CHEMICAL PROPERTIES OF YLIDENE DERIVATIVES OF AZINES.

4.* STRUCTURES OF THE PRODUCTS OF PROTONATION AND TRANSFORMATION OF DIHYDROAZINYLIDENECYANOACETIC ESTERS IN CONCENTRATED SULFURIC ACID

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It was demonstrated by UV and ^{13}C NMR spectroscopy that in concentrated sulfuric acid ylidene derivatives of dihydropyridine (Ia) and dihydropyridazine (IIa) have aromatic structures Ib and IIb, while derivatives of dihydropyrimidines IIIa and IVa, dihydropyrazine Va, and dihydro-s-triazine VIa retain ylidene structures IIIb-VIb, respectively, which determines their greater stability in these solutions. When solutions of Ib-VIb in 95% H_2SO_4 were allowed to stand, they were converted to the corresponding azinylmalonic ester monoamides or azinylacetamides, depending on the reaction temperature.

The structures of dihydro-2-pyridylidene- (Ia), dihydro-2-pyrimidinylidene- (IIIa), and dihydro-6-pyrimidinylidenecyanoacetic ester (IVa)‡ in various strongly acidic media were investigated in [2], the degree of protonation was evaluated, and it was shown that they form protonation products with different structures. In studying the reactivities of the potentially tautomeric ylidene derivatives of di- and triazines we examined the structures of the products of protonation of other dihydroazinylidenecyanoacetic esters in which the nitro heteroatoms are located in the α, β, or γ positions relative to one another in concentrated sulfuric acid. As noted in a previous review [3], dihydroazinylidenecyanoacetic esters can exist in the form of mixtures of tautomeric forms (aromatic and ylidene), but the equilibria for Ia-VIa in solid form and in most organic solvents are shifted to favor the ylidene tautomers, the structures of which are also presented in our paper. It has been shown [2] for dihydropyridine derivative Ia that in sulfuric acid it undergoes protonation to give cation Ib with an aromatic structure, for which the absence of a long-wave absorption maximum in the UV spectrum (Table 1), a shift of the signal of the $C_{(7)}$ atom as compared with the precursor to strong field by 20 ppm, and its appearance in the form of a doublet in the ^{13}C NMR spectrum (Table 2) are characteristic. In the present paper the ^{13}C NMR spectrum of Ia in concentrated sulfuric acid was refined, since new signals due to further transformations of the side chain of Ib begin to appear under the recording conditions.

The assignments of the signals of the carbon atoms for I-VI were made on the basis of the character of the splitting in the monoresonance spectra, the intensities of the signals, the ^{13}C chemical shifts, and the ^{13}C–^{1}H spin-spin coupling constants (SSCC). In addition, we used the known principle of the strong-field shift of the signal of the carbon atom adjacent to the nitrogen atom at which protonation occurs [4].

A long-wave absorption maximum is absent in the UV spectrum of the light-yellow solution of dihydropyridazine IIa in 95% sulfuric acid (see Table 1), which corresponds to the formation of aromatic cation IIb. The ^{13}C NMR spectrum of this solution is also in good agreement with the formation of cation IIb (see Table 2 for the shift of the $C_{(7)}$ signal to strong field and its appearance in the form of a doublet). The probability of the formation of an isomeric cation that differs with respect to the site of protonation (at the adjacent nitrogen atom rather than at the $N_{(1)}$ atom) is low, since the signal of the $C_{(5)}$ atom is not shifted to strong field.

*See [1] for communication 3.

†Deceased.

‡The numbering of the atoms in the rings of II and IV in the schemes does not correspond to the IUPAC rules, but was selected so that it would be convenient to compare the spectral parameters.

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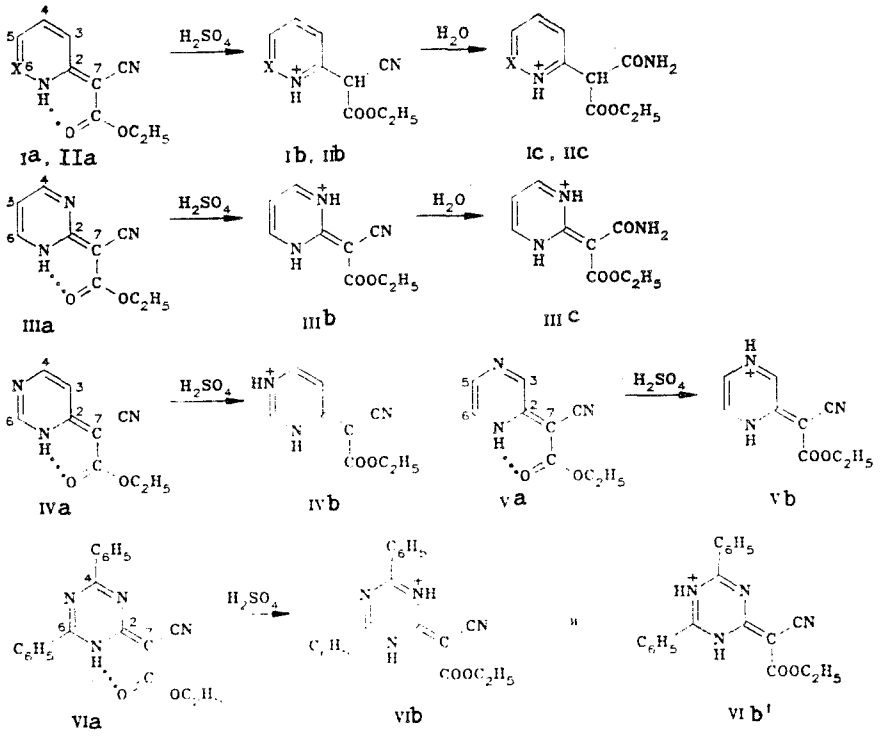


