Synthesis and thermal transformations of 5-nitropyrimidin-4-yl dialkyldithiocarbamates

*O. B. Ryabova,[a] V. A. Makarov,[a] V. V. Chernyshev,[b] and V. G. Granik[a]**

[a]National Research Center of Antibiotics,
3a ul. Nagatinskaya, 117105 Moscow, Russian Federation.
Fax: +7 (095) 231 4284. E-mail: makar-cl@ropnet.ru
[b]Department of Chemistry, M. V. Lomonosov Moscow State University,
Leninskie Gory, 119992 Moscow, Russian Federation.
Fax: +7 (095) 939 3654. E-mail: cher@biocryst.phys.msu.su

On heating, 5-nitropyrimidin-4-yl dialkyldithiocarbamates undergo two types of transformations. One type of these transformations involves intramolecular *ipso*-substitution of the nitro group to form bis(4-dialkylcarbamoylthiopyrimidin-5-yl) disulfides, whereas another type of transformations involves elimination of carbon disulfide to give 4,6-diamino-5-nitropyrimidine derivatives. The reaction pathway is controlled by the steric effect of the substituent at position 6 of the pyrimidine ring.

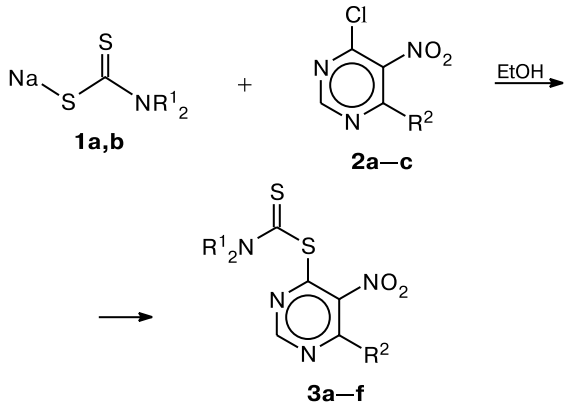
Key words: dialkyldithiocarbamate, 5-nitropyrimidine, 1,3-dithiolo[4,5-*d*]pyrimidine, nucleophilic substitution, *ipso*-substitution, X-ray diffraction analysis.

Dialkyldithiocarbamates are of considerable interest in biological studies. Certain dithiocarbamic esters exhibit fungicidal, insecticidal, and herbicidal activities.[1,2] In medicine, thiocarbamic acid derivatives are known as compounds possessing hypolipodemic and hypotensive activities[3] and antifungicidal action. The antihelmintic action of these compounds was investigated.[4,5] Recently, particular dithiocarbamates have been found to serve as efficient inhibitors of the enzyme NO synthase responsible for the synthesis of nitrogen oxide in living organisms through oxidation of the endogenous ligand, *viz.*, L-arginine.[6] Therefore, a search for biologically active compounds in a series of poorly studied hetaryl derivatives of dithiocarbamates is of considerable importance.

Initially, we studied the reactions of sodium dithiocarbamates **1a,b** with 6-substituted 4-chloro-5-nitropyrimidines **2a—c** prepared earlier[7,8] and synthesized 5-nitropyrimidine derivatives **3a—f** (Scheme 1).

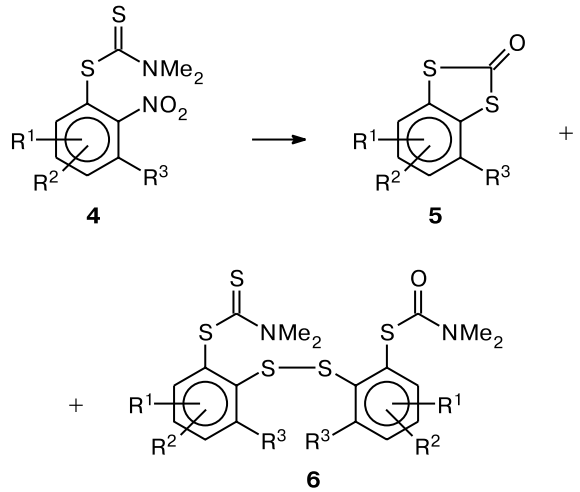
For particular benzene analogs of the compounds synthesized in our study, the pathways of their thermal transformations have been investigated. For example, ther-

Scheme 1



1: R^1 = Me (**a**), Et (**b**); **2:** R^1 = NHMe (**a**), NMe_2 (**b**), OMe (**c**); **3:** R^2 = NHMe, R^1 = Me (**a**), Et (**b**); R^2 = NMe_2, R^1 = Me (**c**), Et (**d**); R^2 = OMe, R^1 = Me (**e**), Et (**f**)

