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4-DIALKYLDITHIOCARBAMOYL-5-NITROPYRIMIDINES. SYNTHESIS, STRUCTURE, PROPERTIES

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The reaction of 4-chloro-5-nitropyrimidines with sodium dialkyldithiocarbamates gives the corresponding 4-dialkyldithiocarbamoyl derivatives. On heating these derivatives the nitro group is displaced and disulfides are formed at position 5 of the pyrimidine ring. Transformation to 1,3-dithiolo[4,5-d]pyrimidines has been demonstrated.

It is known that esters of dithiocarbamic acid possess various biological activities [1-3], but the heterocyclic derivatives of this class of compound have not been studied adequately. We have synthesized 4-dialkyldithiocarbamoyl-5-nitropyrimidines and have studied some of their properties as a continuation of our investigations of the reactions of 4-chloro-5-nitropyrimidines with carbonic acid derivatives.

The reaction of the 4-chloro-5-nitro-6-substituted pyrimidines (Ia, b) with sodium diethyl- and dipropyl-dithiocarbamate gave the corresponding dialkyldithiocarbamoyl derivatives (IIa-d) in high yield.

It was known previously that on pyrolysis substituted dinitrophenyl dimethyldithiocarbamates form derivatives of 1,3-dibenzodithiol-2-one and bis(dialkylthiocarbamoylmononitroaryl) disulfides, depending on the character of the substituent in the aromatic ring [3]. The analogous process in the case of dialkyldithiocarbamates of the heterocyclic series has several special features. The thermal conversion of substituted 2-dimethyldithiocarbamoyl-3,5-dinitropyridines leads to 2-dimethylamino-3,5-dinitropyridine in addition to derivatives of 1,3-dithiolo[2,3-c]pyridin-2-one and bis(dialkylthiocarbamoylpyridyl) disulfides. In the case of 3-dimethyldithiocarbamoyl-2,4-dinitrothiophen only the corresponding thieno[2,3-d]-1,3-dithiol-2-one was formed in low yield [4]. The structure of compounds (IIa-d) led us to think that this conversion might be formed. This system was first synthesized in 1991 from the product of the reaction of 5-phenyliodoniumbarbituric acids with sodium diethyldithiocarbamate [5, 6].

However, it was established that pyrolysis of the 4-dialkyldithiocarbamoyl-5-nitropyrimidines (IIa, b) leads exclusively to the bis(4-dialkylthiocarbamoyl-6-%-5-pyrimidyl) disulfide (IIIa, b). The presence of derivatives of 1,3-dithiolo[4,5-d]pyrimidine in the reaction products was not established. The formation of dipyrimidyl disulfides in this reaction is evidently due to an intramolecular displacement of the nitro group, which is in agreement with the literature data given above. The mass spectra of the substances obtained are characterized by the presence of peaks for the molecular ions $M^{+\cdot}$ 544 and $M^{+\cdot}$ 570. It was shown for compound (IIIa) that the fragmentation of the molecular ion is explained by fission of the S–S bond with the formation of the corresponding ion of *m/z* 272 and subsequent elimination of the sulfur atom (*m/z* 240), and also the stepwise removal from M^+ of the thiocarbamate substituents: $[M\text{-}CONEt_2]^+$ (444), $[M\text{-}SCONEt_2]^+$ (412), $[M\text{-}CONEt_2\text{–}NEt_2]^+$ (372). The ion with *m/z* 100 $(O{=}C{=}NEt_2)^+$ had the maximum intensity in the spectrum.

