INTRAMOLECULAR REARRANGEMENTS

III. The Rearrangement of S-Aminoalkyl Derivatives of 2-Mercaptopyrimidine and 2-Mercapto-4, 6-diaminopyrimidine*

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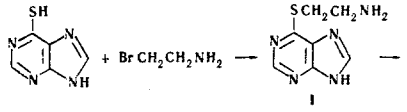
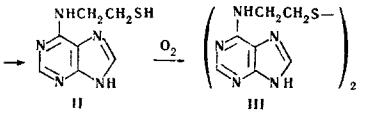
It has been shown that S-β-aminoalkyl derivatives of 2-mercaptopyrimidine and 2-mercapto-4, 6-diaminopyrimidine, containing primary and secondary amino groups, undergo S → N rearrangement in neutral or weakly alkaline solution, with the formation of the corresponding aminothiols. In the case of derivatives of 2-mercapto-4, 6-diaminopyrimidine, however, the S → N rearrangement proceeds more slowly, apparently as a result of the difficulty of formation of the intermediate cyclic compound.

It has been reported previously that the intramolecular rearrangement of isothioureas [1–5] and isoselenoureas [5, 6], which proceeds via the formation of an intermediate cyclic compound, has been extended to some other thio compounds [2, 7–9]. In particular, it has been shown that S-β(γ)-aminoalkyl derivatives of 2-mercaptoimidazoline [9], 2-mercaptothiazoline [7, 9], and 2-mercaptooxazoline [8] also undergo S → N rearrangement in neutral and weakly alkaline media with the formation of the corresponding aminothiols. A similar rearrangement was later observed in S-derivatives of 6-mercaptopurine [10], 8- and 2-mercaptoadenine, and also 8-mercaptocaffeine [11]. Thus, the reaction between 6-mercaptopurine and β-bromoethylamine leads invariably to the formation of 6-mercaptopurine, β-(6-purinylamino)ethanethiol (II), and the disulfide corresponding to the latter (III), instead of the expected 6-(β-aminoethylmercapto)purine (I). It has been suggested [10] that I is formed initially, and that this rearranges under alkaline conditions to II.

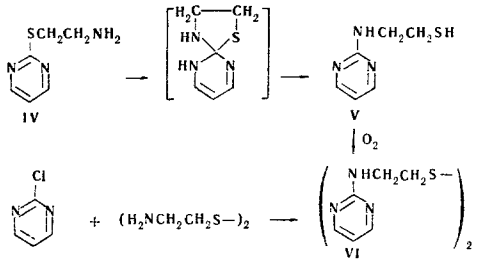


I



II III

We assumed that S → N rearrangement could also occur in the case of the S-aminoalkyl derivatives of 2-mercaptopyrimidine. For this purpose, we prepared 2-(β-aminoethylmercapto)pyrimidine (IV), and examined its rearrangement in aqueous solution at pH ~ 7. It was shown that at room temperature, even after the first few minutes about 27% of the thiol (V) was formed (the latter was isolated and identified as the disulfide (VI)). The analytical data, IR spectrum and ability to undergo reduction to the thiol of the disulfide were identical to those of the disulfide prepared by the alternative route from 2-chloropyrimidine [10].

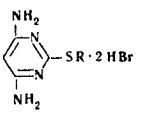


IV V VI

We observed a similar rearrangement in the case of the S-aminoalkyl derivatives of 2-mercapto-4, 6-diaminopyrimidine. Here, as would also be expected, the formation of N-substituted aminothiols occurred only with those S-aminoalkyl compounds containing an unsubstituted or monosubstituted amino group (table, compounds VII and IX).

Thus, our results confirm that the previously established mechanism of the S → N rearrangement

*For part II, see [9].



