DERIVATIVES OF 2-MERCAPTO-6-METHYLURACIL

I. Reaction of the Sodium Salt of 2-Mercapto-6-methyluracil with α, ω-Dibromoalkanes

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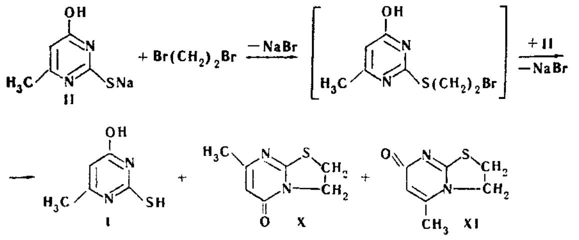
The reaction of the sodium salt of 2-mercapto-6-methyluracil with α, ω-dibromoalkanes $Br(CH_2)_nBr$ (n = 1, 4, 5, 6) has given the corresponding α, ω-bis(4-hydroxy-6-methyl-2-pyrimidinylthio) alkanes. The reaction of the same salt with 1, 2-dibromoethane gave 7-methyl-5-oxo-2, 3, 4, 5-tetrahydrothiazolo[3, 2-a]pyrimidine and 5-methyl-7-oxo-2, 3, 4, 7-tetrahydrothiazolo[3, 2-a]pyrimidine, and its reaction with 1, 3-dibromopropane led to 8-methyl-6-oxo-3, 4, 5, 6-tetrahydro-2H-pyrimidino[2, 1-b]-1, 3-thiazine.

Continuing investigations on the reaction of 2-mercaptopyrimidines with various α,ω-dihaloalkanes [1, 2], we have studied the reaction of the sodium salt of 2-mercapto-6-methyluracil (II) (I represents 2-mercapto-6-methyluracil itself) with dibromethane (III), 1, 2-dibromoethane (IV), 1, 3-dibromopropane (V), 1, 4-dibromobutane (VI), 1, 5-dibromopentane (VII), and 1, 6-dibromohexane (VIII), (in a ratio of 2 : 1).

As was to be expected, in the reaction of II with III, VI, VII, and VIII, the corresponding α,ω-bis(4-hydroxy-6-methyl-2-pyrimidinylthio) alkanes (IXa–d) were formed in high yield.

However, it was impossible to isolate the analogous compounds from the reaction of II with IV and V. In both cases, 2-mercapto-6-methyluracil (I) was isolated with a yield of ~50%. In addition, the reaction of II with IV gave 7-methyl-5-oxo-2, 3, 4, 5-tetrahydrothiazolo[3, 2-a]pyrimidine (X) and 5-methyl-7-oxo-2, 3, 4, 7-tetrahydrothiazolo[3, 2-a]pyrimidine (XI). The reaction of II with V gave only 8-methyl-6-oxo-3, 4, 5, 6-tetrahydro-2H-pyrimidino[2, 1-b]-1, 3-thiazine (XII).

It may be assumed that the reaction takes place in the following way:



To elucidate the structure of the isomers X and XI, their IR spectra were considered. One of the possible isomers must possess a p-quinoid structure in the pyrimidine ring, while the other isomer will have the o-quinoid structure. The presence of fixed quinoid structures must lead to a difference in the frequencies of the C═O vibrations. The vibration of the C═O bond in six-membered nitrogen-containing systems should be in the 1700–1665 cm^{-1} region for o-quinoid structures (analogous to α, β-unsubstituted ketones) and in the 1670–1650 cm^{-1} region for p-quinoid structures (analogous to α, β, α', β'-unsaturated ketones). Thus, in the spectra of 1-methyl-2-pyrimidinone and 3-methyl-4-pyrimidinone, which have the o-quinoid structure, the C═O vibrations appear in the 1670 and 1675 cm^{-1} regions, respectively, and in the case of 1-methyl-4-pyrimidinone, which has the p-quinoid structure, they appear in the 1653 cm^{-1} region [3]. An analogous picture is found in the α- and γ-pyridones [4].

The vibrations of the C═O bond in the spectrum of the low-melting isomer are in the 1660–1680 cm^{-1} region and in the spectrum of the high-melting isomer they are in the 1640 cm^{-1} region. Consequently, the first of them has the o-quinoid structure (X), and the second the p-quinoid structure (XI).

In the spectrum of compound XII, the C═O vibrations are in the 1640–1680 cm^{-1} region, with a maximum at 1680 cm^{-1}. The IR spectrum of 1, 4-dimethyl-2-methylthio-6-pyrimidinone has strong bands in the 1596 cm^{-1} region and the 1651–1685 cm^{-1} region with a maximum at 1685 cm^{-1} [5]. Consequently, the o-quinoid structure is most probable for XII. This is also confirmed by the presence of a strong band at 1580 cm^{-1}, which is also found in the spectrum of compound X. There is no well-defined band in this region of the spectrum of XI.

