** and **5b** with a fused thiophene ring were converted to give the corresponding 2,3,9,10-tetramethyl-4H,11H-[1,2,4]thiadiazolo[3,2-*b*:5,4-*b*']bis(thieno[2,3-*d*]pyridimidine)-5,14-dione (**8**), whose structure was in accord with the IR and mass spectral data as well as elemental analysis.



5a,b **7, 8**

5a, **7** R = R^1 = Me; **5b**, **8** R + R^1 = $(–CH_2–)_4$

We might assume that the oxidative cyclocondensation of condensed 2-thioxo-4-pyrimidinones proceeding in the presence of acid involves the protonation of the pyrimidine ring necessary for the transfer of electron density from the second ring to the pyrimidine ring. Of course, the presence of electron-donor substituents in this ring and its excess electron density facilitate the oxidative cyclocondensation. Two competing sites for N-protonation exist in thioxopyrido[2,3-*d*]pyrimidin-4-one (**4**). One such site exists in the pyridine ring, while the other exists in the pyrimidine ring. Pyridines are stronger bases than pyrimidines [3, 4] and, to a greater extent, than thioxo-4-pyrimidinones. Furthermore, the basicity of the pyridine fragment is even further enhanced for thioxopyrido[2,3-*d*]pyrimidin-4-one (**4**) due to the +*I*-effect of the two methyl groups. Thus, the protonation proceeds at the pyridine ring such that the electron density in the pyrimidine fragment and the capacity of **4** to undergo oxidative cyclocondensation are sharply reduced.

Hence, the oxidative cyclocondensation of condensed 2-thioxo-4-pyrimidinones depends strongly on the nature of ring, to which the pyrimidine ring is fused. A heterocycle with deficient π-electron density hinders this reaction, while a heterocycle with excess π-electron density will facilitate it.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for KBr pellets. The mass spectra were taken on MKh-1303, MKh-1321, and MKh-1310 mass spectrometers. The ^{1}H NMR spectra were taken on JNM-4H-100

and Tesla BS-567A spectrometers at 100 MHz with TMS or HMDS as the internal standards. Thin-layer chromatography was carried out on Silufol UV-254 plates with development by iodine vapor, UV light, $KMnO_4 + H_2SO_4 + H_2O$ (0.5 g/2 ml/48 ml). The solvents were purified and dried by a standard procedure.

Ethyl Esters of 4,5-Disubstituted 2-Amino-3-thiophenecarboxylic Acids were prepared by cyclization of ethyl cyanoacetate with sulfur and the corresponding ketone (methyl ethyl ketone or cyclohexanone) [6, 7].

5,7-Dimethyl-2-tioxopyrido[2,3-*d*]pyrimidin-4-one (4) was obtained by a variant of the method of Khodzhanizov [8]. Acetylacetone (0.84 ml, 8 mmol) was added to a suspension of 6-amino-2-thioxo-4-pyrimidinone (1 g, 7 mmol) [8] in trifluoroacetic acid (2.8 ml). The mixture was heated on a water bath for 2.5 h and cooled. Water was added and the precipitate formed was filtered off, dried, and recrystallized from benzene to give 1.3 g (90%) **4**, mp 292°C, R_f 0.57 (8:1 chloroform–methanol). IR spectrum, ν, cm^{-1}: 1680 ($\nu_{C=O}$), 3080, 3150 (ν_{NH}). Mass spectrum, *m/z* (I_{rel}, %): 207 $[M]^+$ (100), 179 $[M–CO]^+$ (6), 174 $[M\text{-}SH]^+$ (14), 148 $[M–HNCS]^+$ (19), 121 $[M–CO–NCS]^+$ (13). ^1H NMR spectrum, δ, ppm: 2.35 (3H, s, 5-CH_3); 2.58 (3H, s, 7-CH_3); 7.30 (1H, s, H-6).

5,6-Dimethyl-2-thioxothieno[2,3-*d*]pyrimidin-4-one (5a) was obtained by a modification of the method of Shodiev [9] from the ethyl ester of 2-amino-3-thiophenecarboxylic acid and ammonium thiocyanate (instead of potassium thiocyanate). A suspension of ethyl ester of 2-amino-3-thiophenecarboxylic acid (20 g, 0.1 mol), ammonium thiocyanate (7.6 g, 0.1 mol), and *o*-xylene (50 ml) was heated with stirring on a water bath. Concentrated hydrochloric acid (15 ml, 0.1 mol) was added dropwise over 30 min. Heating was continued at this temperature for an additional 6 h. After cooling, the precipitate formed was filtered off, washed with water, and dried. The precipitate was dissolved in 10% aqueous potassium hydroxide. The insoluble fraction was filtered off. The mother liquor was neutralized by adding acetic acid. The precipitate formed was separated, washed with water, and dried to give 15.5 g (73%) **5a**, mp 313-315°C (acetone), R_f 0.45 (1:3 acetone–benzene). IR spectrum, ν, cm^{-1}: 1670 ($\nu_{C=O}$), 3410 (ν_{NH}). Mass spectrum, *m/z* ($I_{rel.}$, %): 212 $[M]^+$ (100), 179 $[M–SH]^+$ (15), 153 $[M–HNCS]^+$ (60). ^1H NMR spectrum, δ, ppm: 2.00 (6H, s, 5-CH_3, 6-CH_3).

