INTRAMOLECULAR REARRANGEMENT OF SUBSTITUTED 1,2,3,6-TETRAHYDROPYRIMIDINE-2-THIONES

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The intramolecular rearrangement of substituted 1,2,3,6-tetrahydropyrimidine-2-thiones to the isomeric 2-alkyl(aryl)amino-4H-1,3-thiazines was studied. The rearrangement proceeds in acid media to form the intermediate 4-hydroxyhexahydropyrimidine-2-thiones and their tautomeric 3-oxoalkylthioureas and is accompanied by ring cleavages of the tetrahydropyrimidine-2-thiones.

In a previous communication [1] we described the rearrangement of substituted 4-hydroxyhexahydropyrimidine-2-thiones (II) to substituted 2-amino-4H-1,3-thiazines (VI) in the presence of mineral acids. In connection with the fact that VI manifest high activity as polyfunctional reagent in rubbers, we undertook an attempt to synthesize these compounds from substituted 1,2,3,6-tetrahydropyrimidine-2-thiones (I), which are more accessible than II. The assumption of the hydration of I to the corresponding hydroxy derivatives (II) was a presupposition for the possibility of the rearrangement of I to VI.

4,6,6-Trimethyl-3-alkyl(aryl)-1,2,3,6-tetrahydropyrimidine-2-thiones (I), obtained via a well-known method [2], were selected as the objects for the study. The synthesis of 3-alkyl-substituted I by this method was complicated by the obtaining of a mixture of I with their hydration products (II), which either were separated by fractional crystallization or converted to I by heating with acetic anhydride. The structures of I were confirmed by IR and UV spectra (Table 1). The IR spectra of I contained a band for the $C=C$ double bond at 1680-1700 cm^{-1} [3] and an intense band for the $NH-C=S$ group at 1530-1545 cm^{-1} [4]. In the UV spectra, the maximum of the absorption band of the $C=C-\underset{|}{N}-C=S$ system is observed at 260 to 275 nm, depending on the substituent attached to the nitrogen.

As we expected, I are converted to the isomeric 4,4,6-trimethyl-2-alkyl(aryl)amino-4H-1,3-thiazines (VI) (see the reaction scheme) by heating with excess 6 to 10 N hydrochloric acid. Ring cleavage of I occurs simultaneously to form substituted thioureas (VII), mesityl oxide (VIII), amines (IX), hydrogen sulfide, and other cleavage products.

In acid media, I are hydrated, and a proton adds to the sulfur atoms [5-7] to form the mesomeric 4-hydroxyhexahydropyrimidine-2-thione cation (IIa), the charge of which is apparently delocalized between the nitrogen and sulfur atoms. The formation of IIa was demonstrated by its isolation in the form of the hydrochloride salt on treatment of I ($R = p\text{-}C_6H_4CH_3$, $p\text{-}C_6H_4OCH_3$) with 10 N hydrochloric acid at 20 deg C. The band from the valence vibrations of the $C=C$ bond at 1690 cm^{-1} vanishes in the IR spectra of salts IIa, the intensity of the band from the thioamide group at 1540 cm^{-1} decreases significantly, and an intense band appears at 1600 cm^{-1}, which apparently corresponds to the valence vibrations of the $C=N$ bond, which makes a significant contribution to the mesomeric structure of the cation.