EXPERIMENTAL

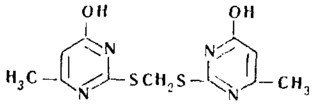
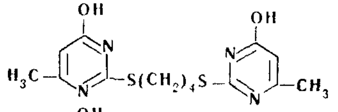
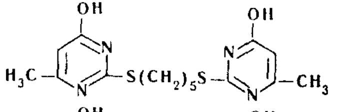
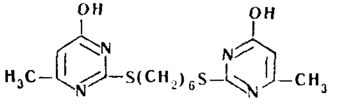
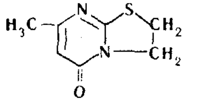
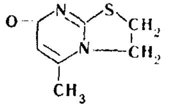
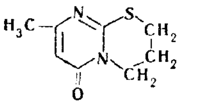
Starting materials. 2-Mercapto-6-methyluracil [6] was converted into the sodium salt II by the action of 1 mole of NaOH in aqueous solution. Compounds III, IV, and V were commercial materials purified by redistillation. Compounds VI, VII, and VIII were obtained by known methods [7, 8].

The IR spectra were recorded on a UR-10 spectrophotometer. The samples were prepared in the form of mulls in paraffin oil.

1, 6-Bis(4'-hydroxy-6'-methyl-2'-pyrimidinylthio)hexane (IXd). To a stirred suspension of 10 g (0.061 mole) of the dry salt II in 15 ml of dry dimethylformamide at +17° C was added 7.44 g (0.0305 mole) of VIII. The temperature of the reaction mixture rose to 36°, and it was then heated at 50–60° for 15 min, cooled to room temperature, and triturated with water. The precipitate was filtered off and washed with water to give 10.6 g (95%) of IXd, mp 209–210° (from ethylcellosolve). Compounds IXa–c were obtained similarly (see table).

Reaction of the sodium salt of 2-mercapto-6-methyluracil (II) with 1, 2-dibromoethane (IV). In drops, 5.74 g (0.0305 mole) of IV was slowly added to a vigorously-stirred solution of 10 g (0.061 mole) of the dry salt II in 40 ml of dry dimethylformamide at 70–82°. The mixture was heated at 70–80° for 10 min, cooled to room temperature, and poured into water. The precipitate was filtered off and washed with water and with acetone, which gave 3.9 g of 2-mercapto-6-methyluracil (I), mp 318–319° (decomp.). The solvent was distilled off from the aqueous solution in vacuum; 100 ml of ethanol was added and this was again distilled off. The residue was boiled with a mixture of ethylcellosolve and chloroform (2 : 3), and the NaBr was filtered off.

Properties of the Compounds Obtained

Compound	Structural formula	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield of unpurified substance, %
				C	H	N	C	H	N	
IXa		>350 (decomp.)	$C_{11}H_{12}N_4O_2S_2$	44.36	4.33	18.80	44.59	4.06	18.92	90—95
IXb		236—238	$C_{14}H_{18}N_4O_2S_2$	49.62	5.33	17.04	49.70	5.33	16.57	90—95
IXc		196.5—197.5	$C_{15}H_{20}N_4O_2S_2$	50.79	6.04	15.51	51.14	5.68	15.91	80—95
IXd		209—210	$C_{16}H_{22}N_4O_2S_2$	52.46	6.10	15.24	52.46	6.01	15.30	85—95
X		123—124	$C_7H_8N_2OS$	49.84	5.15	16.58	50.00	4.76	16,67	83.8
XI		229—230 (decomp.)	$C_7H_8N_2OS$	49.57	5.01	16.48	50.00	4.76	16.67	
XII		119,5—121	$C_8H_{10}N_2OS$	52.84	5.62	15.15	52.75	5.49	15.38	73.9

Another 0.25 g of I deposited from the filtrate (a total of 4.15 g, 47.9%). The solution was diluted with chloroform (200 ml) and an additional amount of NaBr was filtered off. The crystals that were left after the solvent had been distilled off were filtered off after 3 hr and washed with chloroform and ether. This gave 2.3 g of a substance melting at 152–170°. Another 2.0 g of this substance was isolated from the mother solution; 2.3 g of the reaction product was triturated with cold dry chloroform (40 ml), and 0.85 g of XI with mp 229–230° C (decomp., from ethylcellosolve) was filtered off. After evaporation of the filtrate, 1.2 g of X with mp 123–124° (from chloroform) was obtained. The total yield of the mixture of isomers was 4.3 g (83.8% calculated on the IV).

Both compounds are colorless crystalline substances. Compound X is very readily soluble in chloroform and moderately soluble in water and dioxane. Compound XI is moderately soluble in water and ethyl cellosolve, sparingly soluble in chloroform and dioxane, and practically insoluble in acetone. Their constants and analytical data are given in the table.

Compound XII was obtained similarly.

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