SYNTHESIS OF SUBSTITUTED 2-AMINO-5,6-DIHYDRO-4H-1,3-THIAZINES AND 2-IMINOTETRAHYDRO-1,3-THIAZINES

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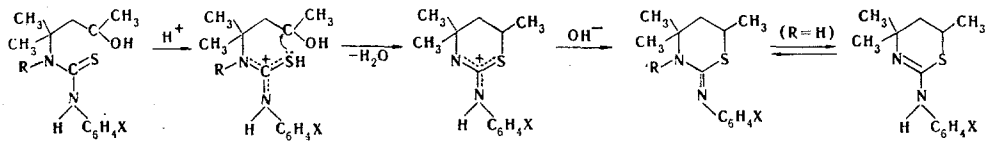
N-Aryl-N'-(2-methyl-4-hydroxy-2-pentyl)thioureas are cyclized in acidic media to 4,4,6-trimethyl-2-arylimino-5,6-dihydro-4H-1,3-thiazines, the methylation of which with methyl iodide gives 4,4,6-trimethyl-2-methylarylamino-5,6-dihydro-4H-1,3-thiazines. 3,4,4,6-Tetramethyl-2-aryliminotetrahydro-1,3-thiazines were synthesized by cyclization of N-aryl-N'-methyl-N'-(2-methyl-4-hydroxy-2-pentyl)thioureas.

2-Amino-5,6-dihydro-4H-1,3-thiazines are known compounds (for example, see [1-4]), but data on the structure and tautomerism of these compounds are scanty and contradictory [1, 3].

In the present communication we describe the synthesis of 4,4,6-trimethyl-2-arylamino-5,6-dihydro-4H-1,3-thiazines (IV), which was realized via the scheme in [2].



I–IV R = H; V–VIII R = CH_3

N-Aryl-N'-(2-methyl-4-hydroxy-2-pentyl)thioureas (I) [5] are protonated at the sulfur atom in a saturated alcohol solution of hydrogen chloride to give isothiourea cations (II); this is attested to by the hypsochromic shift (by 40 nm) of the maximum of the absorption band in the UV spectra of I in 4 N HCl in methanol as compared with the maximum of the absorption band in the UV spectra of I in methanol (λ_{max} 254 nm). This sort of shift of the maximum of the absorption band in acidic media is characteristic for the S-protonated forms of compounds that contain a thioamide group [6, 7].

At high temperatures cations II are cyclized as a result of nucleophilic attack by the sulfur atom on the carbinol carbon atom to give aminothiazine salts III, which were converted to the bases of the corresponding aminothiazines (IV, Table 1) as a result of treatment with saturated potassium carbonate solution.

In order to study the amino–imino tautomerism possible for IV, we also synthesized the corresponding model compounds with fixed imino and amino structures. The starting compounds for the synthesis of the imino models – 3,4,4,6-tetramethyl-2-aryliminotetrahydro-1,3-thiazines (VIII) – were N-aryl-N'-methyl-N'-(2-methyl-4-hydroxy-2-pentyl)thioureas (V), which were cyclized in concentrated hydrochloric acid through intermediate cations VI to 3,4,4,6-tetramethyl-2-aryliminotetrahydro-1,3-thiazine hydrochlorides (VII), from which bases VIII were isolated by the usual method.

The lability of N,N',N'-trisubstituted thioureas V, which we have previously noted [8], increases in acidic media: aromatic amines, arylthioureas, and other unidentified products of the destruction of thio-

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TABLE 1. 4,4,6-Trimethyl-2-arylamino-5,6-dihydro-4H-1,3-thiazines (IVa-f)

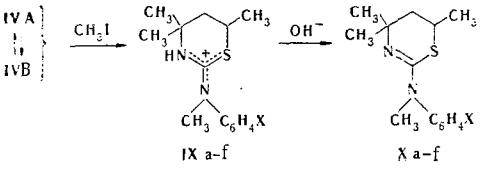
Compound	X	mp, °C (from alcohol)	Empirical formula	Found, %		Calc., %		Yield, %
				N	S	N	S	
IVa	*p*-OCH_3	177—178	$C_{14}H_{20}N_2OS$	10,5	11,8	10,5	12,1	94
IVb	*p*-CH_3	147—148	$C_{14}H_{20}N_2S$	11,2	12,6	11,3	12,9	96
IVc	*m*-CH_3	117—117,5	$C_{14}H_{20}N_2S$	11,2	12,7	11,3	12,9	92
IVd	H	150—151	$C_{13}H_{18}N_2S$	12,1	13,5	12,0	13,7	90
IVe	*p*-Br	185—186	$C_{13}H_{17}BrN_2S$	8,7	10,0	8,9	10,2	87
IVf	*m*-Cl	137—138	$C_{13}H_{17}ClN_2S$	10,2	11,8	10,4	11,9	85

