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ACYLATION OF 2H,6H-2,6-DIMETHYL-4-AMINO-1,3,5-DITHIAZINE AND TAUTOMERISM OF THE REACTION PRODUCTS

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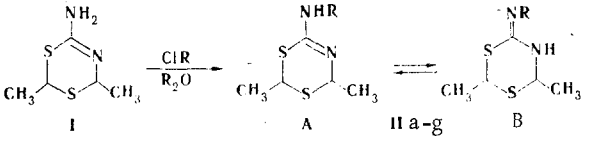
The acylation of 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine with the chlorides and anhydrides of saturated carboxylic and sulfonic acids leads to N-monoacyl derivatives of dithiazine in 85-96% yields. It was established by IR and UV spectroscopy that 2H,6H-2,6-dimethyl-4-acylamino-1,3,5-dithiazines with donor substituents exist primarily in the amino form and that the equilibrium is shifted to favor the imino form for compounds with acceptor substituents to a greater degree in solutions than in the crystalline state.

The present communication, which is devoted to the synthesis and study of the tautomerism of N-acyl derivatives of 2H,6H-2,6-dimethyl-4-amino-1,3,5-dithiazine (I) by IR and UV spectroscopy, is a continuation of research on the physicochemical properties of this compound, which was obtained from divinyl sulfide and thiourea [1], and is directed to the search for new potentially biologically active compounds [2].

The action of chlorides and anhydrides of saturated carboxylic acids on dithiazine I gives N-monoacyl derivatives IIa-g in 85-96% yields, which can exist in tautomeric forms A or B:



I A IIa-g B

IIa R=$COCH_3$; b R=$COCH_2Cl$; c R=COC_3H_7-*n*; d R=COC_4H_9-*n*; e R=COC_4H_9-*t*; f R=COC_6H_5; g R=$SO_2C_6H_4CH_3$-4

The reaction of dithiazine I with acid chlorides is realized in chloroform or benzene, and the HCl is tied up by excess dithiazine I or Na_2CO_3. Acylation with excess amounts of carboxylic acid anhydrides proceeds readily and quantitatively. The formation of diacylation products is not observed either under severe conditions or in the presence of catalytic amounts of H_2SO_4. The use of pyridine as the solvent [3] lowers the yield of acylated product IIg, which can be explained by the instability of dithiazine I to the action of amines [4].

The reaction of acrylyl chloride with dithiazine I gives, instead of the expected monoacyl derivative, polymeric products, which are isolated in the form of powders that are soluble in acetone and dimethyl sulfoxide (DMSO) and have molecular masses of 900 to 2100.

The PMR spectrum of these powders in d_6-DMSO contains a number of broad peaks that are characteristic for polymeric products. Signals of the protons of the methyl groups are ob-

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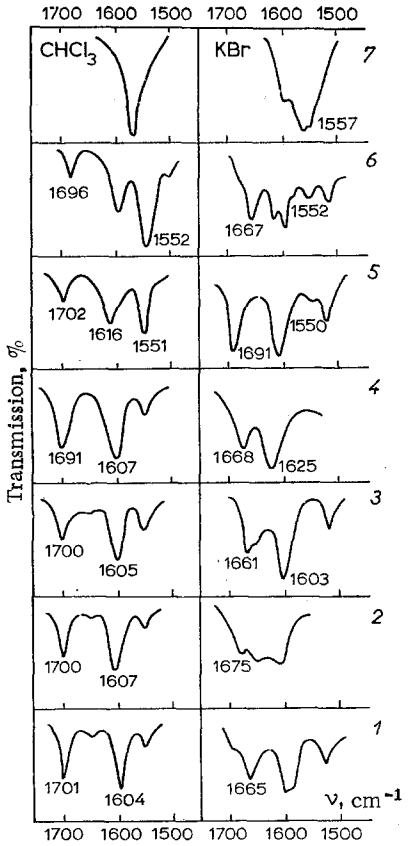
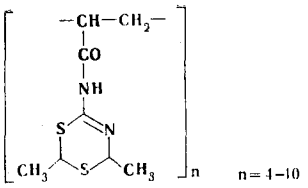


Fig. 1. IR spectra of 2H,6H-2,6-dimethyl-4-acylamino-1,3,5-dithiazines (in $CHCl_3$, c = 0.1 mole/liter, d = 0.01 cm): 1) IIa; 2) IIc; 3) IId; 4) IIe; 5) IIb; 6) IIf; 7) IIg.

served at 1.46-1.49 ppm, while a signal of the $CHCH_2$ fragment is observed at 2.69 ppm. The weak diffuse signal at 6.34 ppm is related to a terminal $CH{=}CH_2$ group.