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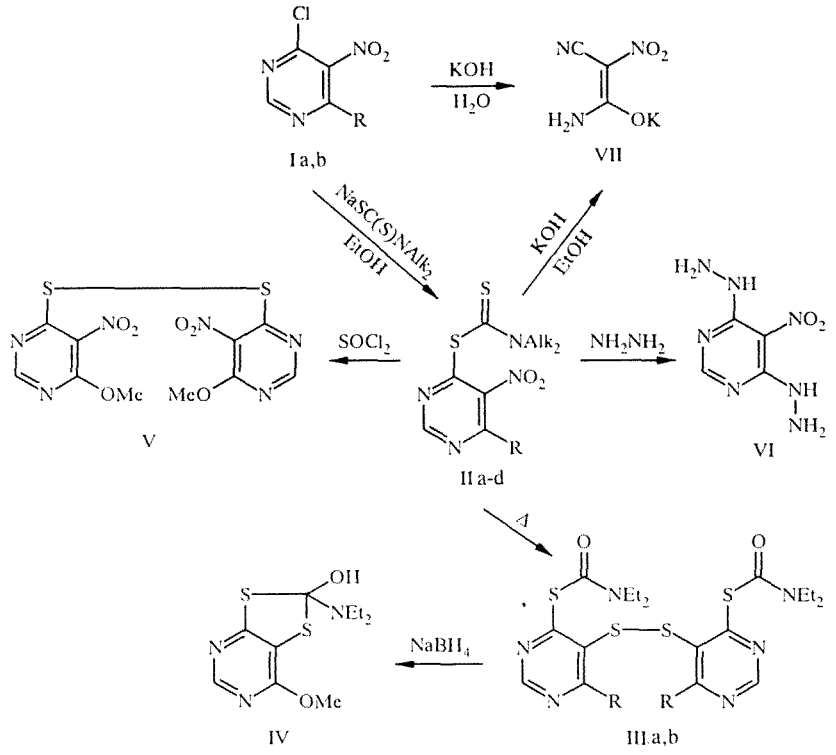

I, IIIa R = OMe, b R = NMe_2; IIa R = OMe, Alk = Et, b R = OMe, Alk = Pr, c R = NMe_2, Alk = Et, d R = NMe_2, Alk = Pr

A derivative of 1,3-dithiolo[4,5-d]pyrimidine was obtained only when R = OMe by treating (IIIa) with sodium borohydride. Signals were observed in the PMR spectrum of the product (IV) for protons of the Et groups at 1.15 and 3.34 ppm, broadened probably by hindered internal rotation. Signlas for the protons of the OMe group and the pyrimidine ring were found at 3.91 and 8.53 ppm respectively, and for the OH group at 14.10 ppm (strongly broadened signal).

Some properties of the 4-dithiocarbamoyl derivatives (IIa-d) were studied using compound (IIa) as an example. It was discovered that on reaction with $SOCl_2$ in toluene the dipyrimidyl disulfide (V) was formed in place of the expected thiomido-chloride [7]. The reaction of (IIa) with hydrazine hydrate led to 4,6-dihydrazino-5-nitropyrimidine (VI) due to the substitution by hydrazine of both the methoxy and the dithiocarbamoyl groups. By treating compound (IIa) with alcoholic KOH the potassium salt of nitrocyanoacetamide (VII) was formed. This compound was also formed by an alternate synthesis by reacting 4,6-dichloro-5-nitropyrimidine with alkali in aqueous dioxan. The structure of (VII) was confirmed by analytical data and by the presence in the IR spectrum of absorption bands for an amino group (3368, 3270, 3210), a CN group (2206), and a CO group (1650 cm^{-1}).

4-Dialkyldithiocarbamoyl derivatives of 5-nitro-pyrimidine have been synthesized for the first time by us and some of their properties have been studied. A new approach to the synthesis of 1,3-dithiolo[4,5-d]pyrimidine has been discovered.

EXPERIMENTAL

The IR spectra were taken on a Perkin–Elmer spectrophotometer (nujol suspension). The NMR spectra were obtained on a Varian XL 200 spectrometer. Chemical shifts are given on the δ scale, internal standard was TMS. The mass spectra were drawn on a MAT 118 spectrometer with direct insertion of the substance into the ion source. A check on the purity of compounds and the course of reactions was effected chromatographically on Silufol UV 354 plates.

The data of elemental analysis for C, H, N, Cl, and S of all compounds synthesized corresponded to calculated values.

