THE INTRAMOLECULAR REARRANGEMENT OF SUBSTITUTED 4-HYDROXY-HEXAHYDROPYRIMIDINE-2-THIONES

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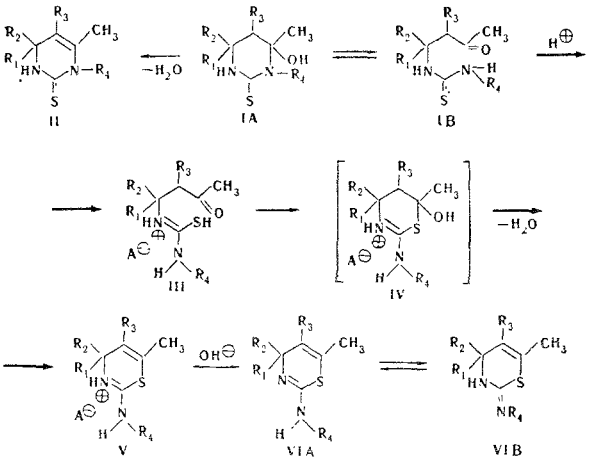
It has been found that, on being heated with 36% hydrochloric or 85% orthophosphoric acid, substituted 4-hydroxyhexahydropyrimidine-2-thiones (IA) undergo an intramolecular rearrangement connected with the transformation of the cyclic forms IA into the linear tautomers IB and accompanied by dehydration with the formation of substituted 2-alkylamino- or 2-arylamino-4H-1,3-thiazines.

In the development of our previous investigations [1–2], we have studied the stability of substituted 4-hydroxyhexahydropyrimidine-2-thiones (IA) with respect to hydrochloric and phosphoric acids. In accordance with the work of Mathes [3] we expected that this reaction would give products of the dehydration of IA—substituted 1, 2, 3, 6-tetrahydropyrimidine-2-thiones (II).

When 3-ethyl-4-hydroxy-4, 6, 6-trimethylhexahydropyrimidine-2-thione (Ib) was heated with 36% hydrochloric acid (2 hr, 90° C), instead of the expected 3-ethyl-4, 6, 6-trimethyl-1, 2, 3, 6-tetrahydropyrimidine-2-thione (IIb), which we had obtained independently from 2-isothiocyanato-2-methylpentan-4-one and ethylamine [3], we isolated a substance corresponding to IIb only in its elementary composition but differing from it in all its physical constants, chemical behavior, and IR and UV spectra.

In view of this, and also by analogy with examples described in the literature [4–7] we assumed the possibility of the occurrence under the conditions described of an intramolecular rearrangement of IA into the 2-alkylamino- or 2-arylamino-6-hydroxytetrahydro-1,3-thiazines (IV) isomeric with them, with their subsequent dehydration to 2-alkylamino- or 2-arylamino-4H-1,3-thiazines (VI). The most probable mechanism for the rearrangement is shown in the following scheme:



I, VIa–g: a $R_1 = R_2 = R_4 = CH_3$,
d $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$,
$R_3 = H$; b $R_1 = R_2 = CH_3$, $R_3 = H$, $R_4 = C_2H_5$, c $R_1 = R_2 = CH_3$, $R_3 = H$, $R_4 = n\text{-}C_3H_7$;
e $R_1 = R_2 = H$, $R_3 = CH_3$, $R_4 = C_2H_5$; f $R_1 = R_2 = H$, $R_3 = CH_3$, $R_4 = C_6H_5$;
g $R_1 = R_2 = CH_3$, $R_2 = H$, $R_4 = n\text{-}C_3H_7$

We have shown previously [2, 8] that IA undergoes ring opening in solutions in chloroform and CCl_4 with transformation into the tautomeric acyclic forms—N-alkyl- or N-aryl-N'-oxoalkylthioureas (IB). In agreement with this, it may be assumed that the formation of the acyclic form IB also takes place in hydrochloric acid, a confirmation of which is the production of 2, 4-dinitrophenylhydrazones with respect to the carbonyl group [1].