According to the data in [5-8], acylation of heterocyclic compounds with a thiourea fragment shifts the tautomeric equilibrium to favor the imine form (with an exocyclic C=N bond); this is evidently due to the advantageousness of conversion of the system to the conjugated for (—N=C—NH—C=O → —NH—C=N—C=O). A similar effect should have been expected for 2H,6H-2,6-dimethyl-4-acylamino-1,3,5-dithiazines (IIa-g). A previous analysis of the PMR spectra of dithiazine I and its acylated derivatives [9] showed that the acylation of I takes place at the exocyclic nitrogen atom with preponderance of amino form A.

In the interpretation of the IR spectra of IIa-g difficulties arise in the assignment of the bands, since the characteristic absorptions of the amino and imino forms lie in close regions. These difficulties are aggravated by the lack of standards with a fixed form that excludes tautomeric transformations. We used the IR spectra of N-alkylacetimido(amido)thiazolidines [5], which have structures that are similar to those of the investigated reaction products, for comparison.

The spectra of IIa-g in the 1500-1700 cm^{-1} range contain a number of bands with complex forms (asymmetrical bands with several shoulders and broad bands), and the spectra of the crystals and solutions differ substantially (Fig. 1). Appreciable changes in the intensity and form of the components of the multiplet at 1500-1700 cm^{-1} are not observed in the spectra

TABLE 1. 2H,6H-2,6-Dimethyl-4-acylamino-1,3,5-dithiazines

Compound	mp, °C	UV spectra		Found, %				Empirical formula	Calculated, %			
		solvent	λ_{max}, nm ($\varepsilon \cdot 10^{-4}$)	C	H	N	S		C	H	N	S
IIa	168,5—169[a] (ethanol)	Ethanol	221 (11,9), 250 (3,64)	41,4	5,9	13,8	31,4	$C_7H_{12}N_2OS_2$	41,1	5,9	13,7	31,4
		Diethyl ether	220 (15,5), 250 (5,09)									
IIb[b]	104—105 (methanol)	Ethanol	223 (11,8), 263 (5,4)	—	—	11,8	27,5	$C_7H_{11}ClN_2OS_2$	—	—	11,7	26,8
		Diethyl ether	220 (10,7), 270 (3,8)									
IIc	65—67 (hexane)	Ethanol	222 (11,2), 244 (3,6)	46,1	6,8	12,0	26,8	$C_9H_{16}N_2OS_2$	46,5	6,9	12,1	27,6
		Diethyl ether	221 (13,3), 250 (4,4)									
IId	90—91 (ethanol)	Ethanol	221 (12,6), 244 (4,4)	49,1	7,4	11,3	26,3	$C_{10}H_{18}N_2OS_2$	48,7	7,4	11,4	26,0
IIe	121—122 (ethanol–acetone)	Ethanol	222 (12,1); 248 (5,07)	48,8	7,3	11,5	25,4	$C_{10}H_{18}N_2OS_2$	48,7	7,4	11,4	26,0
IIf	72—74 (ether)	Ethanol	242 (18,1)	54,1	5,4	10,7	23,7	$C_{12}H_{14}N_2OS_2$	54,1	5,3	10,5	24,1
		Diethyl ether	241 (18,7)									
IIg	132—134			46,0	5,5	8,9	30,5	$C_{12}H_{16}N_2O_2S_3$	45,5	5,1	8,8	30,4

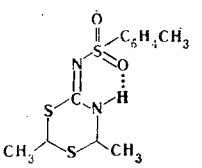
[a]With decomposition. [b]Found: Cl 14.9%. Calculated: Cl 14.8%.

of partially deuterated (at the NH group) samples of IIa, b, in which intense bands of stretching vibrations of an N–D bond (2200-2500 cm^{-1}) appear; this constitutes evidence for the small contribution of deformation vibrations of the NH groups to the overall spectral pattern.

In the crystalline state most of the acylthiazines have a characteristic amide band at 1660-1670 cm^{-1} (C=O), while in the case of chloroacetyl derivative IIb this band is shifted to the high-frequency region (1691 cm^{-1}), probably due to the inductive effect of the electronegative chlorine atom. The assignment of the absorption band at 1600-1628 cm^{-1} to ring $\nu_{C=N}$ is confirmed by the presence of bands in this region in the case of acyl derivatives of 2-aminothiazolines [5, 10]. A weak band at 1552 cm^{-1}, which is due to stretching vibrations of an exocyclic C=N group of imino form B [5, 10], is observed in the spectra for compounds with acceptor substituents (IIb, f, g). This band is absent in the spectra of acyldithiazines with donor substituents (IIIa, c, d, e), which consequently exist in the crystalline state primarily in amino form A.

