SYNTHESIS OF DERIVATIVES OF 5-AMINO-7-OXO(6H)-1,3-DITHIOLO[4,5-d]PYRIMIDINE ON THE BASIS OF 2-AMINO-(1H,5H)PYRIMIDINE-4,6-DIONE

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The betaine of 2-amino-5-phenyliodonio(1H,5H)pyrimidine-4,6-dione, upon interaction with sodium diethyldithiocarbamate, forms the previously unknown 2-amino-5-diethylaminothiocarbonylthio(1H,5H)pyrimidine-4,6-dione, the cyclization of which in concentrated sulfuric acid leads to salts of 2-diethylimmonio-5-amino(6H)-1,3-dithiolo[4,5-d]pyrimidin-7-one — a new heterocyclic system. The salts serve as the starting material for obtaining 5-amino-7-oxo(6H)-1,3-dithiolo[4,5-d]pyrimidine-2-selenone and -2-thione.

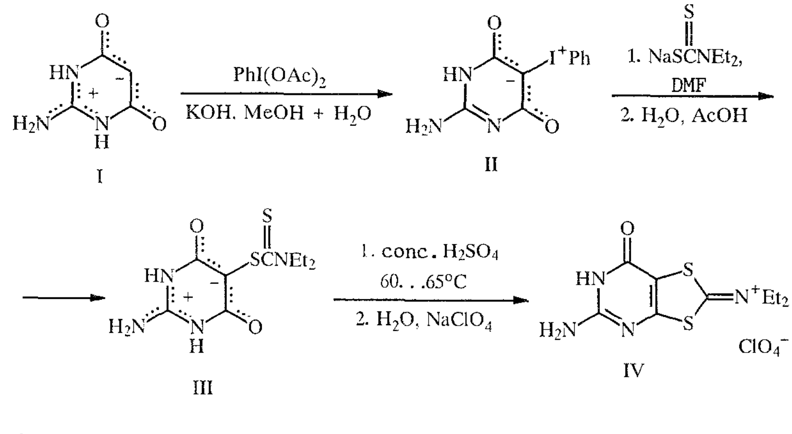
It is known that diaryliodonium salts react with dithiocarbamates, forming S-aryldithiocarbamates [1].

In the example of dimedone we have shown that phenyliodonium betaines of β-dicarbonyl compounds react under mild conditions with sodium diethyldithiocarbamate, forming previously unknown diethylaminothiocarbonylthio derivatives of β-diketones, which can serve as starting materials for the synthesis of new 1,3-dithiolium systems [2].

We found that this reaction also extends to derivatives of dihydroxypyrimidines. In the present work we investigated conversions of 2-amino(1H,5H)pyrimidine-4,6-dione (I), for which, on the basis of spectroscopic studies of derivatives of 4,6-dihydroxypyrimidine [3, 4], we can assume an inner salt structure (betaine).

We had previously synthesized phenyliodonium betaines of barbituric acids [5] and uracil [6]. Data have also been reported in the literature on the synthesis of iodonium betaines of phenyl-substituted (1H,5H)pyrimidine-4,6-diones [7].

In the work reported here, we obtained for the first time the betaine of 2-amino-5-phenyliodonio(1H,5H)pyrimidine-4,6-dione (II) with nearly quantitative yield, by the interaction of pyrimidinedione I with phenyliodosyl diacetate in alkaline aqueous methanol solution at room temperature. The betaine of II is a colorless, fine-crystalline, difficultly soluble, and difficulty filterable substance; when heated above 230°C, it gradually darkens and decomposes. The betaine of II turns yellow during extended storage. The solubility of the betaine of II in water at room temperature is less than 10^{-2} M; it is soluble in dilute solutions. Upon dissolving in hydrochloro or hydrobromic acid, the betaine is cleaved, with the evolution of iodobenzene and apparently with the formation of 5-chloro- or 5-bromo-2-amino(1H,5H)pyrimidine-4,6-dione, respectively.



When the betaine of II is stirred for an extended period with sodium diethyldithiocarbamate in DMF, 2-amino-5-diethylaminothiocarbonylthio(1H,5H)pyrimidine-4,6-dione (III), a high-melting, colorless substance, is formed with a high yield.