Substituted 2-Alkylamino- and 2-Arylamino-4H-1, 3-thiazines (VI)

Compound	Mp, °C (solvent for crystallization)	R_f*	Empirical formula	Found, %	Calculated, %	Yield, %
VIa	64—65 (hexane)	0.72	$C_8H_{14}N_2S$	N 16.40; S 19.11	N 16.45; S 18.80	73.5
VIb	29—30 (petroleum ether)	0.75	$C_9H_{16}N_2S$	N 15.20; S 18.00	N 15.20; S 17.38	33.2
VIc	39—40 (petroleum ether)	0.80	$C_{10}H_{18}N_2S$	N 14.30; S 16.11	N 14.13; S 16.13	61.5
VId	67—68**	0.69	$C_7H_{12}N_2S$	C 53.62; H 7.26; N 17.70	C 53.81; H 7.75; N 17.93	65.5
VIe	57—58**	0.71	$C_8H_{14}N_2S$	C 56.20; H 8.51; S 19.39	C 56.43; H 8.30; S 18.80	52.3
VIf	108—109 (ethanol)	0.59	$C_{12}H_{14}N_2S$	N 12.6; S 14.7	N 12.8; S 14.7	66.1
VIg***	135—137 (ethanol)	—	$C_{10}H_{19}N_2ClS$	Cl 15.14; S 13.48	Cl 15.12; S 13.62	35.0

*Al_2O_3 of activity II, benzene–ether (1 : 1) system.
**After sublimation at 80-90° C (10 nm).
***Data given for the hydrochloride.

By analogy with alkyl-substituted thioureas [9], in hydrochloric acid IB form isothiouronium salts capable, by the interaction of the C=O and SH groups, of ring closure with the formation of the cyclic semimercaptals IV. It is known [10] that the stability of the cyclic semimercaptals depends strongly on their structure; the spontaneous dehydration of semimercaptals during their preparation has been described in a number of cases [11, 12].

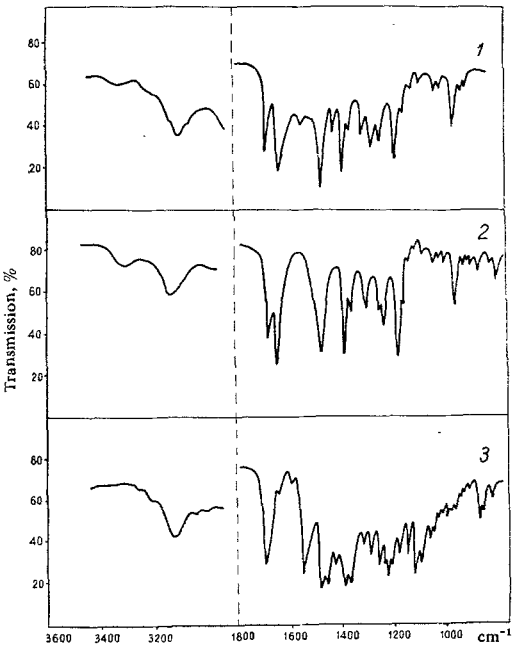


Fig. 1. IR spectra: 1) 4, 4, 6-trimethyl-2-methylamino-4H-1, 3-thiazine; 2) 2-ethylamino-4, 4, 6-trimethyl-4H-1, 3-thiazine; 3) 3-ethyl-4, 6, 6-trimethyl-1, 2, 3, 6-tetrahydropyrimidine-2-thione.

It is evident that a similar elimination of water takes place in the rearrangement products, since it is impossible to isolate the semimercaptals IV. The reaction forms only the products of the dehydration of IV—hydrochlorides of 2-alkylamino- or 2-arylamino-4H-1, 3-thiazines (V)—from which it is easy to isolate the bases VI, which are capable of existing in two tautomeric forms: the amino form VIA and the imino form VIB. The properties and yields of the compounds VI synthesized are given in the table.

The rearrangement of IA into IV with subsequent dehydration to VI also takes place when IA is heated with 85% orthophosphoric acid. Thus, the reaction of Ib, Id, and Ie with H_3PO_4 (30 min, 100° C) leads to the formation of, respectively, VIb, VId, and VIe—in admixture with the product of direct dehydration, IIb, in the first case.