On passing from crystals to solutions in $CHCl_3$ the bands of the amide carbonyl group undergo a high-frequency shift (1690-1700 cm^{-1}). The intensity of these bands also decreases in the case of IIb, f. The bands at 1600-1625 cm^{-1}, which were assigned to the exocyclic C=N bond, undergo a considerably smaller change in their frequency and intensity. A band of an exocyclic C=N bond (1552-1575 cm^{-1}) also appears in the spectra of IIa, c-e with donor substituents. However, in the spectra of IIb, f, g with acceptor substituents it becomes the most intense band. These spectral changes can be explained for IIb, f, g by an increase in the fraction of imine form B in solutions. The polarity of the solvent does not have an appreciable effect on the position of the A $\rightleftarrows$ B tautomeric equilibrium. Thus no changes whatsoever in the ratio of the intensities of the bands are observed for any of the investigated compounds, except for chloro-substituted IIb, for which the band of the exocyclic C=N bond decreases in acetonitrile.

The high-frequency region of the spectra of solutions of acyldithiazines IIa, c-e, g in $CHCl_3$ contains one intense absorption band at 3400 cm^{-1}, which can be assigned to the stretching vibrations of the free NH groups in amino form A [6], although, according to the data in [5], the frequencies of the stretching vibrations of the free NH groups in the amino and imino forms virtually coincide. The appearance of an absorption band at 3378 cm^{-1} in the spectra of IIb, g more likely indicates the presence of imino form B in appreciable concentrations [6, 11]. In the spectrum of sulfonamide IIg this band is a low-intensity band and appears in the form of a shoulder on the strong broad band at 3256 cm^{-1}. The ratio of the intensities of these bands remains constant as the concentration of sulfonamide IIg is varied from $1 \cdot 10^{-1}$ to $5 \cdot 10^{-3}$ mole/liter, and the low-frequency band can therefore be assigned to an intramolecular hydrogen bond (IHB) between the NH and sulfo groups.



Evidence for the formation of strong IHB between the OH group and the oxygen atom of the SO_2 group in sulfones was obtained in [12]. In this case the absorption band at 3378 cm^{-1} can actually be assigned to vibrations of the NH groups in imino form B, since the formation of an H bond of the indicated type is possible only in a structure with an exocyclic C=N bond. An absorption band at 1610 cm^{-1}, which belongs to a ring C=N bond, is not observed in the spectrum of a solution of sulfonamide IIg (Fig. 1), and this confirms our conclusion. However, the spectrum of sulfonamide IIg contains an intense absorption band at 846 cm^{-1}, which in [7] was assigned to the $-N=C-NSO_2$ fragment.

Thus in solutions acyldithiazines with donor substituents (IIa, c-e) exist primarily in amino form A, while acceptor substituents (CH_2Cl, Ph, $SO_2C_6H_4Me$) shift the equilibrium to favor the imino form. This conclusion regarding the structure and tautomerism of acyldithiazines IIa-g is also confirmed by a study of their UV spectra, in which two absorption maxima (220-225 and 240-260 nm) are observed. Their intensities change somewhat as a function of the polarity of the solvent and the electronegativity of the acyl residue (Table 1).

The spectrum of IIg contains only an absorption band at 242 nm. Intense bands at 220-223 nm, followed by a small prominence at 240-260 nm, are observed in the spectra of IIa-e. In [13] it was shown that conversion of α-aminopyridine derivatives to the imino form is accompanied by a significant shift of the principal absorption band to the long-wave part of the spectrum. By analogy, the bands at 220-223 nm can be assigned to amino form A, while the bands at 240-260 nm can be assigned to form B. This assignment is confirmed by the presence of a band with a maximum at 264 nm in the UV spectrum of 3-methyl-2-acetimidothiazolidine with an imine fragment [5].

EXPERIMENTAL

The IR spectra of KBr pellets and solutions in chloroform and acetonitrile of all of the investigated compounds were obtained with a UR-20 spectrometer at 700-3700 cm^{-1}. The UV spectra of solutions in alcohol and diethyl ether were recorded with a Specord spectrophotometer. Acrylyl chloride was synthesized by the method in [14]. Trimethylacetyl and chloroacetyl chlorides were similarly obtained. p-Toluenesulfonyl chloride was obtained by the method in [15].