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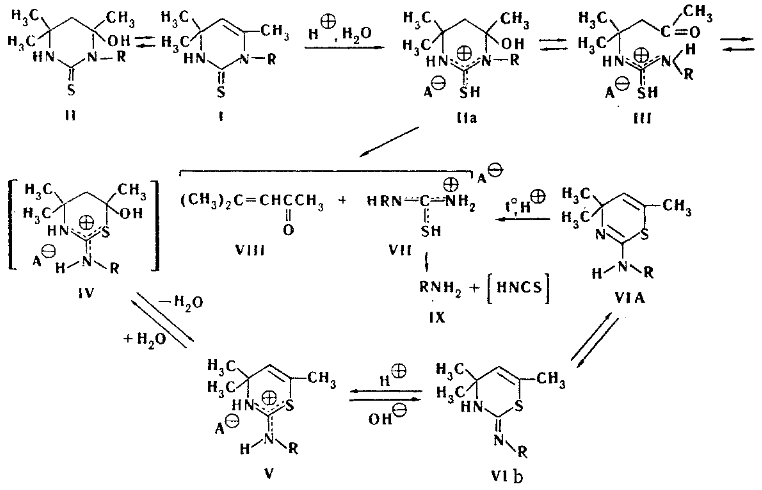

The formation in acid solution of a protonated form is also confirmed by the UV spectra of I in 10 N hydrochloric acid in which a hypsochromic shift of the absorption band by 40-50 nm is observed (Table 1). A similar change in the UV spectra on passing from neutral to acid media was described for thioamides [8,9].

In acid solutions, IIa is in equilibrium with the acyclic tautomeric form – oxoalkylthiourea cation III [10] – as demonstrated by the isolation of 1-aryl-3-(oxoalkyl)thioureas (R = p-$C_6H_4CH_3$, p-$C_6H_4OCH_3$) in the form of 2,4-dinitrophenylhydrazones. III is then cyclized as a result of nucleophilic attack by the sulfur atom on the electrophilic carbonyl group center to form the 4,4,6-trimethyl-6-hydroxy-2-alkyl(arylhexahydro-1,3-thiazine cations (IV), which are cyclic hemimercaptals. The high propensity of hemimercaptals to eliminate water is well known [11,12]. In our case, intermediate hemimercaptals IV are spontaneously dehydrated to form salts V; these were then converted to free bases VI (Table 2), which are capable of amino-imino tautomerism. This tautomerism is not discussed in this communication.

The following facts constitute proof for the structure of VI and for their difference from isomers I: the negative iodine–azide reaction for the C=S group [13] characteristic for I, the increased basicity of VI on titration in methanol with perchloric acid as bases with pK_a 6-7.5, and the IR and UV spectra of VI. The IR spectra of VI contained a band for the vibrations of the C=C double bond at 1660-1670 cm^{-1}, the band for the thioamide group at 1530-1545 cm^{-1} [4,14] vanishes, and a new intense band for the valence vibrations of the C=N bond appears at 1620-1635 cm^{-1}. In the UV spectra of VI the absorption maximum is shifted hypsochromically by 8 to 15 nm for 3-aryl-substituted VI and by 50 to 60 nm for 3-alkyl-substituted VI, as compared with the corresponding I (Table 3).

TABLE 1. Spectral Characteristics of 4,6,6-Trimethyl-3-alkyl(aryl)-1,2,3,6-tetrahydropyrimidine-2-thiones (I).

Compound	R	IR spectra		UV spectra			
		3100-3600 cm^{-1}	1500-1750 cm^{-1}	in alcohol		in 10 N hydrochloric acid	
				λ_{max}, nm	lg ε	λ_{max}, nm	lg ε
a	CH_3	3200—3240	1698, 1545	262	4,06	213	4,20
b	C_3H_7	3200—3250	1695, 1545	270	4,18	222	3,98
c	n-C_4H_9	3200—3300	1690, 1635, 1530	270	4,21	217	4,08
e	$CH_2C_6H_5$	3200—3300	1697, 1640, 1600, 1535	271	4,13	215	4,25
f	C_6H_5	3170—3200	1700, 1600, 1535	275	4,11	227	4,23
g	p-$C_6H_4CH_3$	3160	1687, 1600, 1530	270	4,11	225	4,18
h	p-$C_6H_4OCH_3$	3170	1696, 1612, 1540	273	4,11	229	4,17
i	p-$C_6H_4NO_2$	3200	1650, 1600, 1530	267	4,17	223	4,11