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TABLE 1. Spectral Characteristics of Synthesized Compounds II-V, VII, VIII, and X

Compound	IR spectrum,* cm^{-1}		PMR spectrum, δ, ppm DMSO-d_6
	3600...2800	1800...900	
II†	3260 sh 3160 s, 3048 s,2872 m	1682 s,1630 vs 1548 s 1536 s 1268 w, 1200 m, 1096 w, 992 s	
III	3492 s 3392 w, 3150 2900 m, 2776 m	1718 m, 1616s, 1498s, 1274 m 1204 m, 1122w, 1076 w, 980 m,. 914 w	1,13 & 1,24 (6H, sts CH_3), 3,73...3,88 (4H, m, CH_2), 7,03 (2H, s NH_2) 10,6 (br.s NH)
IV	3528 s,3396 w, 3260 m,3124 s 2800 w	1692 m, 1652 vs , 1602 s 1572 s, 1536 m, 1492 s, 1238 m,1200 w, 1112 vs 996 m	1,28 (6H, t, CH_3), 3,82 (4H, m, CH_2), 7,3 (2H, s, NH_2), 11,9 (1H, br.s NH)
V	3300...3100 s,2980 m, 2940 sh	1692 vs, 1620vs, 1580 s 1500s, 1274s, 1198 m, 1146s, 1078 m, 960s	1,26 (6H, m, CH_3), 3,92 (4H, m, CH_2), 7,38 (2H, s, NH_2), 11,5 (br.s NH)
VII	3400s, 3296s, 3112 vs 2924 w	1680 sh 1632 vs. 1570s 1532 m, 1228 w 1044 m 960 s	7,15 (2H, s, NH_2). 11,63 (1H, br.s NH)
VIII	3280 vs, 3160 vs, 2972 m, 2928w	1688 m, 1622 vs, 1584 s, 1496 s, 1272s, 1202 m, 1144 s, 1077 m; 978 m, 912 m	1,15 & 1.22 (6H, sts CH_3), 3,81 (4H, m CH_2) 7,22 (2H, s, NH_2), 11,3 (br.s NH)
X	3408 s, 3300 m, 3088 vs 2930 m	1680 sh, 1640 s, 1576 s, 1534 m, 1231w, 1104m 1062 m, 1046 m, 952 w	7,15 (2H, s, NH_2) 11,64 (1H, br.s, NH)

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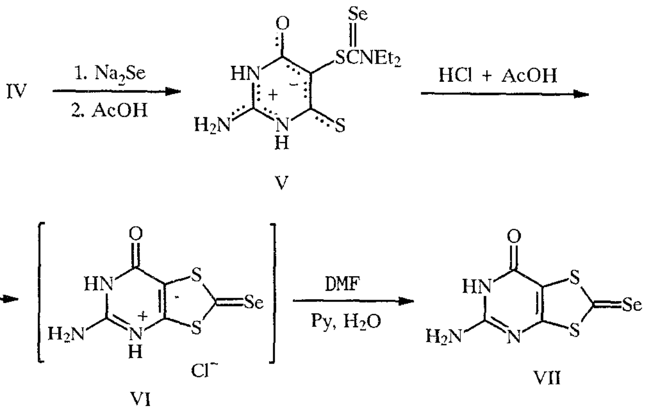
*vs) Very strong; s) strong; m) medium; w) weak; sh) shoulder.

†No PMR spectrum was obtained on compound II, owing to poor solubility.

Note. The original does not give any notation for the PMR data, but it appears to be conventional: s) singlet; t) triplet; m) multiplet; br) broad.

When compound III is heated in concentrated sulfuric acid, it is cyclized, forming the hydrosulfate of 2-diethylimmonio-5-amino(6H)-1,3-dithiolo[4,5-d]pyrimidin-7-one. The pyrimidone is recovered from the reaction mixture in the form of the relatively insoluble perchlorate IV. This compound is a representative of a new heterocyclic system, a 1,3-dithiolo[4,5-d]pyrimidine.

With the aim of obtaining 5-amino-7-oxo(6H)-1,3-dithiolo[4,5-d]pyrimidine-2-selenone (VII), we carried out the reaction of the perchlorate IV with an aqueous solution of sodium selenide. From the reaction mixture, after acidification with acetic acid, we recovered the product of ring opening, 2-amino-5-diethylaminoselenocarbonylthio-6-mercapto(3H)pyrimidin-4-one (V), a nearly colorless, high-melting substance, which apparently has an inner salt structure.