2H,6H-2,6-Dimethyl-4-acetamido-1,3,5-dithiazine (IIa). A) A solution of 0.38 g (4 mole) of acetyl chloride in 5 ml of chloroform was added to 1.59 g (9 mole) of dithiazine I in 30 ml of chloroform, and the synthesis was carried out at 20°C for 7 h. The reaction mixture was washed with water (four 20-ml portions), and the chloroform was removed *in vacuo* to give 0.9 g (90%) of IIa, which was recrystallized from ethanol (Table 1). Workup of the aqueous extracts gave 0.96% g (98%) of the hydrochloride of I with mp 143.5-145°C (ethanol).

B) A solution of 4.8 g (47 mole) of acetic anhydride in 5 ml of benzene was added to a solution of 2 g (12 mole) of dithiazine I in 25 ml of benzene, after which two to three drops of concentrated H_2SO_4 were added to the reaction mixture. After 3 h, the solvent and excess anhydride were removed *in vacuo* to give 2.4 g of IIa (Table 1).

2H,6H-2,6-Dimethyl-4-benzamido-1,3,5-dithiazine (IIf). A solution of 2.76 g (20 mmole) of benzoyl chloride in 5 ml of benzene was added with cooling (with cold water) to 3.2 g (20 mmole) of dithiazine I and 1.9 g of Na_2CO_3 in 30 ml of benzene, after which another 0.66 g of Na_2CO_3 and 30 ml of benzene were added, and the mixture was maintained at 20°C for 1 h and heated at 70°C for 5 h. The precipitate was removed by filtration and washed with hot benzene. The benzene was removed *in vacuo* to give 5.2 g of a viscous resinous product, which was recrystallized from ether to give 4.7 g IIf (Table 1).

2H,6H-2,6-Dimethyl-4-tosylamino-1,3,5-dithiazine (IIg). A solution of 1.9 g (10 mmole) of 4-toluenesulfonyl chloride in 30 ml of chloroform was added to a solution of 3.25 g (20 mmole) of dithiazine I in 20 ml of chloroform, and the synthesis was carried out at 60°C for 5 h. The reaction mixture was washed with water (20 5-ml portions). The chloroform was removed *in vacuo* to give 2.7 g of IIg (Table 1). Workup of the aqueous solution gave 1.8 g of the hydrochloride of I with mp 145-146°C (ethanol). Compounds IIb-e were obtained by similar methods.

Reaction of Dithiazine I with Acrylyl Chloride. A) A 1.8-g (20 mmole) sample of acrylyl chloride was added to 3.2 g (20 mmole) of dithiazine I and 2.2 g (20 mmole) of Na_2CO_3 in 30 ml of benzene, and the synthesis was carried out at 20°C for 3 h and at 40°C for 2h. The precipitate was removed by filtration and washed with hot benzene. The benzene was removed

in vacuo to give 4.5 g of a polymer, which was reprecipitated from acetone by pouring the solution into ether. The powdery polymer was washed with ether (20 5-ml portions) and dried to give 3 g of a polymer with a molecular mass of 900 (isopiestically in acetone) and mp 96-100°C. IR spectrum (in KBr pellets): 1620 (C=N); 1692, 1702 (shoulder) (C=O); 3430 cm^{-1} (NH). Found: C 40,6; H 5.6; N 12.2; S 27.4%.

B) A solution of 1.8 g (20 mmole) of acrylyl chloride in 5 ml of benzene was added with cooling (with cold water) to 6.4 g (40 mmole) of dithiazine I in 35 ml of benzene, and the synthesis was carried out at 20°C for 3 h. The precipitate was separated, washed successively with hot benzene and ether, and recrystallized twice from hot water to give 1.4 g of the hydrochloride of dithiazine I. Removal of the benzene *in vacuo* gave 4.4 g of a polymer, which was dissolved in a small amount of acetone and precipitated with ether. The resulting powder (0.6 g) was washed with water (20 5-ml portions) and dried to give a product with mp 85-105°C (dec.). Found: C 42.6; H 4.9; N 11.6; S 26.9%. The product had a molecular mass of 2100 (isopiestically in acetone). Removal of the solvents from the ether—acetone fraction gave 3.6 g of a polymer with mp 135-145°C (dec.). IR spectrum (in KBr pellets): 1630 (C=N); 1718, 1698 (shoulder) (C=NO); 3440 cm^{-1} (NH). Found: C 45.5; H 5.3; N 10.5; S 24.4%.

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