SYNTHESIS OF SUBSTITUTED 2-ARYLIMINO-2,3-DIHYDRO-4H-1,3-THIAZINES

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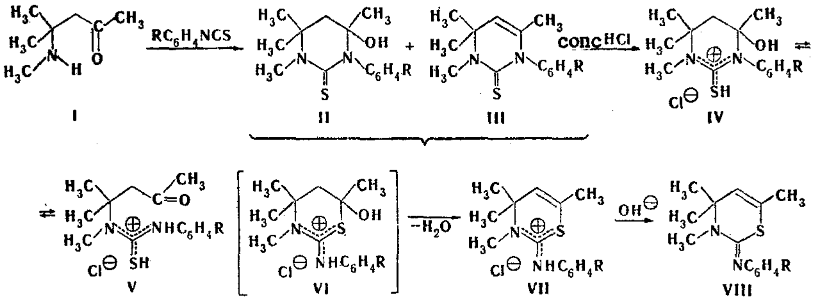
The synthesis of 3,4,4,6-tetramethyl-2-arylimino-2,3-dihydro-4H-1,3-thiazines, which have a fixed imino structure, was accomplished by two methods: by intramolecular rearrangement of 1,4,6,6-tetramethyl-3-aryl-1,2,3,6-tetrahydropyrimidine-2-thiones and by amination of 3,4,4,6-tetramethyl-2,3-dihydro-4H-1,3-thiazine-2-thione methiodide.

In connection with a study of amine–imine tautomerism of substituted 2-amino-4H-1,3-thiazines, we reported [1] the synthesis of 4,4,6-trimethyl-2-methylarylamino-4H-1,3-thiazines, which are model compounds with a fixed amino structure. In the present paper we describe the synthesis of a series of model compounds that have a fixed imino structure – 3,4,4,6-tetramethyl-2-arylimino-2,3-dihydro-4H-1,3-thiazines (VIII). The synthesis of VIII was accomplished by two methods (methods A and B).



Method A is based on the reaction of 2-methylamino-2-methyl-4-pentanone (I) with p- and m-substituted aryl isothiocyanates, which leads to the formation of a mixture of two products – 1,4,6,6-tetramethyl-3-aryl-4-hydroxyhexahydropyrimidine-2-thiones (II) and 1,4,6,6-tetramethyl-3-aryl-1,2,3,6-tetrahydropyrimidine-2-thiones (III). The next step in the synthesis of VIII consists in the intramolecular rearrangement of pyrimidinethiones II and III on heating them with 6-10 N hydrochloric acid. We have previously [2,3] demonstrated that, under these conditions, both II and III are converted to identical rearrangement products through common protonated forms of intermediates IV and V. This made it possible to carry out subsequent transformations of II and III without separating them. In two cases, we isolated individual compounds IIIa and IIIb from mixtures of II and III and subjected them to rearrangement. Moreover, it was shown that the course of the process is the same when individual IIIa,b are used as the starting materials and when mixtures of the corresponding II and III are used. The probable mechanism of the rearrangement of compounds of the II and III types through intermediates IV, V, and VI was previously discussed in detail in [2,3]. As a result of the reaction, we isolated 3,4,4,6-trimethyl-2-arylimino-2,3-dihydro-4H-1,3-thiazine hydrochlorides (VII), which are converted to the corresponding bases (VIII, Table 1) by the action of aqueous alkali solutions at 0°.

We also obtained VIII by method B. The reaction of I with carbon disulfide in alkaline media gives an unstable addition product – N-methyl-N-(2-methyl-4-oxo-2-amyl)dithiocarbamic acid (IXA) – which is ap-

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TABLE 1. 3,4,4,6-Tetramethyl-2-arylimino-2,3-dihydro-4H-1,3-thiazines (VIIIa-f)

Comp.	R	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
				N	S	N	S	
VIIIa	*p*-OC_2H_5	61,0—61,5	$C_{16}H_{22}N_2OS$	9,54	10,95	9,65	11,04	54,8
VIIIb	*p*-OCH_3	49,5—51,0	$C_{15}H_{20}N_2OS$	10,11	11,58	10,14	11,60	61,2
VIIIc	*m*-CH_3	21,0—22,0	$C_{15}H_{20}N_2S$	—	12,21	—	12,35	48,3
VIIId	*p*-Br	75,5—76,0	$C_{14}H_{17}BrN_2S$	8,60	9,70	8,61	9,87	56,4
VIIIe	*m*-Cl	40,5—41,5	$C_{14}H_{17}ClN_2S$	9,71	11,27	9,81	11,35	51,2
VIIIf	H	67,0—68,0	$C_{14}H_{18}N_2S$	11,48	12,93	11,37	13,01	58,0

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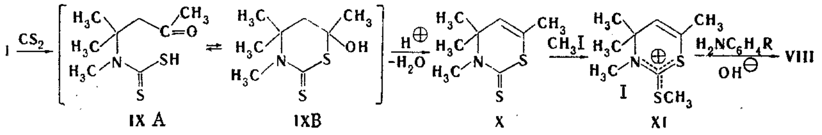
*The composition of VIIIa and VIIIc was confirmed by additionally determining the C and H content.

parently in equilibrium with the cyclic tautomeric form – 3,4,4,6-tetramethyl-6-hydroxytetrahydro-1,3-thiazine-2-thione (IXB) – as was previously [4] demonstrated for the analogous structures. Compound IX without isolation was converted to 3,4,4,6-tetramethyl-2,3-dihydro-4H-1,3-thiazine-2-thione (X) in 60-65% yield by heating with 80% sulfuric acid. Compound X was methylated with methyl iodide in acetone to give methiodide XI, an unstable compound that is readily converted to the starting thiazinethione (X) on heating. Compound XI is converted to iminothiazines, which proved to be identical to VIII obtained by method A, in 55-60% yields on reaction with aromatic amines (p-anisidine and p-phenetidine) in methanol at 20°.