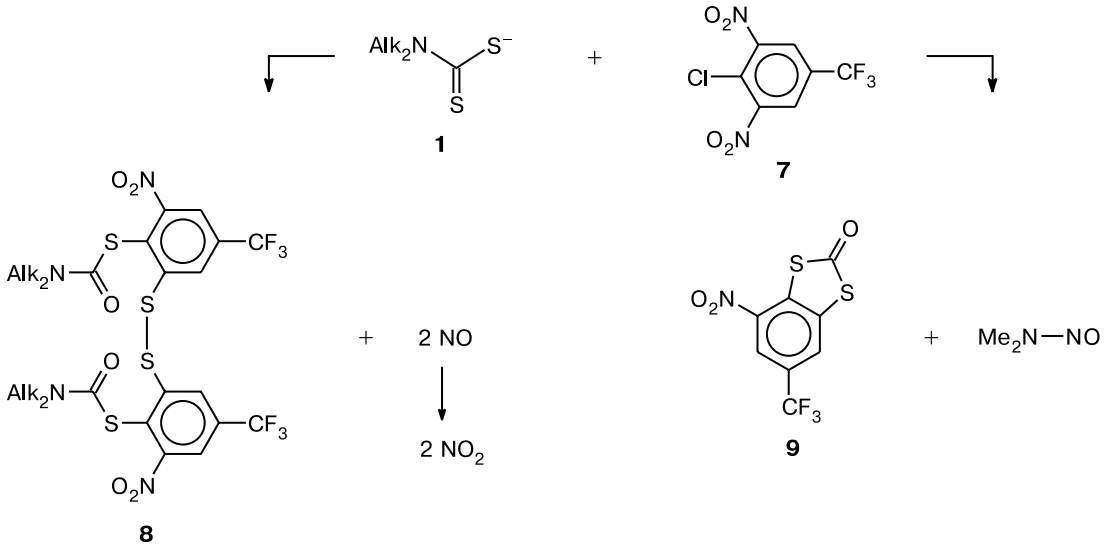
Scheme 2



R^1 = H, Cl, $NAlk_2$; R^2, R^3 = NO_2; R^3 = H, Me, CF_3, NO_2, CN

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 846—852, April, 2004.

Scheme 3



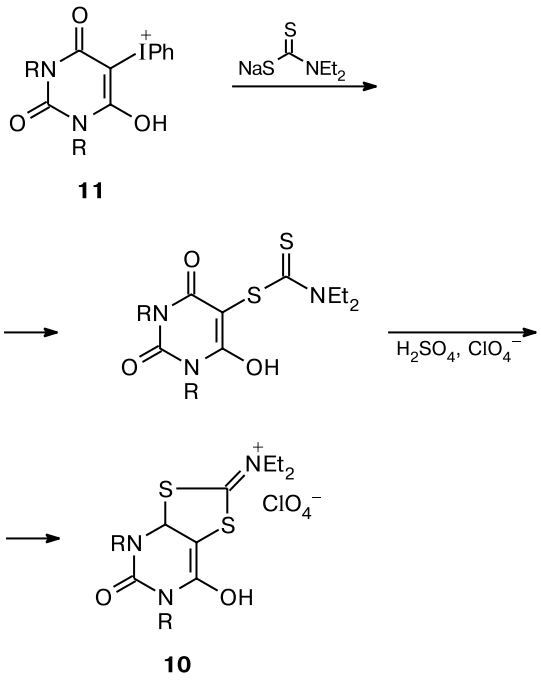
molysis of substituted *S*-2,4(2,3)-dinitrophenyl *N*,*N*-dimethyldithiocarbamates **4** was described.[9] It was demonstrated that the reactions afforded benzo-1,3-dithiol-2-one derivatives **5** and diaryl disulfides **6** in different ratios depending on the character of the substituent (R^3) (Scheme 2).

The reactions of dithiocarbamates **1** with 1-chloro-2,6-dinitro-4-trifluoromethylbenzene **7** giving rise to disulfide **8** (Scheme 3) were studied in detail.[10] In the course of the reactions, nitrogen oxide as well as nitrogen dioxide, which was formed due to oxidation of nitrogen oxide in air, were collected and identified. The mechanism of transformation of the initially formed dithiocarbamates into disulfides **8** and benzodithiolone **9** was discussed in the investigation.[11]

Since 5-nitropyrimidin-4-yl dithiocarbamates **3** synthesized in our study are structurally similar to compounds **4**, derivatives of the pyrimidine series would be expected to undergo analogous transformations to form the heterocyclic system, *viz.*, 1,3-dithiolo[4,5-*d*]pyrimidine **10**. This compound was first synthesized in 1991.[12] In the cited study, an original but preparatively very complicated procedure was developed for the synthesis of compound **10** by the reaction of 5-phenyliodoniobarbituric acids **11** with sodium diethyldithiocarbamate (Scheme 4).