TABLE 2. 4,4,6-Trimethyl-2-methylarylamino-5,6-dihydro-4H-1,3-thiazines (Xa-f)

Compound	X	mp, °C	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	N	S	C	H	N	S	
Xa	*p*-OCH_3	56—56	$C_{15}H_{22}N_2OS$	64,6	7,8	—	11,5	64,7	8,0	—	11,5	91
Xb	*p*-CH_3	43—44	$C_{15}H_{22}N_2S$	68,5	8,5	10,5	—	68,7	8,5	10,7	—	93
Xc	*m*-CH_3	53—54	$C_{15}H_{22}N_2S$	68,6	8,4	—	12,1	68,7	8,5	—	12,2	92
Xd	H	105—106	$C_{14}H_{20}N_2S$	—	—	11,2	12,8	—	—	11,3	12,9	95
Xe	*p*-Br	81—81,5	$C_{14}H_{19}BrN_2S$	—	—	8,4	9,6	—	—	8,6	9,8	93
Xf	*m*-Cl	31—32	$C_{14}H_{19}ClN_2S$	—	—	10,1	11,0	—	—	9,9	11,3	95

ureas V were detected in the reaction mixture. For this reason, the yields of iminothiazines VIII are substantially lower than the yields of the corresponding IV.

Model compounds with a fixed amino structure – 4,4,6-trimethyl-2-methylarylamino-5,6-dihydro-4H-1,3-thiazines (X) – were obtained by methylation of aminothiazines IV with methyl iodide in acetone.



In this case, we obtained single methylation products in high yields (Table 2); this provides evidence that the reaction proceeds primarily at one of the two reaction centers. On the basis of the differences in the physicochemical characteristics of the methylation products and VIII, the imino structure of which is determined by the structure of the starting compounds, we assume that the methylation of aminothiazines IV is realized at the exocyclic nitrogen atom. The spectral parameters of IV, VIII, and X and the amino-imino tautomerism IVA⇌IVB will be discussed in our next communication.

EXPERIMENTAL

4,4,6-Trimethyl-2-anilino-5,6-dihydro-4H-1,3-thiazine (IVd). A solution of 10 g (0.04 mole) of thiourea Id in 50 ml of ethanol was saturated with dry hydrogen chloride, after which the ethanol was removed by distillation, and the residue was neutralized with a saturated potassium carbonate solution. The organic portion was extracted with ether, and the extract was dried with magnesium sulfate. The ether was removed by distillation, and the residue was crystallized from alcohol to give 8.3 g of aminothiazine IVd.

A similar method was used to obtain IVa-c, e, f (Table 1).

3,4,4,6-Tetramethyl-2-phenyliminotetrahydro-1,3-thiazine (VIIIc). A mixture of 4.0 g (0.015 mole) of thiourea V and 15 ml of concentrated hydrochloric acid was heated at 90-95° for 10 min, after which the acid was removed by vacuum distillation, and the residue was neutralized with saturated potassium carbonate solution. The organic portion was extracted with ether, the ether was removed from the extract by distillation, and the residue was recrystallized from alcohol to give 2.4 g (63%) of VIIIc with mp 72-73°. Found: N 10.9; S 12.5%. $C_{14}H_{20}N_2S$. Calculated: N 11.3; S 12.9%.

A similar method was used to obtain 3,4,4,6-tetramethyl-2-(p-methoxyphenyl)iminotetrahydro-1,3-thiazine (VIIIa, 18% yield, mp 71.5-72°. Found: N 9.8; S 11.2%. $C_{15}H_{22}N_2OS$. Calculated: N 10.1; S 11.5%)

and 3,4,4,6-tetramethyl-2-(p-tolyl)iminotetrahydro-1,3-thiazine (VIIIb, 23% yield, mp 116-117°. Found: N 10.5; S 11.9%. $C_{15}H_{22}N_2S$. Calculated: N 10.7; S 12.2%).

4,4,6-Trimethyl-2-N-methylanilino-5,6-dihydro-4H-1,3-thiazine (Xd). A 4.8 g (0.034 mole) sample of methyl iodide was added to a solution of 4 g (0.017 mole) of IVd in 15 ml of acetone, and the mixture was allowed to stand at 20° for 30 h. Dry ether (20 ml) was added, and the precipitated crystals of salt IXd were removed by filtration and treated with a saturated potassium carbonate solution. The organic portion was extracted with ether, and the ether extract was dried with magnesium sulfate. The ether was removed by distillation to give 3.4 g of aminothiazine Xd. A similar method was used to obtain Xa-c, e, f (Table 2).

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