A proof of the structure of compounds VI and their difference from the compounds II isomeric with them is, in addition to the difference in their physical constants, the negative result in the case of VI of the iodine-azide reaction for a C=S group [13], which is clearly expressed in the case of II, and also the increased basicity of compounds VI, which readily form hydrochlorides while the feebly basic compounds II do not give hydrochlorides under the same conditions.

The IR spectra of I and the dehydration products II have a characteristic absorption band at 1530–1560 cm^{-1} relating to a thioamide grouping (amide II) [14], and compounds II also have a band at 1690 cm^{-1} (C=C bond conjugated with the p-electrons of the hetero atoms) [15]. In the spectra of VI, on the other hand, there are no bands of the thioamide group but strong bands appear at 1620–1635 cm^{-1} (C=N) and the bands at 1670 cm^{-1} (C=C) are retained (Fig. 1).

The difference in the UV spectra of I, II, and VI is illustrated in Fig. 2. While the initial compounds I have an absorption maximum at 245–248 nm, and compound II at 270 nm (π, p conjugation >C=C—N—C=S), in the UV spectra of VI there is a marked hypsochromic shift (λ_{max} 220 nm) due to the passage of the exocyclic sulfur atom into the ring.

The assignment of the products of the rearrangement of VI to one of the two possible tautomeric forms, namely the amino from VIA, was made solely on the basis of literature analogies in other classes of heterocyclic compounds with a similar structure [16–18] and requires further investigation.

EXPERIMENTAL

5, 6-Dimethyl-2-methylamino-4H-1, 3-thiazine (VId). A) A mixture of 6 g (0.034 mole) of Id and 30 ml of 36% HCl was heated at 90° C for 2 hr. The excess of acid was distilled off in vacuum, and 5.4 g (75%) of the hydrochloride Vd was obtained in the form of snow-white crystals readily soluble in water and ethanol with mp 251–251.5° C (from isopropanol). Found, %: C 43.59; H 6.78; Cl 18.84; S 16.57. Calculated for $C_7H_{13}N_2ClS$, %: C 43.63; H 6.81; Cl 18.42. A S 16.61. A solution of 3 g of Vd in 15 ml of water was saturated at 3–5° C with solid caustic soda. The oil separated out was extracted with acetone, the extract was dried with magnesium sulfate, and the acetone was distilled off to give 1.8 g of VId in the form of snow-white needles soluble in the majority of organic solvents. The passage of dry hydrogen chloride into an ethereal solution of the base VId yielded the hydrochloride of Vd with mp 251–252° C giving no depression with the hydrochloride obtained directly from the reaction.

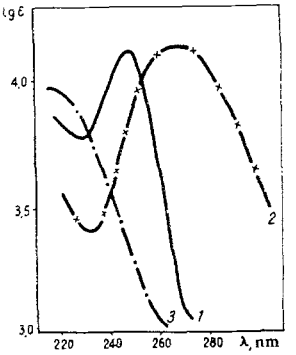


Fig. 2. UV spectra: 1) 3-ethyl-4-hydroxy-4, 6, 6-trimethylhexahydropyrimidine-2-thione; 2) 3-ethyl-4, 6, 6-trimethyl-1, 2, 3, 6-tetrahydropyrimidine-2-thione; 3) 2-ethylamino-4, 4, 6-trimethyl-4H-1, 3-thiazine.

B) A mixture of 4 g (0.023 mole) of Id and 20 g of 85% orthophosphoric acid was heated at 100° C for 30 min. Then the solution,

cooled to 0° C, was treated with 20 ml of ice water and the mixture was decomposed with potassium carbonate. The crystals that floated to the top were extracted with ether, the extract was dried with magnesium sulfate, and the ether was distilled off to give 3.2 g (65.6%) of VId, showing no depression with a sample obtained by method (A). R_f 0.67 [benzene–ether (1:1), Al_2O_3, activity II].

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