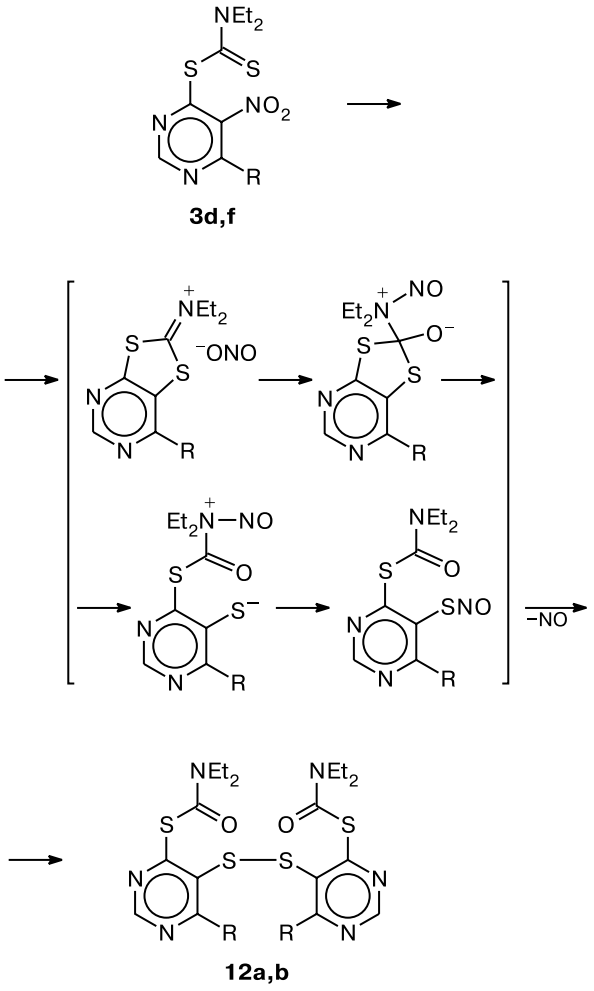
We demonstrated that thermal decomposition of dithiocarbamates **3d,f** afforded exclusively bis(4-*N*,*N*-diethylcarbamoylthio-6-R-pyrimidin-5-yl) disulfides (**12a,b**), whereas 1,3-dithiolo[4,5-*d*]pyrimidine derivatives were not detected. In the course of the reaction, NO_2 was eliminated as a brown gas with a characteristic odor. Based on the results of the earlier investigation,[11] it can be concluded that this reaction proceeds according to Scheme 5.

Scheme 4



The structures of disulfides **12a,b** were confirmed by elemental analysis and spectroscopic data. The mass spectra of these compounds have molecular ion peaks at *m/z* 544 $[M]^{+\bullet}$ and 570 $[M]^{+\bullet}$, respectively. Using 6-methoxy derivative **12b** as an example, one can follow the characteristic fragmentation of the molecular ion involving the S—S bond cleavage giving rise to the ion with *m/z* 272 and elimination of the S atom (*m/z* 240) as well as the stepwise elimination of the carbamate sub-

Scheme 5



3d,f **12a,b**

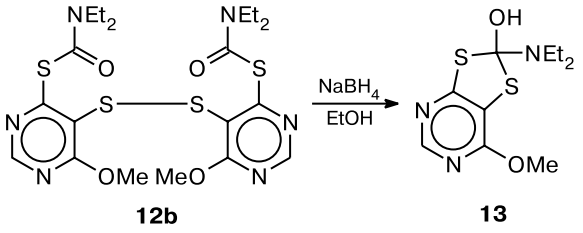
R = NMe_2 (**a**), OMe (**b**)

stituents from $[M]^+$: *m/z* 444 $[M - CONEt_2]^+$, 412 $[M - SCONEt_2]^+$, and 372 $[M - CONEt_2 - NEt_2]^+$. The peak of the $O{=}C{=}N^+Et_2$ ion has the maximum intensity. The IR spectra of the compounds under consideration show absorption bands of the CO groups at 1664 and 1668 cm^{-1}. The ^1H NMR spectroscopic data for compound **12b** (DMSO-d_6, δ) are also in complete agreement with the proposed structure: 8.45 (s, 2 H, 2 CH of pyrimidine); 3.90 (s, 6 H, 2 OMe); 3.02 (m, 8 H, 4 $C\underline{H}_2Me$); 0.56 (m, 12 H, 4 $CH_2C\underline{H}_3$).

We failed to prepare the 1,3-dithiolo[4,5-*d*]pyrimidine derivative by the direct synthesis. Hence, we attempted to reduce disulfide **12b** with sodium borohydride (Scheme 6). According to the results of elemental analysis, mass spectrometry, and IR and NMR spectroscopy, the reaction afforded 2-diethylamino-2-hydroxy-7-methoxy[1,3]dithiolo[4,5-*d*]pyrimidine (**13**).

The IR spectrum of compound **13** has broad absorption bands in the region of 3600—3100 cm^{-1}, which can

Scheme 6

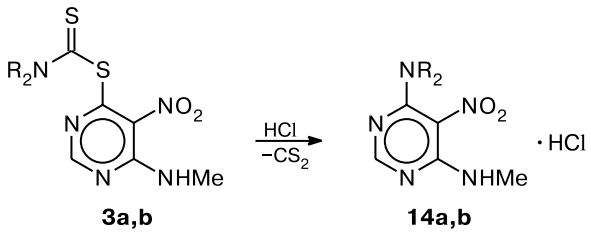


12b **13**

be assigned to stretching vibrations of the associated and free OH groups, whereas the C=O absorption band of the starting compound (1664 cm^{-1}) is absent. The ^1H NMR spectrum of dithiolopyrimidine **13** shows signals of two N—Et groups at δ 1.15 (t, 6 H) and 3.34 (q, 4 H) and signals of MeO and the pyrimidine proton at δ 3.91 (s, 3 H) and 8.53 (s, 1 H), respectively. At low field, a signal of the OH group is observed at δ 14.10 (br.s, 1 H). The ^{13}C NMR spectroscopic data (DMSO-d_6, δ) for pyrimidine **13** are also completely consistent with the proposed structure: 12.9 (2 $N(CH_2\underline{C}H_3)_2$); 42.1 and 44.1 (2 $N(\underline{C}H_2CH_3)_2$); 53.7 ($O\underline{C}H_3$); 100.4 (S—C—S); 110.2 (C(5)); 159.1 (C(2)); 162.6 (C(6)); 171.3 (C(4)). An attempt to transform compound **13** into dithiolopyrimidine by heating failed because of substantial resinification.

