STRUCTURES AND TAUTOMERISM OF SUBSTITUTED 2-AMINO-4H-1,3-THIAZINES

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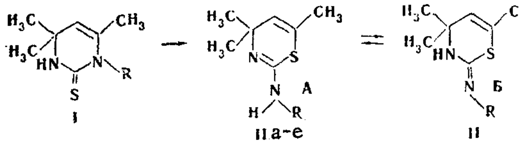
A comparison of the IR and UV spectra of 2-alkyl(aralkyl)amino-4H-1,3-thiazines with the spectra of model compounds showed that the amino form of the aminothiazines predominates. The basicities of the synthesized compounds were determined, and the structure of the cation formed on protonation is discussed.

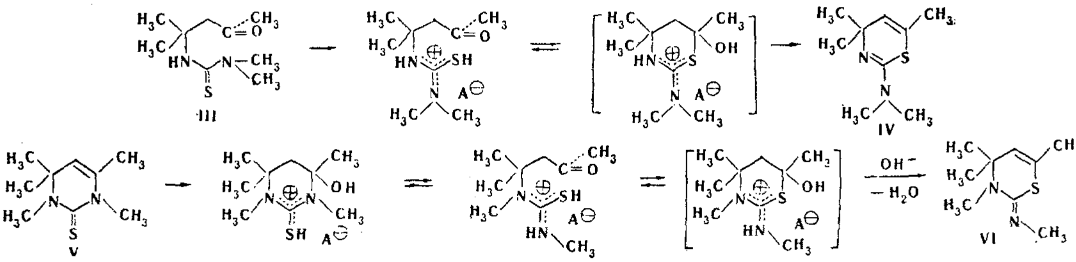
In [1] we reported the intramolecular rearrangement of substituted 1,2,3,6-tetrahydropyrimidine-2-thiones (I), which leads to a previously unreported class of compounds – substituted 2-amino-4H-1,3-thiazines. In this communication we discuss the structures and tautomerism of 4,4,6-trimethyl-2-alkyl(aralkyl)-amino-4H-1,3-thiazines, which are capable of existing both in the amino form (IIA) and in the imino form (IIB):



II a $R=CH_3$; b $R=n\text{-}C_3H_7$; c $R=n\text{-}C_4H_9$; d $R=i\text{-}C_4H_9$; e $R=CH_2C_6H_5$

We made the assignment of amino or imino forms to IIa-e on the basis of a comparison of the spectral characteristics of IIa-e and those of model compounds, viz., 4,4,6-trimethyl-2-dimethylamino-4H-1,3-thiazine (IV) and 3,4,4,6-tetramethyl-2-methylimino-4H-2,3-dihydro-1,3-thiazine (VI) (see Table 1). The structure of IV and VI is unambiguously determined by the structure of the starting materials, viz., N-(2-methyl-4-oxo-2-amyl)-N',N'-dimethylthiourea (III) and 1,3,4,6,6-pentamethyl-1,2,3,4-tetrahydropyrimidine-2-thione (V), which are converted to IV and VI, respectively, in hydrochloric acid (see scheme).

IR Spectra. A band at 1660-1668 cm^{-1}, which we assigned to the valence vibrations of the C =C bond on the basis of the proximity of the frequencies of this band to those of II and those in the starting I [1,2], is observed in the IR spectra of mineral oil suspensions of IIa-e. The lower-frequency band at 1630-1635 cm^{-1} corresponds to the valence vibrations of the C =N bond. The IR spectra of model compounds IV and VI contain $\nu_{C=C}$ bands at 1656 and 1667 cm^{-1}, respectively, while the frequencies that correspond to the vibrations of the endocyclic C =N bond in IV and to the exocyclic C =N bond in VI are substantially different: 1620 cm^{-1} for the amino form and 1588 cm^{-1} for the imino form. These data make it possible to assume that IIa-e exists in amino form IIA in the pure state.



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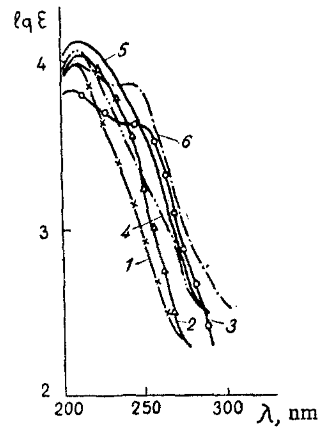


Fig. 1. UV spectra: 1) IIa in hexane; 2) IVc in hexane; 3) VI in hexane; 4) IIa in methanol; 5) IV in methanol; 6) VI in methanol.

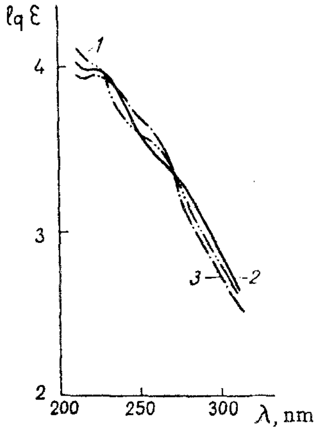


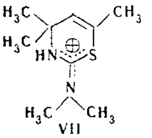
Fig. 2. UV spectra in 0.1 N hydrochloric acid: 1) IIa; 2) IV; 3) VI.