I X=CH, II X=N

An additional set of signals that belong to protonated pyridyl- and pyridazinylmalonic ester monoamides Ic and IIc appears in the ^{13}C NMR spectra of solutions of cations Ib and IIb in 95% H_2SO_4 at room temperature after 10-15 min; this is confirmed by the coincidence of these additional signals with the signals in the spectra of the isolated Id and IId in solution in the same acid. The UV and ^{13}C NMR spectral data are in good agreement with the structures of aromatic cations Ic and IIc (the absence of long-wave absorption maxima, doublets of $C_{(7)}$ signals at 51.75 and 52.91 ppm, singlets of amide CO groups at 171.89 ppm and 172.98 ppm; see Tables 2 and 5).

Solutions of IIIa-VIa in 95% H_2SO_4 have a light-orange color, and the long-wave absorption maxima are retained in the UV spectra (see Table 1). This constitutes evidence in favor of the formation of cations IIIb-VIb, respectively, and is confirmed by data from the ^{13}C NMR spectra (the $C_{(7)}$ signal retains its singlet character, and its position is virtually unchanged). It might be assumed that primarily the more symmetrical VIb cation is formed in the protonation of dihydro-s-triazine derivative VIa, since the signals of the $C_{(4)}$ and $C_{(6)}$ atoms in acidic solution, as compared with the spectrum in $CDCl_3$, are shifted in the opposite direction and merge. New additional signals in the ^{13}C NMR spectra, which correspond to the formation of ylidene cations of monoamides of the IIIc type (singlet of the $C_{(7)}$ signal at 79.17 ppm and of an amide CO group at 168.72 ppm; Table 2), appear in solutions of IIIb-VIb in 95% H_2SO_4 at room temperature only after several hours.

TABLE 1. UV Spectra of Dihydroazinylidenecyanoacetic Esters Ia-VIa and Their Protonation Products Ib-VIb

Compound	Solvent	λ_{max}, nm (lg ε)
Ia*	C_2H_5OH	223 (4,08), 295 (4,29), 373 (4,00)
Ib*	H_2SO_4	260 (3,79)
IIa	C_2H_5OH	305 (4,37), 385 (3,66)
IIb	H_2SO_4	305 (2,76)
IIIa*	C_2H_5OH	300 (4,45), 380 (3,53)
IIIb*	H_2SO_4	296 (4,45), 390 (3,06)
IVa*	C_2H_5OH	303 (4,15), 342 (4,10)
IVb	H_2SO_4	318 (4,27), 350 пл. (3,82)
Va	C_2H_5OH	300 (4,32), 402 (3,89)
Vb	H_2SO_4	303 (4,35), 465 (3,79)
VIa	C_2H_5OH	312 (4,51), 393 (3,48)
VIb	H_2SO_4	310 (4,54), 387 (3,62)

*Data from [2].

TABLE 2. ^{13}C NMR Spectra of I-VI

Compound	Solvent, 22°C	^{13}C chemical shifts, δ, ppm, relative to TMS									
		$C_{(2)}$, s	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	COOEt, s	CN ($CONH_2$), s	OCH_2CH_3, t	OCH_2CH_3, q
Ia*	CH_2Cl_2	155,4	120,0 d	139,9 d	112,6 d	134,6 d	62,0s	170,1	119,1	60,0	14,4
Ib	H_2SO_4	141,11	128,00 d	149,68 d	128,68 d	143,34 d	41,37 d	162,49	109,6	68,11	12,67
Ic	H_2SO_4	141,49	129,78d	149,39 d	128,83 d	143,34 d	51,75 d	164,02	(171,89)	67,74	12,67
IIa	$CDCl_3$**	154,69	128,21d	129,19 d	141,06 d	—	63,77 s	168,26	117,04	60,26	13,99
IIb	H_2SO_4	155,62	136,43 d	139,77 d	148,31 d	—	44,11 d	163,28	109,9	68,04	12,63
IIc	H_2SO_4	156,61	136,55 d	140,89 d	148,31 d	—	52,91 d	165,02	(172,98)	67,62	12,63
IIIa*)	CH_2Cl_2**	161,2	—	163,8 d	108,9 d	144,3 d	65,6s	169,3	118,2	60,0	14,2
IIIb	H_2SO_4	152,12	—	157,59 d	110,25 d	157,59d	65,92 s	168,00	111,0	65,49	12,90
IIIc	H_2SO_4	152,89	—	156,87 d	113,10 d	156,87 d	79,17 s	167,52	(168,72)	66,52	13,04
IVa*)	CH_2Cl_2	156,2	114,9d	153,0d	—	146,8 d	66,7s	169,2	116,7	61,3	14,4
IVb	H_2SO_4	153,15	116,27 d	137,16d	—	149,03 d	77,18 s	167,35	112,7	65,48	12,90
Va	$CDCl_3$**	147,57	146,61 d	—	129,54 d	125,29 d	63,68 s	168,63	116,76	60,11	13,91
Vb	H_2SO_4	149,30	141,14d	—	119,66 d	137,29 d	72,15 s	169,00	111,7	65,89	12,90
VIa	$CDCl_3$***	162,11	—	169,77 s	—	159,88s	68,55 s	170,31	115,93	61,15	14,17
VIb	H_2SO_4****	154,33	—	162,17 s	—	162,03 s	76,40 s	168,37	109,9	66,84	12,89

