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INVESTIGATION OF BISHETERYL DERIVATIVES OF PIPERAZINE AND ITS ANALOGS.

2.* SYNTHESIS AND PROPERTIES OF BIS(DIALKYLDITHIOCARBAMOYL-5-NITRO-4-PYRIMIDYL)PIPERAZINES

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The corresponding 6-dialkyldithiocarbamoyl derivatives are obtained by reacting N,N'bis(2-R-6-chloro-5-nitro-4-pyrimidyl)-carbamates. In one example it was shown that these products may be rearranged on heating with the formation of the bis(1,3-dithiolo[4,5-d]pyrimidyl)piperazine system, and in the presence of an alkaline catalyst may be converted by fission of the pyrimidine ring into the highly polarized N,N'-bis(1-amino-2-cyano-2-nitro-1-ethenyl)-piperidine.

We previously reported the synthesis and certain properties of dialkyldithiocarbamoyl derivatives of 5-nitro-6-substituted pyrimidines [1]. As a continuation of these studies, the symmetrical N,N'bispyrimidyl substituted piperazines (Ia, b) synthesized previously [2] have been reacted with sodium diethyl- and dipropyldithiocarbamate, as a result of which the corresponding derivatives (IIa-d) were obtained. Certain conversions of the latter have been studied using (IIb) as an example.

It was shown that the pyrolysis of compound (IIb) leads to 1,3-dithiolo[4,5-d]pyrimidine (III), unlike the 4-dialkyldithiocarbamoyl-5-nitro-6-R-pyrimidines for which thermal conversion into 4-dialkylthiocarbamoyl-6-R-5-pyrimidyl disulfides [2] is a characteristic. These results are in good agreement with literature data on the conversion under analogous conditions of 2,5- and 2,4-dinitrophenyldialkyldithiocarbamates both to substituted dialkylthiocarbamoylnitrophenyl sulfides and 1,3-benzdithiol-2-one. When a dialkylamino group is present in the aryl substituent the latter are the sole reaction products, their formation being explained by an intramolecular displacement of the nitro group [3, 4].

We also discovered that heating the derivative (IIb) in boiling xylene leads to compound (III), in the PMR spectrum of which multiplet signals were observed for the protons of the propyl substituent, the piperazine ring, and the proton of the pyrimidine ring (see the Experimental section). The complexity of the latter signal is linked both with the different conformations of the dithiolopyrimidine system and with the syn–anti isomerism of the C=N–Pr fragment. The available data enabled the product (III) to be assigned the structure of bis(1,3-dithiolo[4,5-d]pyrimidyl)-piperazine.

Treatment of N,N'-bis(dithiocarbamoylpyrimidyl)-piperazine (IIb) with aqueous KOH solution leads to N,N'bis(1-amino-2-cyano-2-nitro-1-ethenyl)piperazine (IV), the structure of which was confirmed by data of elemental analysis and by the presence in the IR spectrum of absorption bands in the 2200 cm^{-1} region corresponding to the stretching vibration of the $C \equiv N$ group. This same compound was also obtained by us on treating the N,N'-bis-pyrimidylpiperazine (Ia) with aqueous acetic acid. It may be assumed from the literature data [5, 6] that the process of forming product (IV) includes covalent hydration of the pyrimidine ring and its subsequent fission with the formation of a tetrasubstituted ethylene in which the ethylenic bond is the $C_{(4)}=C_{(5)}$ fragment of the pyrimidine ring.

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*For part 1 see [1].

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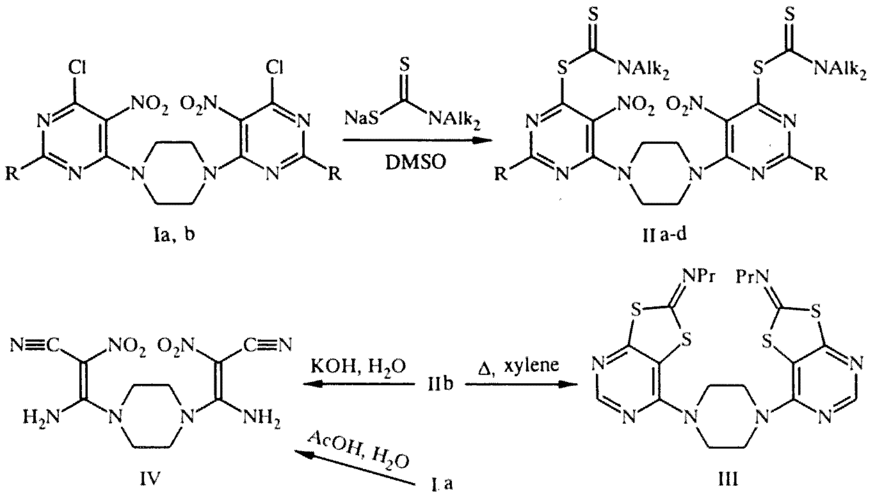

I a R = H, b R = Me; II a R = H, Alk = Et, b R = H, Alk = Pr,
c R = Me, Alk = Et, d R = Me, Alk = Pr

The intramolecular elimination of a nitro group was discovered while studying the properties and conversions of bis(6-chloro-5-nitro-4-pyrimidyl)piperazines. This reaction is new for compounds of the pyrimidine series. A 1,3-dithiolo[4,5-d-pyrimidine system is formed, but has been studied little up to the present time. It was established that the substituted N,N'-divinylpiperazine (IV) is formed on alkaline hydrolysis of the bisdithiocarbamoylbispyrimidylpiperazine (IIb) by fission of the pyrimidine ring.