4-Diethyldithiocarbamoyl-6-methoxy-5-nitropyrimidine (IIa, $C_{10}H_{14}N_4O_3S_2$). A solution of sodium diethyldithiocarbamate trihydrate (2.4 g, 10.66 mmole) in ethanol (20 ml) was added to a solution of 4-chloro-6-methoxy-5-nitropyrimidine (Ia) (2.0 g, 10.55 mmole) in acetone (50 ml) and the mixture kept at 40-45°C for 2.5 h. The reaction mixture was evaporated to 30 ml, poured into water, and the orange crystalline product (2.8 g, 84.3%) filtered off, mp 121-122°C (from hexane). IR spectrum: 1510, 1121, 1057, 985 cm^{-1}.

4-Dipropyldithiocarbamoyl-6-methoxy-5-nitropyrimidine (IIIb, $C_{12}H_{18}N_4O_3S_2$) was obtained analogously from (Ia) (2.0 g, 10.55 mmole) and sodium dipropyldithiocarbamate trihydrate (2.7 g, 10.67 mmole). The yield of orange crystalline substance of mp 96-98°C (from methanol) was 2.8 g (80.4%). IR spectrum: 1561, 1130, 1011, 978 cm^{-1}.

4-Diethyldithiocarbamoyl-6-dimethylamino-5-nitropyrimidine (IIc, $C_{11}H_{17}N_5O_2S_2$) was obtained analogously from 4-chloro-6-dimethylamino-5-nitropyrimidine (Ib) (2.0 g, 9.90 mmole) and sodium diethyldithiocarbamate trihydrate (2.3 g, 10.22 mmole). The yield of orange crystalline substance of mp 106-107°C (from methanol) was 2.8 g (90.0%). IR spectrum: 1555, 1148, 1078, 899 cm^{-1}.

6-Dimethylamino-4-dipropyldithiocarbamoyl-5-nitropyrimidine (IId, $C_{13}H_{21}N_5O_2S_2$) was obtained analogously from (Ib) (2.0 g, 9.90 mmole) and sodium dipropyldithiocarbamate trihydrate (2.5 g, 9.88 mmole). The yield of orange crystalline substance of mp 64-65°C (from hexane) was 1.5 g (44.1%). IR spectrum: 157, 1098, 1031, 947 cm^{-1}.

Bis(4-diethylthiocarbamoyl-6-methoxy-5-pyrimidyl) Disulfide (IIIa, $C_{20}H_{28}N_6O_4S_2$). A. A solution of compound (IIa) (0.5 g, 1.62 mmole) in xylene (40 ml) was boiled for 1 h. The reaction mixture was evaporated, treated with ether (30 ml), and the white coarsely crystalline product (0.37 g, 84.0%) of mp 189-191°C (from ethanol) filtered off. M^+ 544. IR spectrum: 1664 (C=O), 1520, 1244, 1212, 1110, 1025 cm^{-1}.

B. Compound (IIa) (0.5 g: 1.62 mmole) was heated in vacuum to 135-140°C for 15 min. The mass obtained was dissolved in acetone (100 ml) and filtered through a layer of activated carbon and aluminum oxide. The filtrate was evaporated, treated with absolute alcohol (20 ml) and ether (10 ml), and the white crystalline product (0.32 g, 72.7%) filtered off. It had mp 189-191°C and was identical in spectral characteristics to the substance obtained by method A.

Bis(4-diethylthiocarbamoyl-6-dimethylamino-5-pyrimidyl) Disulfide (IIIb, $C_{22}H_{34}N_8O_2S_4$). A solution of compound (IIc) (1.7 g, 5.39 mmole) in xylene (40 ml) was boiled for 5 h. After evaporation of the solvent the residue was treated with a mixture of ethanol (20 ml) and ether (15 ml), and the white crystalline product (0.85 g: 55.5%) of mp 219-221°C (from ethanol) filtered off. M^+ 570. IR spectrum: 1668 (C=O), 1550, 1256, 1218, 1170, 1116, 993, 852 cm^{-1}.

