SYNTHESIS OF 4,4,6-TRIMETHYL-2-ARYLAMINO-4H-1,3-THIAZINES

P. L. Ovechkin, L. A. Ignatova, A. E. Gekhman, and B. V. Unkovskii

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The reaction of 2-isothiocyano-2-methyl-4-pentanone with substituted anilines gave 4,6,6-trimethyl-3-aryl-1,2,3,6-tetrahydropyrimidine-2-thiones, which are converted to the isomeric 4,4,6-trimethyl-2-arylamino-4H-1,3-thiazines by intramolecular rearrangement by heating with hydrochloric acid. In order to study the structure and amino–imino tautomerism of the aminothiazines, their analogs with a fixed amine structure were obtained. The synthesis of model compounds was accomplished by reaction of 2-isothiocyano-2-methyl-4-pentanone with m- and p-substituted N-methylanilines and subsequent cyclization of the resulting N-methyl-N-aryl-N'-(2-methyl-4-oxo-2-amyl)thioureas to 4,4,6-trimethyl-2-methylarylamino-4H-1,3-thiazines.

We have previously [1] reported the conversion of substituted 3-alkyl(aryl)-1,2,3,6-tetrahydropyrimidine-2-thiones to substituted 2-alkyl(aryl)amino-4H-1,3-thiazines by intramolecular rearrangement, which occurs on heating with hydrochloric acid. In order to investigate the structure, reactivity, and biological activity of 2-amino-4H-1,3-thiazines, in the course of developing our research [1,2] we accomplished the analogous rearrangements of the previously undescribed 4,6,6-trimethyl-3-aryl-1,2,3,6-tetrahydropyrimidine-2-thiones (II), which make it possible to synthesize new representatives of 4,4,6-trimethyl-2-arylamino-4H-1,3-thiazines (III).

We accomplished the synthesis of IIa-i (Table 1) via a known method [3] from 2-isothiocyano-2-methyl-4-pentanone (I) and p- and m-substituted anilines. When pyrimidinethiones II are heated with 6-10 N hydrochloric acid, they undergo rearrangement to the isomeric IIIa-i (Table 2).

TABLE 1. 4,6,6-Trimethyl-3-aryl-1,2,3,6-tetrahydropyrimidine-thiones (IIa-i)

Comps. II	R	mp, °C (from alcohol)	Empirical formula	Found, %		Calc., %		Yield, %
				N	S	N	S	
a	*p*-OC_2H_5	176—177	$C_{15}H_{20}N_2OS$	10,36	—	10,13	—	85,2
b	*m*-CH_3	165,5—166	$C_{14}H_{18}N_2S$	11,34	12,62	11,37	13,01	84,0
c	*p*-OH	187—188	$C_{13}H_{16}N_2OS$	11,28	—	11,28	—	78,0
d	*p*-Br	182—183	$C_{13}H_{15}BrN_2S$	9,02	10,18	9,00	10,30	84,2
e	*p*-Cl	191—192	$C_{13}H_{15}ClN_2S$	10,25	11,79	10,50	12,00	85,9
f	*m*-Cl	185—186,5	$C_{13}H_{15}ClN_2S$	10,35	11,61	10,50	12,00	86,4
g	*m*-$COCH_3$	168—169	$C_{15}H_{18}N_2OS$	10,24	11,60	10,21	11,68	87,6
h	*p*-CN	186—187	$C_{14}H_{15}N_3S$	C 65,2	H 5,8	C 65,3	H 5,9	84,3
i	*m*-NO_2	192,5—193,5	$C_{12}H_{15}N_3O_2S$	C 56,1	H 5,6	C 56,3	H 5,4	79,4

*The composition of IIa and IIc was confirmed by additionally determining the C and H content.

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TABLE 2. 4,4,6-Trimethyl-2-arylamino-4H-1,3-thiazines (IIIa-i)