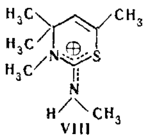
TABLE 1. Spectral Characteristics of 4,4,6-Trimethyl-2-alkyl-(aralkyl)amino-4H-1,3-thiazines

Comp.	pK_a in CH_3OH	IR spectra, cm^{-1}		UV spectra, λ_{max} nm, (log ε),		PMR spectra in CCl_4, δ, ppm				
		C=C	C=N	in CH_3OH	in C_6H_{14}	4-$(CH_3)_2$	6-CH_3	5-H	N—H	other protons
IIa	7,31	1665	1635	210 (4,10)	210 (4,08)	1,17	1,91	5,45	4,30	N-CH_3 2,70
IIb	7,46	1660	1630	210 (4,10)	210 (4,09)	1,18	1,92	5,42	4,32	N-CH_2 3,32
IIc	7,38	1663	1662	210 (4,14)	210 (4,07)	1,18	1,85	5,40	4,60	N-CH_2 3,13
IId	7,35	1663	1635	210 (4,14)	—	1,17	1,92	5,37	4,34	N-CH_2 2,90 NC-CH 1,4
IIe	6,98	1668	1638	210 (4,28)	210 (4,31)	1,19	1,91	5,45	4,07	NCH_2 4,43 H arom. 4,23
IV	7,12	1667	1620	210 (4,14)	210 (4,09)	1,17	1,96	5,43	—	$N(CH_3)_2$ 2,91
VI	7,84	1656	1588	242 (3,87)	247 (3,66)	1,19	1,97	5,35	—	NCH_3 (endo) 2,90 NCH_3 (exo) 2,71

UV Spectra. As seen from the data in Table 1 and Fig. 1, the UV spectra of hexane solutions of IIa-e and IV are absolutely analogous (log ε_{210} 4.10-4.15). At the same time, an absorption band at 242-247 nm (log ε 3.7-3.9) is observed in the UV spectrum of VI, which has a different electronic structure. Thus, it is confirmed that all of the investigated IIa-e exist primarily in the amino form in alcohol and hexane solutions.

The UV spectra of II, IV, and VI in 0.1 N hydrochloric acid and in 0.1 N perchloric acid become extremely similar (Fig. 2), which attests to a monotypic electronic structure for the mesomeric cations formed (VII and VIII). This is possible only in the case of protonation of VI at the exocyclic nitrogen and protonation of IV at the ring nitrogen (VII and VIII):


VII


VIII

Other heterocyclic amines of similar structure [3-5] display similar behavior.

PMR Spectra. Narrow signals of the six protons of the ring geminal methyl groups, doublets of the protons of the CH_3—C group, and unresolved broad signals of the protons attached to the ring double bond (see Table 1) are observed in the spectra of carbon tetrachloride solutions of all of the compounds. A singlet of the six protons of the two methyl groups bonded to the exocyclic nitrogen is observed in the spectrum of VI. Similar PMR spectra were obtained in benzene solution.

The assignment of one of the forms to IIa on the basis of a comparison of the signals of the protons of the CH_3 groups attached to the exocyclic nitrogen in IIa, IV, and VI is unreliable because of the proximity of the signals in comparable compounds.

Splitting of the signal of the protons of the CH_3-N group is absent in the spectrum of IIa, which attests either to the imine structure of IIa (E) or to rapid intermolecular exchange of protons in IIa (A). Considering the character of the signal of the N–H proton (narrow singlet) and the UV spectral data regarding the predominant percentage of the amino form in nonpolar solvents, the second assumption is apparently valid.

To confirm the data on the direction of protonation of II, IV, and VI, we obtained the PMR spectra of trifluoroacetic acid solutions of these compounds. A single singlet of protons of the $(CH_3)_2-N$ group (2.87 ppm) is observed in the spectrum of IV, which attests to protonation of the ring nitrogen (δ_{H-N} 6.45 ppm). In the spectrum of VI, on the other hand, the signal at 2.68 ppm is split (J 4.5 Hz) as a consequence of interaction with the adjacent proton, which makes it possible to assume protonation at the exocyclic nitrogen.

Splitting of the signal of the protons of the CH_3-N group (2.78 ppm) is also observed in the spectrum of IIa in trifluoroacetic acid; this can be explained either by protonation of the endocyclic nitrogen of the amino form (IIa) and interaction of the protons of the $H-\overset{+}{N}-CH_3$ group under conditions of flow exchange in trifluoroacetic acid [6] or by protonation of the imino form of IIa at the exocyclic nitrogen. A triplet single should have been observed in the case of protonation of the amino form of IIa at the exocyclic nitrogen.