5,6-Tetramethylene-2-thioxothieno[2,3-*d*]pyrimidin-4-one (5b) was obtained according to Shodiev [9] in 35% yield (8 g), mp 288-289°C (mp 287-289°C [9]), R_f 0.5 (1:3 acetone–benzene). Mass spectrum, *m/z* (I_{rel}, %): 238 $[M]^+$ (100), 210 $[M–CO]^+$ (20), 179 $[M–HNCS]^+$ (70), 151 $[M–CO–HNCS]^+$ (54). ^1H NMR spectrum, δ, ppm (*J*, Hz) in pyridine-d_5: 0.80 (2H, d, J = 8, H-5); 1.00-1.70 (4H, m, H-6, H-7); 2.40 (d, J = 7, H-8).

2,3,9,10-Tetramethyl-4H,11H-[1,2,4]thiadiazolo[3,2-b:5,4-*b'*]bis(thieno[2,3-*d*]pyrimidine-4,11-dione) (7). A. Iodine (0.25 g, 1.5 mmol) was added to a solution of 5,6-dimethyl-2-thioxothieno-[2,3-*d*]pyridimidin-4-one (212 mg, 1 mmol) in absolute methanol (3 ml), heated at reflux for 15 min, and then cooled. Water was added. The aqueous solution was heated at reflux and cooled. The precipitate formed was filtered off, washed with water, recrystallized from DMF and dried to give 117 mg (61%) **7**, mp 245-247°C, R_f 0.90 (3:2 benzene–acetone). IR spectrum, ν, cm^{-1}: 1675-1680 ($\nu_{C=O}$). Mass spectrum, *m/z* (I_{rel}, %): 388 $[M]^+$ (100), 360 $[M–CO]^+$ (20), 330 $[M–NCS]^+$ (30), 316 $[M–SNCO]^+$ (65). Found, %: C 49.30; H 3.10; N 14.33. $C_{16}H_{12}N_4O_2S_3$. Calculated, %: C 49.47; H 3.11; N 14.42.

B. P_2O_5 (200 mg, 1.4 mmol) was added to a solution of 5,6-dimethyl-2-thioxothieno[2,3-*d*]pyrimidin-4-one (212 mg, 1 mmol) in DMSO (10 ml) and stirred at room temperature for 4 h. Water was added and the precipitate formed was filtered off, washed with water, DMF, and ether, and dried at room temperature to give 134 mg (70%) **7**, mp 245-247°C, R_f 0.90 (3:2 benzene–acetone).

1,2,3,4,10,11,12,13-Octahydro[1,2,4]thiadiazolo[3,2-*b*:5,4*b'*]bis(benzo[*b*]thiophene[2,3-*d*]-pyrimidine-5,14-dione) (8). A. By analogy to the above procedure, 5,6-tetramethylene-2-thioxothieno[2,3-*d*]pyrimidin-4-one (240 mg, 1 mmol) yielded 154 mg (70%) **8**, mp 262-264°C, R_f 0.53 (2:3 acetone–benzene). IR spectrum, ν, cm^{-1}: 1665-1670 ($\nu_{C=O}$). Mass spectrum, *m/z* (I_{rel}, %): 440 $[M]^+$ (100), 412 $[M–CO]^+$ (15), 382 $[M\text{-}NCS]^+$ (15), 362 $[M–SNCO]^+$ (19). Found,%: C 54.40; H 3.52; N 12.51. $C_{20}H_{16}N_4O_2S_3$. Calculated, %: C 54.53; H 3.66; N 12.72.

B. By analogy with the above procedure, 5,6-tetramethylene-2-thioxothieno[2,3-*d*]pyrimidin-4-one (240 mg, 1 mmol) and P_2O_5 (200 mg, 1.4 mmol) in DMSO (10 ml) gave 200 mg (90%) **8**, mp 262-264°C, R_f 0.53 (2:3 acetone–benzene).

5,7-Dimethylpyrido[2,3-*d*]pyrimidin-4-one (6) was obtained according to the preparation of **8** (method B) from **4** (210 mg, 1 mmol). The yield of **6** was 134 mg (70%), mp 316°C, which corresponds to the data given by Khodzhanizov [8], R_f 0.90 (3:1 chloroform–methanol). IR spectrum, ν, cm^{-1}: 1710 ($\nu_{C=O}$), 3200 (ν_{NH}). Mass spectrum, *m/z* (I_{rel}, %): 191 $[M]^+$ (100), 174 $[M–OH]^+$ (4), 163 $[M–CO]^+$ (12), 148 $[M–HNCO]^+$ (44), 121 $[M–CO–NCO]^+$ (54). ^1H NMR spectrum in CF_3CO_2H, δ, ppm: 2.39 (3H, s, 7-CH_3); 2.59 (3H, s, 5-CH_3); 7.10 (1H, s, H-6).

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