When studying these transformations, we observed an unusual phenomenon on heating of 5-nitropyrimidin-4-yl dialkyldithiocarbamates. Thermolysis of dithiocarbamates **3a,b** both is acetone and isopropyl alcohol yielded compounds, whose structures correspond to none of the expected transformation products of dialkyldithiocarbamates. Acidification of the reaction mixture giving rise to the corresponding hydrochlorides proved to be the most convenient procedure for isolation of compounds in individual form. In all cases, the reaction products were obtained in nearly quantitative yields. Gas-liquid chromatography revealed the presence of free carbon disulfide in the reaction mixture. The reaction products did not contain sulfur and physicochemical study unambiguously demonstrated that these compounds have structures of 4-[dimethyl(ethyl)amino]-6-methylamino-5-nitropyrimidines (**14a,b**) (Scheme 7).

Scheme 7



3a,b **14a,b**

R = Me (**a**), Et (**b**)

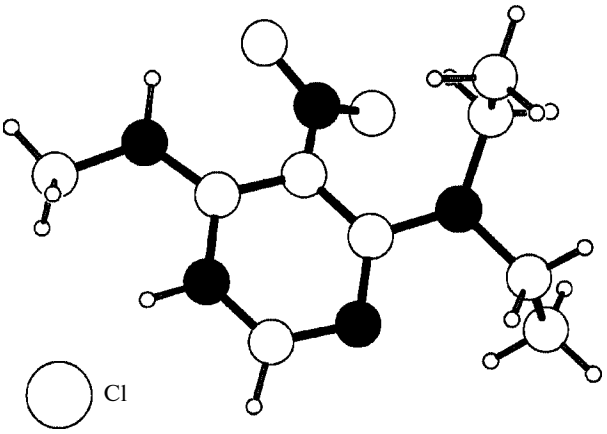


Fig. 1. X-ray structure of compound **14b**.

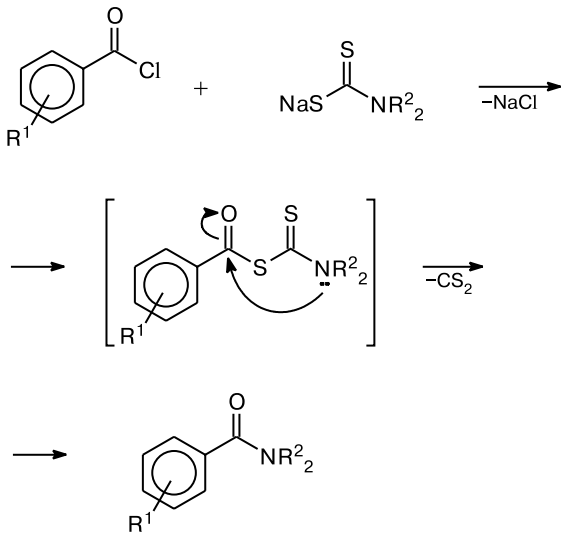
It should be emphasized that dithiocarbamates **3a,b** are transformed into diaminonitropyrimidine **14** only if the pyrimidine ring contains the methylamino group at position 6, whereas analogous derivatives with the dimethylamino substituent do not undergo this transformation.

Study of the structures of the resulting salts showed that these compounds are protonated at the endocyclic N atom. This is evident from the X-ray diffraction data for hydrochloride **14b** (Fig. 1), which is the *N*(1)-protonated product.

Examples of decomposition of dialkyldithiocarbamates accompanied by elimination of carbon disulfide were reported in the literature.[13–15] However, this process, as a rule, takes place in the reactions of sodium dialkyldithiocarbamates with organic acid chlorides (Scheme 8).

To interpret the above-described results, it was necessary to understand why such a small change in the structure of compound **3a—d** (a change from the secondary to tertiary amino group at position 6 of the pyrimidine ring)

Scheme 8



leads to a radical change in the pathway of thermal decomposition. In the presence of the 6-MeNH substituent, the reaction affords (with elimination of carbon disulfide) 4-dialkylaminopyrimidines. In the presence of the 6-Me_2N substituent, the nitro group is eliminated to give disulfide. This change cannot be attributable to an additional and very small electron-donating effect of the second methyl group in the NMe_2 substituent. It seemed most reasonable that steric factors play the major role because the system under consideration contains three bulky substituents at positions 4, 5, and 6 of the pyrimidine ring. To examine this assumption, 6-methylamino-5-nitropyrimidin-4-yl diethyldithiocarbamate (**3b**) (Fig. 2) and 6-dimethylamino-5-nitropyrimidin-4-yl diethyldithiocarbamate (**3d**) (Fig. 3) were studied by X-ray diffraction analysis.