EXPERIMENTAL

The IR spectra were taken on Perkin-Elmer spectrophotometers (Nujol mull). The ^1H NMR spectra were taken on a Varian XL-200 spectrometer. Chemical shifts are given on the δ scale, internal standard was TMS. Mass spectra were obtained on a Varian MAT 118 spectrometer with direct insertion of compounds into the ion source. A check on the purity of products and the course of reactions was effected on Silufol UV-254 plates.

Data of elemental analysis of all the compounds synthesized corresponded to the calculated values for C, H, N, and S.

N,N'-bis(6-Diethyldithiocarbamoyl-5-nitro-4-pyrimidyl)piperazine (IIa) $C_{22}H_{30}N_{10}O_4S_4$. Sodium diethyldithiocarbamate trihydrate (0.85 g, 4.97 mmole) was added to a solution of compound (Ia) (0.65 g, 1.65 mmole) in dimethylformamide. After 20 min methanol (20 ml) and water (20 ml) were added to the reaction mixture. The precipitated solid product was filtered off and washed with water (100 ml). Compound (IIa) (1 g, 71.4%) was obtained as yellow-orange crystals of mp 164-165°C (from methanol). IR spectrum: 1560, 977 cm^{-1}.

N,N'-bis(6-Dipropyldithiocarbamoyl-5-nitro-4-pyrimidyl)piperazine (IIb) $C_{26}H_{38}N_{10}O_4S_4$ was synthesized analogously to (IIa) from compound (Ia) (0.7 g, 1.75 mmole) and sodium dipropyldithiocarbamate trihydrate (0.88 g, 3.46 mmole). The product (IIb) (0.8 g, 67.2%) was obtained as yellow-orange crystals of mp 142-143°C (from ethanol). IR spectrum: 1570, 1482, 1079, 851, 774 cm^{-1}.

N,N'-bis(6-Diethyldithiocarbamoyl-2-methyl-5-nitro-4-pyrimidyl)piperazine (IIc) $C_{24}H_{34}N_{10}O_4S_4$. Sodium diethyl-dithiocarbamate trihydrate (1.2 g, 7.02 mmole) was added to a solution of compound (Ib) (1.5 g, 3.48 mmole) in DMSO (40 ml). After 1 h the reaction mixture was poured into cold water (200 ml) and the product (IIc) (1.3 g, 59.2%) was filtered off as coarse orange crystals of mp 130-131°C (from aqueous methanol). IR spectrum: 1563, 1345, 1272, 860 cm^{-1}.

N,N'-bis(6-Dipropyldithiocarbamoyl-2-methyl-5-nitro-4-pyrimidyl)piperazine (IId) $C_{28}H_{42}N_{10}O_4S_4$ was synthesized similarly to (IIc) from compound (Ib) (1.5 g, 3.48 mmole) and sodium dipropyldithiocarbamate trihydrate (1.76 g, 6.94 mmole). Product (IId) (1.4 g, 58.5%) was obtained as coarse orange crystals of mp 123-125°C (from aqueous methanol). IR spectrum: 1568, 1291, 1056, 865 cm^{-1}.

N,N'-bis(2-Propylimino-1,3-dithiolo[4,5-d]pyrimidinyl-7)piperazine (III) $C_{20}H_{24}N_8S_4 \cdot H_2O$. Compound (IIb) (0.8 g, 1.17 mmole) was added gradually to boiling xylene and the mixture boiled for 30 min. The reaction mixture was cooled, filtered, the mother liquor evaporated, the residue treated with ethanol (20 ml), and the product (III) (0.47 g, 77.0%) filtered off as yellow crystals of mp 91-92°C (from ethanol). IR spectrum: 3450-3200 (H_2O), 1546, 1273, 1108, 1004, 986 cm^{-1}. PMR spectrum (DMSO-D_6): 0.92 (7H, m, $CH_2CH_2CH_3$), 3.73 (2H, m, CH_2), 8.38 ppm (1H, m, H of pyrimidine).

N,N'-bis(1-Amino-2-cyano-2-nitro-1-ethenyl)piperazine (IV) $C_{10}H_{12}N_8O_4$. A. Glacial acetic acid (26.2 ml) was added to a suspension of compound (Ia) (1 g, 2.49 mmole) in water (46.5 ml) and the mixture was boiled for 36 h. After cooling the product was filtered off and treated with methanol. Compound (IV) (0.4 g, 52.6%) was obtained as white crystals of mp 110-111°C (from methanol). IR spectrum: 3100-3600 (NH, H_2O), 2200 (CN), 1620, 1560 cm^{-1} (NH_2, C=C).

B. A solution of compound (IIb) (0.6 g, 1.06 mmole) in water (10 ml) containing potassium hydroxide (0.35 g, 6.25 mmole) was boiled for 5 h. After cooling, the reaction mixture was filtered and the filtrate acidified with 10% HCl to pH 5. The precipitated white crystals were filtered off and a substance (0.3 g, 86.6%) of mp 110°C was obtained which was identical in spectral characteristics to the product obtained by method A.

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