Compound	R	Mp, °C	Molecular formula	Found, %		Calculated, %		Yield, %	Extent of conversion to thiol, % (after 5 min at pH ~7.0)
				Br	S	Br	S		
VII	$CH_2CH_2NH_2$	decomp.>200	$C_6H_{11}N_5S \cdot 2HBr$	45.67	9.29	46.10	9.22	86	47
VIII	$CH_2CH_2CH_2NH_2$	245—246	$C_7H_{13}N_5S \cdot 2HBr$	44.10	9.10	44.32	8.86	86	trace amounts
IX	$CH_2CH_2NHCH_3$	222	$C_7H_{13}N_5S \cdot 2HBr$	43.90	8.52	44.32	8.86	67	19
X	$CH_2CH_2N(CH_3)_2$	242—244	$C_8H_{15}N_5S \cdot 2HBr$	42.64	8.48	42.70	8.57	75	0
XI	C_2H_5	169—173	$C_6H_{10}N_4S \cdot HBr$	31.61	12.70	31.80	12.74	95	0

[1, 2, 4, 5, 9] also operates in the case of 2-mercaptopyrimidine derivatives, but that the rate of conversion is slower, which is probably to be explained by the difficulty of formation of the cyclic intermediate.

EXPERIMENTAL

2-(β-Aminoethylmercapto)pyrimidine dihydrobromide (IV). To a boiling solution of 5.60 g (0.05 mole) of 2-mercaptopyrimidine [12] in 250 ml of 70% isopropanol was added 10.5 g (0.05 mole) of β-bromoethylamine hydrobromide, and the mixture boiled for 20 hr. After removal of the solvent in vacuo, the residue was dissolved in 50 ml of anhydrous ethanol, treated with charcoal, filtered and the filtrate treated with dry ether. The oily material which separated was kept in a vacuum desiccator over P_2O_5 until it crystallized. Yield 6.5 g (40%). The dihydrobromide IV was obtained as yellow, very hygroscopic crystals. Found, %: Br 49.80; S 9.62. Calculated for $C_6H_9N_3S \cdot 2HBr$, %: Br 50.40; S 10.09.

Bis-[β-(2-pyrimidinylamino)ethyl]disulfide (VI). To a solution of 6.5 g (0.02 mole) of IV in 50 ml of water was added carefully 5 ml of 10% aqueous ammonia, and the mixture kept at room temperature. After 4 days, the free base which crystallized from the aqueous solution was filtered off and recrystallized from ethanol. Yield 0.5 g (16%), mp 164–165° C. UV spectrum (in ethanol), λ_{max}, nm (ε): 238 (3800), 302 (5000). Found, %: S 20.40; N 27.51. Calculated for $C_{12}H_{16}N_6S_2$, %: S 20.77; N 27.27. Its properties were identical with those of the disulfide prepared by method [10].

2-(β-Aminoethylmercapto)-4,6-diaminopyrimidine dihydrobromide (VII). A mixture of 7.1 g (0.05 mole) of 2-mercapto-4,6-diaminopyrimidine [13] and 10.3 g (0.05 mole) of β-bromoethylamine hydrobromide in 50 ml of isopropanol was boiled for 3 hr. The mixture became homogeneous in about 30 min, followed by the slow separation of a crystalline precipitate. After cooling, the product was filtered off, washed with ether and dried.

Compounds VIII–XI (see table) were prepared similarly.

Bis-[β-(4,6-Diaminopyrimidinyl-2-amino)ethyl] disulfide dihydrobromide. To a solution of 7 g (0.02 mole) of VII in 20 ml of water was added carefully a 1 N solution of sodium hydroxide until the pH reached ~7.0, the mixture filtered and kept for three days. The precipitate which separated was filtered off and crystallized from ethanol. Yield 2 g (37.5%), mp 204–206° C. Found, %: Br 30.30; S 12.00. Calculated for $C_{12}H_{20}N_{10}S_2 \cdot 2HBr$, %: Br 30.18; S 12.07. The disulfide was reduced quantitatively to the thiol by zinc in hydrochloric acid.

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