TABLE 2. 4,6,6-Trimethyl-2-alkyl(aryl)amino-4H-1,3-thiazines (VIa-i)

Compounds VI	R	Reaction conditions		Mp* (bp/mm)	Empirical formula	Found, %				Calc., %				Yield, %
		time, min	temp.			C	H	N	S	C	H	N	S	
a	CH_3	15	95	72,5—73	$C_8H_{14}N_2S$	—	—	16,40	19,11	—	—	16,45	18,80	64,2
b	C_3H_7	15	95	(88—88,5/4)	$C_{10}H_{18}N_2S$	—	—	14,30	16,11	—	—	14,13	16,13	84,0
c	n-C_4H_9	5	95	(101,5—102,5/4)	$C_{11}H_{20}N_2S$	62,65	9,46	—	14,49	62,21	9,49	—	15,05	67,5
d	i-C_4H_9	5	95	(91,8—92/4)	$C_{11}H_{20}N_2S$	62,24	9,75	—	—	62,21	9,49	—	—	84,8
e	$CH_2C_6H_5$	5	95	(149—150/4)	$C_{14}H_{18}N_2S$	67,89	7,29	12,00	12,68	68,29	7,36	11,37	13,01	71,2
f	C_6H_5	15	95	120—121	$C_{13}H_{16}N_2S$	—	—	11,91	14,20	—	—	12,03	13,88	65,1
g	p-$C_6H_4CH_3$	15	95	144—145	$C_{14}H_{18}N_2S$	68,34	7,25	11,33	—	68,25	7,36	11,37	—	63,0
h	p-$C_6H_4OCH_3$	40	95	129—130	$C_{14}H_{18}N_2OS$	—	—	10,83	12,21	—	—	10,68	12,22	55,1
i	p-$C_6H_4NO_2$	25	95	139—140	$C_{13}H_{15}N_3O_2S$	—	—	15,24	11,57	—	—	15,16	11,55	56,1

*Compound VIa was recrystallized from ethanol, VIi was recrystallized from petroleum ether—(8:2), and the remaining compounds were recrystallized from petroleum ether.

It is important to emphasize that all of the conversions of I presented in the scheme occur only in acid media. The starting materials are not changed by prolonged heating of I (100 deg for 100 h) in water or alkali solutions. Consequently, mesomeric cation IIa, the positive charge of which promotes both ring opening to III and more profound destruction of the molecule to form the substituted thioureas and mesitylene oxide isolated by us from the reaction mixture, is responsible for both rearrangement and ring cleavage. The formation of the amines also isolated and characterized by us may occur as a result of decomposition of the isothiuronium salts (VII) formed and as a result of splitting out of amines from the disubstituted oxoalkylthioureas (III).

The ratio of the products of transformations of I depends on the reaction time, temperature, and pH. Thus the optimum time for obtaining VI is 5-15 min; an increase in the heating time promotes secondary decomposition processes. By special experiments we showed that aminothiazines VI are also cleaved by heating with acid to form VII, VIII, and IX, which indicates the reversability of the V ⇌ IV ⇌ III transformations, since the formation of VII and VIII can occur only via oxoalkylthioureas III.

It is interesting to note that the rearrangement of I to VI does not occur in 1 N hydrochloric acid, although the formation of the mixture (IIa ⇌ III) also occurs, according to the UV spectra. We isolated only decomposition products of I by heating I for 10 h in 1 N HCl at 90-95 deg. Thus the formation of the IIa ⇌ III cation is a necessary but in sufficient condition for the conversion of I to VI. A decrease in the proton concentration apparently decreases activation of the carbonyl group, which precedes cyclization of III to IV, or decreases the rate of dehydration of IV to V.

EXPERIMENTAL

The IR spectra in mineral oil suspensions or in thin layers were recorded with a UR-10 spectrometer. The UV spectra in alcohol and 10 N and 1 N hydrochloric acid ($5 \cdot 10^{-3}$ M) were obtained with an SF-4 spectrophotometer.