Comps. II	R	Reaction time, h	mp, °C (from alcohol)	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	N	S	C	H	N	S	
a	*p*-OC_2H_5	40	142—143	$C_{15}H_{20}N_2OS$	—	—	10,28	11,53	—	—	10,13	11,60	52,3
b	*m*-CH_3	15	98—99	$C_{14}H_{18}N_2S$	68,22	7,35	—	—	68,25	7,36	—	—	54,1
c	*p*-OH	25	83—84	$C_{13}H_{16}N_2OS$	62,81	6,54	—	12,71	62,87	6,49	—	12,91	64,5
d	*p*-Br	30	157—158	$C_{13}H_{13}BrN_2S$	—	—	8,97	10,25	—	—	9,00	10,30	61,1
e	*p*-Cl	30	155,5—156,5	$C_{13}H_{15}ClN_2S$	58,41	5,65	10,22	—	58,60	5,70	10,50	—	58,2
f	*m*-Cl	30	138—139	$C_{13}H_{15}ClN_2S$	—	—	10,41	11,64	—	—	10,50	12,00	55,6
g	*m*-$COCH_3$	35	110,5—111,5	$C_{15}H_{18}N_2OS$	65,70	6,60	10,24	11,45	65,67	6,61	10,21	11,68	68,0
h	*p*-CN	25	169—170	$C_{14}H_{15}N_3S$	65,60	5,98	—	—	65,33	5,88	—	—	44,1
i	*m*-NO_2	25	151—152	$C_{13}H_{15}N_3O_2S$	—	—	15,14	11,60	—	—	15,16	11,55	42,1

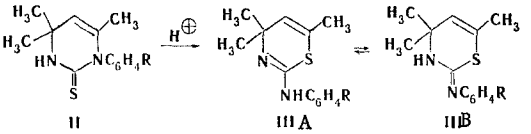
TABLE 3. N-Methyl-N-aryl-N'-(2-methyl-4-oxo-2-amyl)- thioureas (IVa-e)

Comps. IV	R	mp, °C (fr. alco.)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
a	*p*-OC_2H_5	94,5—95	$C_{16}H_{24}N_2O_2S$	—	S 10,3	9,13	—	S 10,4	9,08	46,6
b	*p*-OCH_3	77,5—78,5	$C_{15}H_{22}N_2O_2S$	61,33	7,18	9,44	61,22	7,52	9,52	47,4
c	*p*-CH_3	126—127	$C_{15}H_{22}N_2OS$	64,59	7,93	S 11,4	64,71	7,96	S 11,5	51,9
d	*m*-CH_3	102—103	$C_{15}H_{22}N_2OS$	64,70	7,96	S 11,5	64,71	7,96	S 11,5	46,2
e	H	62—62,5	$C_{14}H_{20}N_2OS$	64,00	7,85	11,02	63,61	7,62	10,59	56,7

TABLE 4. 4,4,6-Trimethyl-2-methylarylamino-4H-1,3-thiazines (VIIIa-e)

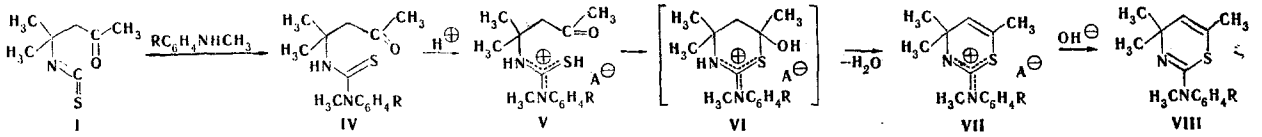
Comps. VIII	R	mp, °C (from hexane)	Empirical formula	Found, %		Calc., %		Yield, %
				N	S	N	S	
a	*p*-OC_2H_5	48—48,5	$C_{16}H_{22}N_2OS$	9,45	10,84	9,65	11,04	49,2
b	*p*-OCH_3	53—54	$C_{15}H_{20}N_2OS$	10,01	11,57	10,14	11,60	48,3
c	*p*-CH_3	52—53	$C_{15}H_{20}N_2S$	10,95	12,13	10,80	12,31	53,4
d	m-CH_3	28—29	$C_{15}H_{20}N_2S$	—	12,32	—	12,31	45,8
e	H	52,5—53,2	$C_{14}H_{18}N_2S$	11,66	—	11,37	—	51,0

*The composition of VIIId,e was confirmed by additionally determining the C and H content.



II IIIA IIIB

The existence of amine (IIIA) and imine (IIIB) forms, which are in tautomeric equilibrium, can be assumed for IIIa-i. It has been established [2] that 4,4,6-trimethyl-2-alkylamino-4H-1,3-thiazines both in solution and in the crystalline state have primarily the amine structure (IIIA). To solve the problem of the structure of IIIa-i, which contain aryl substituents attached to the exocyclic nitrogen atom, it is necessary to compare the physicochemical characteristics of IIIa-i and their analogs, which have fixed amino and imino structures [4]. For this, as models of the amine type* we selected 4,4,6-trimethyl-2-methylarylamino-4H-1,3-thiazines (VIII), the synthesis of which was accomplished via the scheme presented below.