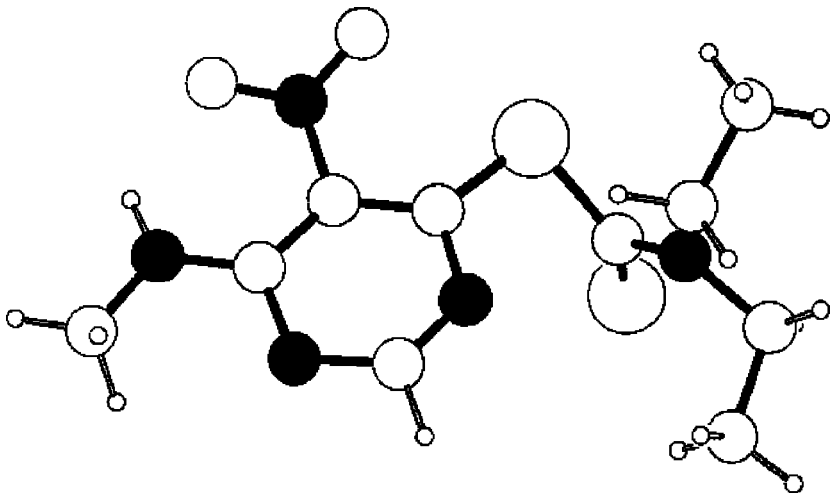


Fig. 2. X-ray structure of compound **3b**.

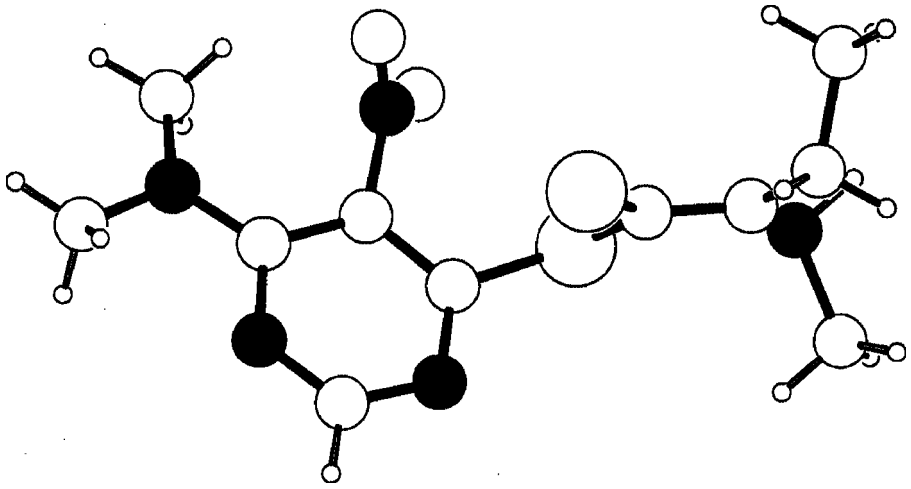


Fig. 3. X-ray structure of compound **3d**.

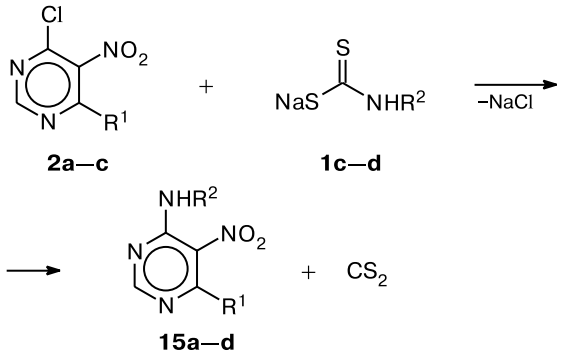
As can be seen from Fig. 2, both the nitro and methylamino groups in 6-methylamino derivative **3b** lie in the plane of the pyrimidine ring. The methyl group of the NHMe substituent is turned away from the nitro group, and the proton of this substituent forms a weak hydrogen bond with one of the O atoms of the nitro group. In this case, a partial positive charge is, evidently, located on the C(6) atom of pyrimidine. As a consequence, this atom is attacked by the electron pair of the N atom of the diethylthiocarbamoyl fragment resulting in elimination of carbon disulfide to give diaminonitropyrimidine **14b**.

The structure of molecule **3d** differs radically from that of 6-methylamino derivative **3b** in that the nitro group deviates from the plane of the pyrimidine ring (it is twisted by almost 90° under the influence of the bulky S atom and the dimethylamino group lying in the plane of the pyrimidine ring). This phenomenon is accompanied by disruption of the conjugation and a noticeable decrease in the electron-withdrawing effect of the nitro group on the C(6) atom of pyrimidine, which bears a substantially lower positive charge compared to that in compound **3b**. This positive charge is insufficient for the attack of π electrons on the N atom and the formation of the corresponding diaminopyrimidine. As a consequence, thermal decomposition of this type of pyrimidines involves elimination of the nitro group to give disulfides according to the above-discussed scheme.

It should be noted that the presence of the nitro group in the pyrimidine ring facilitates the nucleophilic substitution of the halogen atom at position 4 regardless of the steric requirements of the substituent at position 6. Study of the reactions of 4-chloropyrimidines **2a—c** with the corresponding monoalkyldithiocarbamates **1c—d** demonstrated that these reactions afforded compounds **15** containing the alkylamino group at position 4 (Scheme 9).