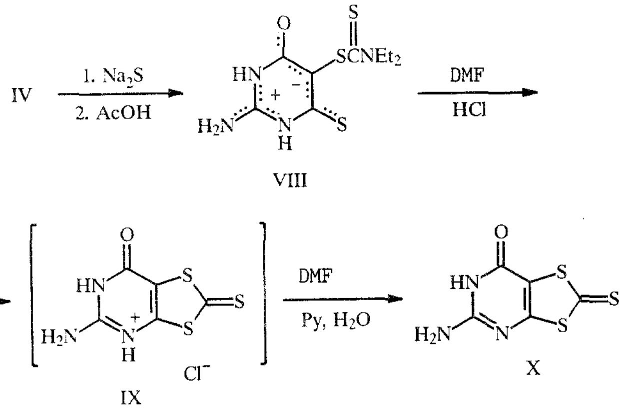


The pyrimidinone V, upon heating in a mixture of acetic and hydrochloric acids, is cyclized to a selenone, which is segregated presumably in the form of the hydrochloride of 5-amino-7-oxo(6H)-1,3-dithiolo[4,5-d]pyrimidine-2-selenone (VI) — a red crystalline substance which, however, we were not able to obtain in adequately pure form for identification (in the elemental analysis the chlorine content was low).

Upon hydrolysis of the hydrochloride VI with water in DMF solution in the presence of pyridine, we obtained 5-amino-7-oxo(6H)-1,3-dithiolo[4,5-d]pyrimidine-2-selenone (VII) — a red crystalline substance.

In the same manner as for the selenone VII, we obtained 5-amino-7-oxo(6H)-1,3-dithiolo[4,5-d]pyrimidine-2-thione (X).

Upon interaction of the perchlorate IV with an aqueous solution of sodium sulfide, followed by acidification of the reaction mixture with acetic acid, we obtained 2-amino-5-diethylaminothiocarbonylthio-6-mercapto(3H)pyrimidin-4-one (VIII). Upon cyclization of the pyrimidinone VIII by hydrochloric acid in DMF solution, we obtained the presumed hydrochloride of 5-amino-7-oxo(6H)-1,3-dithiolo[4,5-d]pyrimidin-2-thione (IX) which, upon hydrolysis with water in DMF solution, was converted to the corresponding thione X — a yellow crystalline substance.



In the IR spectra of the synthesized compounds II-V, VII, VIII, and X (Table 1), we observe carbonyl group absorption in the 1720-1620 cm^{-1} interval, stretching vibrations of the pyrimidine ring at 1580-1500 cm^{-1}, and intense absorption by $C=S$ and $C=Se$ groups in the 1100-950 cm^{-1} region, along with bending vibrations of the pyrimidine ring. In addition, in the 3600-2800 cm^{-1} region, absorption bands of the amino group are manifested at 3400-3300 cm^{-1}, and also stretching vibrations of alkyl groups at 3000-2800 cm^{-1}.

Compounds III-V, VII, VIII, and X were also characterized by their PMR spectra (see Table 1). Here we must note that for compounds III, V, and VIII, the signal of the NH-group protons of the ring at ~ 11 ppm and the signals of the ethyl-group protons had a ratio of integral intensities of 1.5:10 instead of 2:10. We assume that this discrepancy can be explained by partial ionization with respect to the N—H bonds.

Thus, as a result of our studies, we have developed methods of synthesis for new 1,3-dithiolo[4,5-d]pyrimidines, methods that can be used to obtain new, strong electron donors — derivatives of tetrathiafulvalene.

EXPERIMENTAL

The IR spectra of the compounds were taken in a Specord M-80 instrument, the PMR spectra in a Bruker WH-90 instrument with TMS internal standard.

The elemental analyses of compounds II-V, VII, VIII, and X for C, H, Cl, I, N, and S matched the calculated values.

Betaine of 2-Amino-5-phenyliodonio(1H,5H)pyrimidine-4,6-dione (II, $C_{10}H_8IN_3O_2$). To a solution of 1.45 g (0.01 mole) of 2-amino(1H,5H)pyrimidine-4,6-dione (I) [8] in 50 ml of 0.4 N aqueous sodium hydroxide solution, a solution of 3.22 g (0.01 mole) of phenyliodosyl diacetate in 40 ml of methanol was added. After 1 h the colorless, finely crystalline betaine of II that precipitated was filtered out and washed on the filter with water and then with acetone. It was recovered in practically pure form. The substance was difficultly soluble in organic solvents. When purification was necessary, 0.2 g of the betaine was dissolved in 40 ml of a 1% $HClO_4$ solution at 20°C; the filtered solution was neutralized with sodium bicarbonate and cooled to 5°C, obtaining 0.8 g (40%) of the pure betaine of II. Upon heating above 230°C, the betaine gradually decomposed. Yield of betaine of II 3.16 g (96%).