I IV V VI VII VIII

The reaction of I with m- and p-substituted N-methylanilines in ether gave N-methyl-N-aryl-N'-(2-methyl-4-oxo-2-amyl)thioureas (IVa-e, Table 3). Protonation of the sulfur atom [5-7] to give protonated forms V, which is characteristic for thioamides, occurs when IV react with 6-10 N hydrochloric acid. This is confirmed by the hypsochromic shift of the maximum of the absorption band in the UV spectra of IV in 1 N hydrochloric acid (λ_{max} 250 nm) as compared with the maximum of the absorption band in 50% alcohol (λ_{max} 290 nm) [7]. As a consequence of intramolecular nucleophilic attack by sulfur of the electrophilic center of the carbonyl group, V are converted to cyclic hemimercaptals (VI), which undergo spontaneous dehydration during the reaction to give 4,4,6-trimethyl-2-methylarylamino-4H-1,3-thiazine hydrochlorides (VII).

The ability of N,N-disubstituted thioureas IV to cyclize to aminothiazines VII on heating with hydrochloric acid confirms our previously [1] proposed mechanism for the intramolecular rearrangement of tetrahydropyrimidine-2-thiones (I) to aminothiazines (II), which assumes opening of the ring of I to form substituted oxo alkylthioureas and subsequent cyclization of them to protonated forms. The corresponding bases (VIIIa-e, Table 4) were isolated by the action of aqueous alkali solutions on salts VIIa-e at 0°.

Absorption at 1670-1680 cm^{-1} ($\nu_{C=C}$), 1500 and 1600 cm^{-1} (aromatic ring vibrations), and 1620 cm^{-1} (stretching vibrations of the endocyclic C=N bond) are present in the IR spectra of VIIIa-e.

A comparison of the spectral characteristics of aminothiazines III and model compounds VIII in order to study the structure and tautomerism of III will be described in a separate communication.

EXPERIMENTAL

4,6,6-Trimethyl-3-(p-ethoxyphenyl)-1,2,3,6-tetrahydropyrimidine-2-thione (IIa). A 15.7-g (0.1 mole) sample of I [3] was added to a solution of 13.7 g (0.1 mole) of p-phenetidine in 75 ml of ether at 25°, and the precipitate that formed after 2 h was removed by filtration, washed with ether, and dissolved in 100 ml of acetic anhydride. The solution was heated at 95-100° for 40 min, and the acetic anhydride was removed in vacuo. The residue was recrystallized from isopropyl alcohol to give 23.5 g of IIa. A similar method was used to obtain IIb-i.

4,4,6-Trimethyl-2-(p-ethoxyphenylamino)-4H-1,3-thiazine (IIIa). A mixture of 13.8 g (0.05 mole) of IIa and 100 ml of concentrated HCl was heated at 90-95° for 30 min, and the acid was removed in vacuo. The residue was dissolved in 50 ml of water, and the insoluble crystals of starting IIa were removed by filtration. The mother liquor was neutralized at 0° with potassium carbonate, and the precipitate was removed by filtration and recrystallized from alcohol to give 7.2 g of IIIa. A similar method was used to obtain IIIb-i.

N-Methyl-N-(p-ethoxyphenyl)-N'-(2-methyl-4-oxo-2-amyl)thiourea (IVa). A 15.7-g (0.1 mole) sample of I was added to a solution of 12.1 g (0.08 mole) of N-methyl-p-phenetidine in 50 ml of absolute ether, and

*The synthesis of model compounds with a fixed imino structure (IIIB) will be described in a subsequent communication.

the mixture was allowed to stand at 25° for 48 h. The ether solution was saturated with dry HCl, and the resulting oil was washed with ether to remove starting I and dissolved in 30 ml of water. The aqueous solution was neutralized with saturated potassium carbonate solution, and the organic portion was extracted with three 30-ml aliquots of hexane. The hexane was removed by distillation, and the residual crystals were recrystallized from alcohol to give 11.5 g of IVa. A similar method was used to obtain IVb-e.

4,4,6-Trimethyl-2-methyl(p-ethoxyphenyl)amino-4H-1,3-thiazine (VIIIa). A mixture of 6.2 g (0.02 mole) of IVa and 60 ml of concentrated HCl was heated at 95° for 30 min. The acid was removed by vacuum distillation, and the residue was dissolved in water. The aqueous solution was neutralized with saturated potassium carbonate solution, and the organic portion was extracted with 50 ml of hexane. The extract was dried with magnesium sulfate, and the hexane was removed by distillation. The residue was chromatographed on activity II aluminum oxide with elution by hexane–ether (4:1). The eluent was removed by distillation, and the residue was recrystallized from hexane to give 3.04 g of VIIIa. A similar method was used to obtain VIIIb-e.

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