Changes in the reaction conditions (a decrease in the temperature, the use of another solvent, changes in the

Scheme 9



1: R^2 = Me (**c**), Et (**d**), $NHCH(CH_2)_2$ (**e**);
15: R^1 = NHMe, R^2 = Me (**a**); R^1 = NMe_2, R^2 = Et (**b**); R^1 = NMe_2, R^2 = $CH(CH_2)_2$ (**c**); R^1 = OMe, R^2 = Me (**d**)

reaction time) did not lead to the formation of pyrimidinyl dithiocarbamates. Hence, it can be concluded that the latter very readily undergo decomposition. In all reaction mixtures, we identified free carbon disulfide. This indicates that the reactions proceed according to the mechanism of thermal decomposition of pyrimidinyl dithiocarbamates accompanied by elimination of carbon disulfide (see above).

Therefore, heating of 5-nitro-6-R-pyrimidin-4-yl dialkyldithiocarbamates can result in two reaction pathways giving correspondingly disulfides **12** and 4,6-diamino-5-nitropyrimidine derivatives **14**. The former pathways is of particular importance because it involves the intramolecular *ipso*-substitution of the nitro group accompanied by elimination of nitrogen oxide, which is one of the key regulators of cell metabolism in mammalian organisms.[17] Since it is not inconceivable that processes of this type are enzymatic, it seems probable that compounds containing the *ortho*-arranged nitro and

dithiocarbamoyl substituents can serve as donors of nitrogen oxide in living organisms. Consequently, one would expect that particular compounds of this series might exhibit biological activity.

Experimental

The IR spectra were recorded on a Perkin—Elmer 457 instrument. The mass spectra (EI) were obtained on a Finnigan SSQ-710 mass spectrometer with direct inlet of the sample into the ion source. The ^{1}H NMR spectra were measured on Varian Unity 400 and Bruker AC-300 spectrometers in DMSO-d_6. The purity of the products and the course of the reactions were monitored by TLC on Merck TLC-254 Silicagel 60 plates (hexane—acetone, 3 : 1, as the eluent; visualization with UV light). The melting points were determined on an Electrothermal 9100 instrument (UK). The physicochemical characteristics, results of elemental analysis, and the ^{1}H NMR spectroscopic data for the compounds synthesized are given in Table 1.

The detailed results of powder X-ray diffraction study, the solution and refinement of the crystal and molecular structures of **3b,d** and **14b**, and the atomic coordinates were published in the study.[16]

6-R-5-Nitropyrimidin-4-yl dialkyldithiocarbamates (3a—e). The corresponding sodium dialkyldithiocarbamate (10.7 mmol) was added to a solution of 4-chloro-6-R-5-nitropyrimidine[7,8] **2** (10.5 mmol) in EtOH (50 mL). The reaction mixture was kept at ~20 °C for 2—10 h. The course of the reactions was monitored by TLC (a 2 : 1 hexane—acetone or 9 : 1 chloroform—methanol mixture as the eluent). The reaction mixture was poured into water and the bright-yellow precipitate of pyrimidine **3** was filtered off.

Bis(4-diethylcarbamoylthio-6-dimethylaminopyrimidin-5-yl) disulfide (12a). A solution of diethyldithiocarbamate **3d** (1.7 g, 5.39 mmol) in xylene (40 mL) was refluxed for 5 h and then concentrated. The residues was treated with a mixture of anhydrous EtOH (20 mL) and diethyl ether (15 mL) and the white crystalline product that formed was filtered off in a yield of 0.85 g (56%). M.p. 219—221 °C (EtOH). Found (%): C, 46.45;

Table 1. Results of elemental analysis, spectroscopic data, and physicochemical characteristics of the compounds synthesized