We determined the basicities of the compounds by potentiometric titration in methanol using perchloric acid as the titrant (see Table 1). A comparison of the pK_a values of IV and VI shows that VI has a higher basicity and, consequently, higher energetic favorability of the amine form for the investigated tautomeric compounds (IIa-e) [7]. This is apparently explained by the more favorable electronic configuration of the amino form in which overlapping of the p orbitals of the exocyclic nitrogen with the π orbitals of the ring C=N bond is possible.

EXPERIMENTAL

Compounds IIa-e were synthesized by the method described in [1]. The IR spectra were recorded with a UR-10 spectrophotometer. The spectra of mineral oil suspensions or thin layers of the compounds were recorded. The UV spectra in methanol, hexane, 0.1 N HCl, and 0.1 N $HClO_4$ solutions ($5 \cdot 10^{-5}$ M) were recorded with a Hitachi spectrometer. The PMR spectra in carbon tetrachloride, benzene, and trifluoroacetic acid solutions were recorded with an RS-60 spectrometer with an operating frequency of 60 MHz; the internal standard was hexamethyldisiloxane. The potentiometric titration was carried out with an LPU-01 potentiometer in anhydrous methanol using 0.1 N perchloric acid in methanol as the titrant. The pK_a values were calculated in accordance with [8]; the error in determining the pK_a value did not exceed ±0.02.

N-(2-Methyl-4-oxo-2-amyl)-N',N'-dimethylthiourea (III). A mixture of 10 g (0.055 mole) of 2-isothiocyano-2-methyl-4-pentanone [9] and 3.08 g (0.068 mole) of dimethylamine as a 25% aqueous solution was held at 20° for 24 h. The aqueous solution was extracted with ether, and the extract was dried with magnesium sulfate. The ether was removed by distillation, and the residue was chromatographed on silica with elution by petroleum ether–ether (2:1) to give 9.4 g (75.5%) of III as a yellow oil. The 2,4-dinitrophenylhydrazone of III had mp 214-214.5°. Found %: C 46.9; H 5.7; S 8.3. $C_{15}H_{22}N_6O_4S$. Calculated %: C 47.1; H 5.8; S 8.4.

1,3,4,6,6-Pentamethyl-1,2,3,4-tetrahydropyrimidine-2-thione (V). Mesityl oxide [8.44 g (0.086 mole)] was added gradually with vigorous stirring at 0-5° to 2.67 g (0.086 mole) of methylamine as a 25% aqueous solution. The mixture was stirred for 30 min at 20-22°, and the 2-methylamino-2-methyl-4-pentanone was extracted with ether. The ether extract was vacuum evaporated to a volume of 100 ml, and 4.9 g (0.067 mole) of methyl isothiocyanate in 30 ml of ether was added at 5°. The precipitate that formed after 1 h was filtered, washed with ether, and dried to give 8.2 g of a mixture of 4-hydroxy-1,3,4,6,6-pentamethylhexahydropyrimidine-2-thione and V. The mixture was dissolved in 100 ml of acetic anhydride and heated for 20 min on a boiling-water bath. The excess anhydride was removed by vacuum distillation, and the residue was treated with saturated potassium carbonate solution. The organic layer was extracted with ether, and the extract was dried with magnesium sulfate. The ether was removed by distillation to give 7.4 g (60.0%) of V with mp 78-78.5° (from alcohol) and R_f 0.78 (activity II Al_2O_3 with elution by chloroform). Found %: C 58.6; H 8.9; N 14.8. $C_9H_{16}N_2S$. Calculated %: C 58.7; H 8.8; N 15.2.

4,4,6-Trimethyl-2-dimethylamino-4H-1,3-thiazine (IV). A mixture of 4.2 g (0.023 mole) of III and 50 ml of concentrated HCl was heated at 100° for 15 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, the ether was removed by distillation, and the residue was chromatographed on silica with elution by petroleum ether–ether (95 : 5). The eluate was distilled to give 3.8 g (91.1%) of a yellowish oil with bp 69-70° (2.5 mm). Found %: C 58.7; H 8.8; N 14.9. $C_9H_{16}N_2S$. Calculated %: C 58.7; H 8.8; N 15.2.

3,4,4,6-Tetramethyl-2-methylimino-4H-2,3-dihydro-1,3-thiazine (VI). A mixture of 3 g of V and 100 ml of concentrated HCl was heated at 100° for 30 min. The acid was removed by vacuum distillation, and the residue was neutralized at 0° with potassium carbonate solution. The mixture was extracted with ether, and the ether was removed by distillation. The residue was vacuum distilled to give 0.6 g (20.0%) of VI with bp 91-92° (2 mm) and R_f 0.3 (activity II Al_2O_3 with elution by chloroform). Found %: C 58.8; H 8.8. $C_9H_{16}N_2S$. Calculated %: C 58.7; H 8.8.

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