The structure of VIII was confirmed by the IR spectra: the band at 1670-1680 cm^{-1} corresponds to the stretching vibrations of the C=C bond of the thiazine ring, and the band at 1580 cm^{-1} characterizes the stretching vibrations of the exocyclic C=N bond.

EXPERIMENTAL

The IR spectra of mineral-oil suspensions were recorded with a UR-10 spectrometer.

1,4,6,6-Tetramethyl-3-(p-methoxyphenyl)-1,2,3,6-tetrahydropyrimidine-2-thione (IIIb). A 12.3-g (0.125 mole) sample of mesityl oxide was added with stirring at 5° to 3.8 g (0.125 mole) of methylamine in the form of a 25% aqueous solution, and the mixture was stirred at 20-22° for 30 min. The I formed was extracted with ether, and the extract was dried with magnesium sulfate. The ether was removed by distillation, and 20.6 g (0.125 mole) of p-methoxyphenylisothiocyanate in 30 ml of ether was added at −4°. The crystals that formed after 30 min were removed by filtration and dried to give 20.8 g (60.0% based on mesityl oxide) of IIIb with mp 118-119° (from isopropyl alcohol). Found: C 65.23; H 7.14; N 9.81%. $C_{15}H_{20}N_2OS$. Calculated: C 65.21; H 7.30; N 10.14%.

3,4,4,6-Tetramethyl-2,3-dihydro-4H-1,3-thiazine-2-thione (X). A 42.2-g (0.43 mole) sample of mesityl oxide was added gradually with stirring at 0-5° to 13.3 g (0.43 mole) of methylamine in the form of a 25% aqueous solution. After 30 min, 33.7 g (0.43 mole) of carbon disulfide was added to the resulting I without isolation of the latter, and the mixture was stirred for 45 min, cooled to 5-6°, and treated with 85 ml of concentrated H_2SO_4. The mixture was heated at 65° for 10 min and poured into a mixture of ice and water. The precipitated crystals were removed by filtration to give 51.0 g (63.2%) of XI with mp 46-47° (from isopropyl alcohol). Found: C 50.72; H 6.78; N 7.25; S 34.11%. $C_8H_{13}NS_2$. Calculated: C 51.31; H 7.00; N 7.50; S 34.5%.

3,4,4,6-Tetramethyl-2,3-dihydro-4H-1,3-thiazine-2-thione Methiodide (XI). A 5.62-g (0.03 mole) sample of X was dissolved in 20 ml of acetone, 5.68 g (0.04 mole) of methyl iodide was added, and the mixture was allowed to stand at 20° for 20 h. The precipitated crystals were removed by filtration, washed with ether, and reprecipitated twice from methanol by the addition of dry ether to give 8.9 g (90%) of XI with mp 115-116.5°. Found: C 32.53; H 4.61; N 4.38%. $C_9H_{16}INS_2$. Calculated: C 32.83; H 4.90; N 4.25%.

3,4,4,6-Tetramethyl-2-(p-methoxyphenylimino)-2,3-dihydro-4H-1,3-thiazine (VIIIb). A. A mixture of 11 g (0.04 mole) of IIIb and 200 ml of concentrated HCl was heated at 90-95° for 20 min. The acid was removed by vacuum distillation, and the residue was neutralized at 5° with saturated potassium carbonate solution. The organic portion was extracted with petroleum ether, and the extract was dried with magnesium sulfate. The ether was removed by distillation, and the residue was chromatographed on activity II aluminum oxide with elution by petroleum ether—ether (9:1). The eluent was removed by distillation, and the crystalline residue was vacuum-dried to give 6.7 g (61.2%) of VIIIb with mp 49.5-51°. A similar method was used to obtain VIIIa and VIIIc-VIIIf (Table 1).

B. A 4.9-g (0.04 mole) sample of p-anisidine was added at 20° to a solution of 8.0 g (0.024 mole) of XI in 25 ml of methanol, and nitrogen was bubbled through the mixture at 20° for 10 h until the odor of mercaptan had vanished completely. The methanol was removed by distillation, and the residue was dissolved in ether. The crystals that precipitated were removed by filtration and dissolved in 20 ml of water. The aqueous solution was neutralized with saturated potassium carbonate solution, and the organic portion was extracted with ether. The ether extract was dried with magnesium sulfate, and the ether was removed by distillation to give 5.5 g (83.0%) of VIIIb with mp 49-50° (from alcohol). A similar method was used to obtain VIIIa.

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