Compound	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula	^{1}H NMR (DMSO-d_6), δ	MS, *m/z* (I_{rel} (%))
			C	H	N			
3a	72	164—165 (EtOH)	35.37 / 35.25	3.94 / 4.06	25.38 / 25.62	$C_8H_{11}N_5O_2S_2$	9.35 (br.d, 1 H, NH); 8.21 (s, 1 H, CH); 3.38 (s, 4 H, 2 Me); 3.13 (s, 3 H, NMe)	273 $[M]^+$ (12)
3b	74	142—143 (EtOH)	39.36 / 39.85	4.91 / 5.02	23.27 / 23.24	$C_{10}H_{15}N_5O_2S_2$	9.23 (br.d, 1 H, NH); 8.24 (s, 1 H, CH); 3.84, 3.42 (both q, 2 H each, CH_2); 3.12 (s, 3 H, NMe); 1.25 (m, 6 H, 2 Me)	301 $[M]^+$ (11)
3c	83	64—65 (EtOH)	37.79 / 37.62	4.61 / 4.56	24.38 / 24.37	$C_9H_{13}N_5O_2S_2$	—	287 $[M]^+$ (23)
3d	80	106—107 (MeOH)	42.06 / 41.89	5.42 / 5.43	22.31 / 22.20	$C_{11}H_{17}N_5O_2S_2$	8.31 (s, 1 H, CH); 3.96, 3.90 (both q, 2 H each, CH_2); 3.05 (s, 6 H, NMe_2); 1.25 (t, 6 H, 2 Me)	315 $[M]^+$ (16)
3e	78	96—98 (EtOH)	34.97 / 35.03	3.55 / 3.67	20.34 / 20.42	$C_8H_{10}N_4O_3S_2$	—	274 $[M]^+$ (15)
3f	62	121—122 (hexane)	39.48 / 39.42	4.64 / 4.67	18.73 / 18.53	$C_{10}H_{14}N_4O_3S_2$	8.33 (s, 1 H, CH); 4.11 (s, 3 H, OMe); 3.78, 3.56 (both q, 2 H each, CH_2); 1.27 (m, 6 H, 2 Me)	302 $[M]^+$ (11)
14a	94	146—148 (EtOH—H_2O, 8 : 1)	36.11 / 35.98	5.22 / 5.18	15.37 / 15.17	$C_7H_{11}N_5O_2 \cdot HCl$	9.21 (d, 1 H, NH); 9.01 (s, 1 H, CH); 3.07 (s, 6 H, NMe_2); 2.96 (s, 3 H, NMe)	197 $[M]^+$ (67)
14b	92	118—120 (EtOH—H_2O, 8 : 1)	41.81 / 41.30	6.34 / 6.16	13.33 / 13.55	$C_9H_{15}N_5O_2 \cdot HCl$	9.22 (d, 1 H, NH); 9.03 (s, 1 H, CH); 3.46 (s, 4 H, $N(CH_2)_2$); 1.24 (s, 6 H, 2 Me)	225 $[M]^+$ (72)
15a	70	183—185 (Pr^iOH)	39.20 / 39.34	5.07 / 4.95	38.46 / 38.23	$C_6H_9N_5O_2$	—	183 $[M]^+$ (54)
15b	66 (EtOH)	151—153	45.48 / 45.49	6.31 / 6.20	33.04 / 33.16	$C_8H_{13}N_5O_2$	—	211 $[M]^+$ (100)
15c	69 (EtOH)	139—141	48.25 / 48.42	5.75 / 5.87	31.29 / 21.37	$C_9H_{13}N_5O_2$	—	223 $[M]^+$ (86)
15d	57 (EtOH)	146—147	39.23 / 39.13	4.30 / 4.38	30.17 / 30.42	$C_6H_8N_4O_3$	—	184 $[M]^+$ (93)

H, 5.86; N, 19.59. $C_{22}H_{34}N_8O_2S_4$. Calculated (%): C, 46.29; H, 6.00; N, 19.63. MS, *m/z* (I_{rel} (%)): 570 $[M]^+$ (64), 470 $[M - CONEt_2]^+$ (37), 438 $[M - SCONEt_2]^+$ (30), 285 $[0.5\ M]^+$ (100), 253 $[0.5\ M - S]^+$ (36), 241 $[0.5\ M - NMe_2]^+$ (43), 100 $[O{=}C{=}N^+Et_2]^+$ (760). IR (Nujol mulls), ν/cm^{-1}: 1668 (C=O), 1550, 1256, 1218, 1170, 1116, 993, 852.

Bis(4-diethylcarbamoylthio-6-methoxypyrimidin-5-yl) disulfide (12b). ***A.*** A solution of pyrimidine **3e** (0.5 g, 1.62 mmol) in xylene (40 mL) was refluxed for 1 h, concentrated, and treated with diethyl ether (30 mL). Large white crystals of disulfide **12b** were filtered off in a yield of 0.37 g (84%). M.p. 189—191 °C (EtOH). Found (%): C, 43.98; H, 5.07; N, 15.52. $C_{20}H_{28}N_6O_4S_4$. Calculated (%): C, 44.10; H, 5.18; N, 15.43. MS, *m/z* (I_{rel} (%)): 544 $[M]^+$ (32), 444 $[M - CONEt_2]^+$ (44), 412 $[M - SCONEt_2]^+$ (31), 372 $[M - CONEt_2 - NEt_2]^+$ (17), 272 $[0.5\ M]^+$ (83), 240 $[0.5\ M - S]^+$ (55), 225 $[0.5\ M - S - Me]^+$ (27), 100 $[O{=}C{=}N^+Et_2]^+$ (100). IR (Nujol mulls), ν/cm^{-1}: 1664 (C=O), 1520, 1244, 1212, 1110, 1025.

B. Pyrimidine **3e** (0.5 g, 1.62 mmol) was dried in a vacuum desiccator over P_2O_5 for 1 day and heated *in vacuo* (~40 Torr) to 135—140 °C for 15 min. The resulting black resinous mixture was dissolved in acetone and filtered through a layer of activated carbon and aluminum oxide. The filtrate was concentrated and treated with a mixture of anhydrous EtOH (20 mL) and diethyl ether (10 mL). White crystalline compound **12b** was filtered off in a yield of 0.32 g (73%). A mixture of samples prepared by the methods ***A*** and ***B*** showed no melting point depression. The IR spectra of both samples are identical.