2-Amino-5-diethylaminothiocarbonylthio(1H,5H)pyrimidine-4,6-dione (III, $C_9H_{14}N_4O_2S_2 \cdot 2H_2O$). To a suspension of 3.3 g (0.01 mole) of the betaine of II and 60 ml of dry DMF, 2.26 g (0.01 mole) of sodium diethyldithiocarbamate trihydrate was added. The reaction mixture was stirred for 6 days at 20°C. The colorless suspension was diluted with 250 ml of ether; the precipitate was filtered off and dissolved in ~50 ml of water; if necessary, the unreacted betaine of II was filtered off. The filtrate was acidified with acetic acid to pH ~3-4; obtained 2.0 g (65%) of the colorless dihydrate III. Upon heating above 280°C, the substance gradually darkened; it did not melt up to 340°C. It can be recrystallized from 50% aqueous DMF.

Perchlorate of 2-Diethylimmonio-5-amino(6H)-1,3-dithiolo[4,5-d]pyrimidin-7-one (IV, $C_9H_{13}ClN_4O_5S_2 \cdot 1/2H_2O$). A mixture of 6.2 g (0.02 mole) of compound III and 20 ml of concentrated H_2SO_4 was heated for 1 h at 60-65°C. The resulting solution was poured into 250 ml of ice water, filtered, and neutralized with concentrated sodium hydroxide solution to pH ~2-3. By the addition of a solution of 6 g $NaClO_4$ in 10 ml of water, the colorless perchlorate IV was precipitated. The perchlorate can be recrystallized from dilute $HClO_4$, mp 255-257°C (decomp.). Yield 5.6 g (75%).

2-Amino-5-diethylaminoselenocarbonylthio-6-mercapto(3H)pyrimidin-4-one (V, $C_9H_{14}N_4OS_2Se$). The reaction was carried out in an argon atmosphere at 20°C. From 2.0 g (0.025 mole) of Se and 1.9 g (0.05 mole) of $NaBH_4$ in 25 ml of water, a solution of sodium selenide was prepared; to this solution, while stirring, 7.2 g (0.02 mole) of the perchlorate IV was added gradually. The reaction mixture was stirred for 30 min; the resulting solution was filtered and acidified with acetic acid to pH ~4. Obtained 5.5 g (76%) of compound V, which was slightly rose-colored. For purification, 0.2 g of the substance was dissolved in 3 ml of DMF; the filtered solution was diluted with 3 ml of water, obtaining the colorless compound V, mp 190-192°C (decomp.). The unpurified product was used in subsequent conversions.

5-Amino-7-oxo(6H)-1,3-dithiolo[4,5-d]pyrimidine-2-selenone (VII, $C_5H_3N_3OS_2Se$). A suspension of 3.4 g (0.01 mole) of compound V in 120 ml of acetic acid was heated to 80°C, and 60 ml of concentrated hydrochloric acid was added. After 2 h, the dark-red precipitate of the hydrochloride was filtered off and washed on the filter with a small quantity of acetic acid and then with acetone. Yield 2.0 g. The hydrochloride VI was dissolved in 50 ml of DMF and filtered to remove selenium present as an impurity; ~2 ml of pyridine was added to the filtrate, and then 70 ml of hot water (~70°C) was added gradually. After 1 h, the red precipitate of the selenone VII was filtered off and washed with water. Yield 1.3 g (50%). Upon heating above 340°C, the substance gradually decomposed. It can be recrystallized from a 1:1 mixture of ethanol and DMF.

2-Amino-5-diethylaminothiocarbonylthio-6-mercapto(3H)pyrimidin-4-one (VIII, $C_9H_{14}N_4OS_3$). To a solution of 4.8 g (0.02 mole) of $Na_2S\cdot 9H_2O$ in 110 ml of water, 3.6 g (0.01 mole) of the perchlorate IV was added; after 30 min, the solution was filtered and acidified with acetic acid to pH ~4. After 12 h, the colorless precipitate of the pyrimidione VIII was filtered and washed on the filter with ethanol. It can be recrystallized from dilute (1:1) DMF. Upon heating above 215°C, the substance gradually decomposed. Yield 2.7 g (85%).

5-Amino-7-oxo(6H)-1,3-dithiolo[4,5-d]pyrimidine-2-thione (X, $C_5H_3N_3OS_3$). To a prefiltered solution of 1.16 g (4 mmoles) of compound VIII in 10 ml of DMF, heated to 85°C, 20 ml of concentrated hydrochloride acid was added while stirring. After 2 h, the yellow precipitate of the hydrochloride of IX was filtered off. Yield 0.76 g (76%).

When the hydrochloride of IX was heated above 270°C, it gradually darkened; it did not melt up to 350°C. The hydrochloride of IX was dissolved in 10 ml of DMF; ~1 ml of pyridine was added to the filtrate, then 10 ml of hot water (~70°C). Obtained 0.6 g (69%) of the yellow crystalline thione X, which can be purified by crystallization from dilute (1:1) DMF. Upon heating above 270°C, the substance darkened gradually but did not melt up to 350°C.

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