5-Diethylamino-5-hydroxy-7-methoxy-1,3-dithiolo[4,5-d]pyrimidine (IV, $C_{10}H_{15}N_3O_2S_2$). Sodium borohydride (0.18 g, 4.73 mmole) was added to a solution of the disulfide (IIIa) (0.7 g, 1.28 mmole) in boiling alcohol (30 ml) and the mixture boiled for 2.5 h. The reaction mixture was evaporated, treated with water (20 ml), and acidified with 10% HCl to pH 6. After 15 h the white crystalline product (0.51 g, 72.8%) was filtered off. It had mp 152-153°C (from benzene). M^+ 273. IR spectrum: 3200-3600, 3109 (OH_{ass}), 1648, 1580, 1555, 1288, 1250, 1214, 1150, 1113, 1032 cm^{-1}. PMR spectrum: 1.15 (10H, t, $2CH_2CH_3$), 3.91 (3H, s, OCH_3), 8.35 (1H, s, $H_{pyrimid}$), 14.10 (1H, s, OH).

Bis(4-methoxy-5-nitro-6-pyrimidyl) Disulfide (V, $C_{10}H_8N_6O_6S_2$). Thionyl chloride (4.02 g, 29.77 mmole) was added to a suspension of compound (IIa) (3 g, 9.93 mmole) in toluene (10 ml) and the mixture heated to 70°C for 30 min. The solution was cooled, the resulting oil separated from the solution, which was evaporated, and treated with ethyl alcohol. The precipitated solid was filtered off, and a beige crystalline product (2.1 g, 56.7%) of mp 216-217°C (from ethanol) was obtained. M^+ 372. IR spectrum: 1653, 1577, 1380, 1278, 973, 785 cm^{-1}. PMR spectrum: 4.12 (3H, s, OCH_3), 8.08 (1H, s, H).

4,6-Dihydrazino-5-nitropyrimidine (VI). Hydrazine hydrate (5 ml: 17 mmole) was added to a solution of the dithiocarbamate (II) (3.40 mmole) in ethanol (20 ml) and the mixture left at room temperature for 30 min. The precipitated solid (VI) was filtered off. Yield was 74%, of mp 135°C (from methanol), which corresponds to the data of [8].

Nitrocyanoacetamide Potassium Salt (VII, $C_3H_2N_3O_3K$). A. A solution of potassium hydroxide (0.4 g, 10.0 mmole) in ethanol (20 ml) was added to a solution of compound (IIa) (1 g, 3.47 mmole) in ethanol (40 ml) and the mixture boiled for 3 h. The reaction mixture was cooled and the white crystalline solid (0.38 g, 66.0%) of mp 260-261°C (from ethanol) filtered off. IR spectrum: 3368, 3273, 3210 (NH_2), 2205 (CN), 1650, 1608, 1585, 1560, 1212, 1140, 1065 cm^{-1}.

B. A solution of KOH (1.8 g, 32.1 mmole) in water (8 ml) was added to a solution of 4,6-dichloro-5-nitropyrimidine (2.2 g, 11.3 mmole) in dioxan (50 ml). The reaction mixture was boiled for 2 h, evaporated, and the residue extracted with boiling methanol. After evaporation of the methanol a product was isolated (1.6 g, 93.0%), which was identical in mp and IR spectrum to the substance obtained by method A.

REFERENCES

1. S. Wolfgang, German Patent 3,016,767; Chem. Abs., **96**, 52327 (1981).
2. E. Halbova, E. Sidova, and R. Spaldonova, Chem. Pap., No. 4, 127 (1986).
3. K. Rasheed and J. Warkentin, J. Org. Chem., **42**, 1265 (1977).
4. K. Rasheed and J. Warkentin, J. Heterocycl. Chem., **18**, 1581 (1981).
5. B. I. Adamsone, V. G. Tilika, and I. K. Raiskuma, Chemistry of Dicarbonyl Compounds. Abstracts, Riga, 1991, p. 42.
6. O. Ya. Neiland, B. Ya. Adamsone, and I. Ya. Raiskuma, Khim. Geterotsikl. Soedin., No. 8, 1117 (1992).
7. O. G. Renold and H. D. Fisher, Arch. Pharm. (Weinheim, Ger.), **321**, 191 (1982).
8. R. H. Wiley, J. Sanet, and K. H. Hussung, J. Heterocycl. Chem., **4**, 175 (1964).