2-Diethylamino-2-hydroxy-7-methoxy-1,3-dithiolo[4,5-*d*]pyrimidine (13). Sodium borohydride (0.18 g, 4.73 mmol) was added to a solution of disulfide **14b** (0.7 g, 1.28 mmol) in refluxing EtOH (30 mL). The resulting suspension was refluxed for 2.5 h. The reaction mixture was concentrated. The residue was dissolved in water (20 mL), acidified with 10% HCl to pH ~5, and kept at 6—8 °C for 16 h. The white precipitate of pyrimidine **13** (0.51 g, 73%) that formed was filtered off. M.p. 152—153 °C (benzene). Found (%): C, 43.91; H, 5.43; N, 15.29. $C_{10}H_{15}N_3O_2S_2$. Calculated (%): C, 43.93; H, 5.53; N, 15.37. MS, *m/z* (I_{rel} (%)): 273 $[M]^+$ (27), 200 $[M - HNEt_2]^+$ (36), 172 $[M - COHNEt_2]^+$ (86), 108 $[M - SSCONEt_2]^+$ (100). IR (KBr, ν/cm^{-1}): 3600—3200, 3109 (HO assoc.), 1648, 1580, 1555, 1288, 1214, 1150, 1113, 1032. ^{1}H NMR (DMSO-d_6), δ: 1.15 (t, 6 H, 2 $CH_2C\underline{H}_3$); 3.34 (q, 4 H, 2 $C\underline{H}_2$Me); 3.91 (s, 3 H, OMe); 8.35 (s, 1 H, H of pyrimidine); 14.10 (br.s, 1 H, OH).

4-Dialkylamino-6-methylamino-5-nitropyrimidine hydrochlorides (14a,b). A solution of pyrimidine **3** (10.5 mmol) in acetone (or isopropyl alcohol) (50 mL) was refluxed for 4—8 h until the starting dithiocarbamate was completely consumed (TLC). The reaction mixture was concentrated *in vacuo* and the residue was treated with a 9% methanolic solution of HCl to pH ~3, again concentrated, and triturated with diethyl ether. The beige precipitate of hydrochloride **14** that formed was recrystallized from MeOH (see Table 1).

6-R-4-Dialkylamino-5-nitropyrimidines (15a—d). A solution of the corresponding sodium monoalkyldithiocarbamate (10.7 mmol) was added to a solution of pyrimidine **2** (10.5 mmol) in EtOH (50 mL) and the reaction mixture was kept at ~20 °C for 2—5 h. The course of the reaction was monitored by TLC ($CHCl_3$—MeOH, 9 : 1, as the eluent). The reaction mixture was concentrated *in vacuo* and the residue was treated with cold water (10 mL). The pale-yellow precipitate of dialkylaminopyrimidine **15** that formed was filtered off (see Table 1).

References

1. M. Marinovich, B. Viviani, V. Capra, E. Corsini, L. Anselmi, G. D'Agostino, A. Di Nucci, M. Binaglia, M. Tonini, and C. L. Galli, *Chem. Res. Toxicol.*, 2002, **15**, 26.
2. A. Easton, K. Guven, and D. I. de Pomerai, *J. Biochem. Mol. Toxicol.*, 2001, **15**, 15.
3. Pat. BRD3016767; *Chem. Abstrs*, 1981, **96**, P52327.
4. E. Halbova, E. Sidova, and R. Spaldonova, *Chem. Pap.*, 1986, **4**, 127.
5. R. Sh. Erkasov, A. B. Tosherov, and A. M. Shaikina, *Dokl. Khim. Fak. MGU* [*Dokl. Dept. Chem., Moscow State University*], 1981, 137 (in Russian).
6. V. G. Granik and N. B. Grigor´ev, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 1819 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 1973].
7. V. A. Makarov, A. L. Sedov, M. P. Nemeryuk, N. P. Solov´eva, O. S. Anisimova, and T. S. Safonova, *Khim. Geterotsikl. Soedin.*, 1994, 1420 [*Chem. Heterocycl. Compd.,* 1994, **30**, 1231 (Engl. Transl.)].
8. J. Clark, J. Gelling, J. W. Southon, and M. S. Morton, *J. Chem. Soc., C*, 1970, 494.
9. K. Rasheed and J. D. Warkentin, *J. Org. Chem.*, 1977, **42**, 1265.
10. J. J. D'Amico, C. C. Tung, W. E. Dahl, and D. J. Dahm, *J. Org. Chem.*, 1976, **41**, 3564.
11. K. Rasheed and J. D. Warkentin, *J. Org. Chem.*, 1979, **44**, 267.
12. B. Ya. Adamsone, B. Zh. Tilka, and I. K. Raiskuma, *Abstrs of Papers, Int. Conf. on Chemistry of Dicarbonyl Compounds*, Riga, 1991, P-42.
13. W. Hanefeld and G. Glaeske, *Liebigs Ann. Chem.*, 1981, **8**, 1388.
14. S. N. Singh and M. V. George, *J. Org. Chem.*, 1971, **36**, 615.
15. E. H. Hoffmeister and D. S. Tarbell, *Tetrahedron*, 1965, **21**, 2857.
16. V. V. Chernyshev, K. A. Paseshnichenko, V. A. Makarov, E. J. Sonneveld, and H. Schenk, *Acta Cryst.*, *Sect. C*, 2001, **C57**, 72.
17. P. Vallance and J. Leiper, *Nature Reviews, Drug Disc.*, 2002, **1**, 939.

Received December 18, 2003;
in revised form January 22, 2004