3,4,6,6-Tetramethyl-1,2,3,6-tetrahydropyrimidine-2-thione (Ia). A mixture of 1 g (0.0046 mole) of 4-hydroxy-3,4,6,6-Tetramethylhexahydropyrimidine-2-thione [2], 50 ml of acetic anhydride, and 3 drops of sulfuric acid was heated at 80-85 deg for 1 h. The excess acetic anhydride was removed by distillation to give 0.78 g (86%) of Ia with mp 154-155 deg (from alcohol). Found %: N 16.28; S 18.98. $C_8H_{14}N_2S$. Calc. %: N 16.45; S 18.79.

4,6,6-Trimethyl-3-(p-tolyl)-4-hydroxyhexahydropyrimidine-2-thione Hydrochloride (IIa). Compound Ig [0.5 g (0.002 mole)] was dissolved in 10 ml of concentrated hydrochloric acid. The solution was evaporated to dryness, and the residue was washed with absolute ether to give 0.55 g (90%) of IIa (R = p-$C_6H_4CH_3$) with mp 166-168 deg. Found %: C 55.74; H 7.15; N 9.26. $C_{12}H_{20} \cdot N_2OS \cdot HCl$. Calc. %: C 55.88; H 7.04; N 9.80.

1-(p-Tolyl)-3-(2-oxo-4-amyl)thiourea 2,4-Dinitrophenylhydrazone. This was obtained by treatment of the hydrochloric acid solution of IIa ⇌ III with alcoholic 2,4-dinitrophenylhydrazine and had mp 198-200 deg. Found %: N 7.71. $C_2OH_{24}N_6O_4S$. Calc. %: N 7.21.

TABLE 3. Spectral Characteristics of 4,4,6-Trimethyl-2-alkyl(aryl)-amino-4H-1,3-thiazines (VI-1)

Compounds VI	R	IR spectra		UV spectra (in alcohol)	
		3100-3600 cm^{-1}	1500-1700 cm^{-1}	λ_{max}, nm	lg ε
a	CH_3	3445, 3200	1665, 1638	213	4,22
b	n-C_3H_7	3260—3420	1660, 1630	212	4,09
c	n-C_4H_9	3430—3220	1663, 1635	215	4,13
d	i-C_4H_9	3200—3430	1663, 1635	215	4,14
e	$CH_2C_6H_5$	3230—3420	1668, 1638	215	4,15
f	C_6H_5	3130—3220	1680, 1620, 1591, 1500	262	4,17
g	p-$C_6H_4CH_3$	3130—3220	1672, 1628, 1610, 1510	264	4,15
h	p-$C_6H_4OCH_3$	3100—3200	1670, 1620, 1605, 1510	258	4,64
i	p-$C_6H_4NO_2$		1670, 1620, 1580, 1508	250	4,09

4,4,6-Trimethyl-2-methylamino-4H-1,3-thiazine (VIa). A mixture of 5 g (0.04 mole) of Ia and 35 ml of 10 N hydrochloric acid was heated for 15 min on a boiling-water bath. The mixture was cooled, the acid was removed by distillation, and the residue was made alkaline with saturated aqueous potassium carbonate. The resulting crystals were filtered, washed with water, dried, purified by two vacuum sublimations, and recrystallized from petroleum ether.

VIf-i were similarly obtained.

4,4,6-Trimethyl-2-n-propylamino-4H-1,3-thiazine (VIb). A mixture of 5 g (0.025 mole) of Ib and 100 ml of 10 N hydrochloric acid was heated for 15 min on a boiling-water bath. The acid was removed by distillation, and the residue was treated at 0 deg with a saturated aqueous potassium carbonate solution until it gave an alkaline reaction. The organic layer was extracted three times with ether, and the extract was dried with magnesium sulfate. The ether was removed by distillation, and the residual oil (VIb) was chromatographed on silica gel [ether–hexane (1:9)].

VIc-VIe were similarly obtained.

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