*Data from [2].

**With the addition of a few drops of d_6-DMSO.

***127.37-134.69 ppm (C_6H_5).

****121.15-141.58 ppm (C_6H_5).

TABLE 3. Conditions Used to Carry Out the Hydrolysis of Ia-IIIa, VIa, XI, and XIV in 95% Sulfuric Acid and Yields of the Reaction Products

Starting compound	Reaction temp., °C	Reaction time, h	Reaction product	Yield, %
Ia	60...65	0,5	Monoamide Id, e	70
IIa	20...25	1,5	Monoamide IId,e	70
IIIa	70	7,5	Monoamide IIId	80
VIa	80...85	4,0	Monoamide VId,e	75
XIa	70	2,5	Monoamide XIIa	90
XIb	70	9,0	Monoamide XIIb	73
XIc	70	6,0	Monoamide XIIc	67
XId	70	6,0	Monoamide XIId	89
XIa	95...100	6,0	Acetamide XIIIa	65
XId	100...110	1,0	Acetamide XIIId	65
XIV	80...85	4,0	Monoamide XV	70
XIV	90...95	5,0	Acetamide XVI	75

TABLE 4. Characteristics of the Synthesized Compounds

Compound	Empirical formula	mp, °C (from ethanol)	Compound	Empirical formula	mp, °C (from ethanol)
Id,e	$C_{10}H_{12}N_2O_3$	128...129,5	XIIb	$C_{10}H_{13}N_3O_3$	165...166,5
IId,e	$C_9H_{11}N_3O_3$	135...137	XIIc	$C_{10}H_{13}N_3O_3$	147...148
IIId	$C_9H_{11}N_3O_3$	156...157	XIId	$C_{15}H_{15}N_3O_3$	136...139
VIa	$C_9H_9N_3O_2$	158...160	XIIIa	$C_6H_6BrN_3O$	168...170
VIa	$C_{20}H_{16}N_4O_2$	168...170	XIIId	$C_{12}H_{11}N_3O$	187...189
VId,e	$C_{20}H_{18}N_4O_3$	148...149	XV	$C_{14}H_{13}N_3O_3$	143...144
XIIa	$C_9H_{10}BrN_3O_3$	186...189	XVI	$C_{12}H_{11}N_3O$	135...137

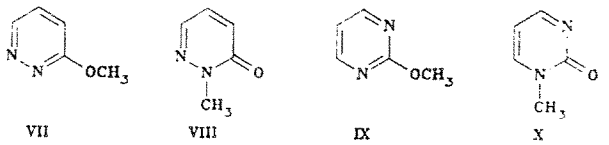
TABLE 5. UV and IR Spectra of Azinylmalonic Ester Monoamides and Azinylacetamides

Compound	UV spectrum (in ethanol), λ_{max}, nm (log ε)	IR spectrum (in KBr), ν, cm^{-1} (at 1400-1800 cm^{-1})
Id,e	255 (3,78), 262 (3,78), 268 (3,70), 300 (3,25), 336 (3,25), 368 (2,89)	1395, 1450, 1490, 1580, 1600, 1670, 1690 sh, 1730
Ic	260 (3,72)*	—
IId,e	214 (3,64), 243 (3,55), 309 (3,74), 380 (3,00)	1400, 1500, 1550, 1620, 1660, 1730sh
IIc	220 (3,30), 246 (3,30)*	—
IIId	218 (3,78), 248 (2,90), 288 (2,40)	1400, 1425, 1580, 1670, 1690 sh 1740
IIIc	232 (3,90), 3,05 (4,38), 367 (2,20)*	—
VId,e	—	1410, 1450, 1550, 1600, 1650 sh, 1680, 1730
XIIa	225 (4,13), 265 (3,33), 300 (2,83)	1400, 1430, 1550, 1660, 1685, 1720
XIIb	210 (3,90), 257 (3,40), 290 (2,60)	1400, 1450, 1580, 1660, 1670, 1695, 1725
XIIc	210 (3,88), 250 (3,49), 275 (2,60)	1395, 1450, 1560, 1595, 1670, 1695, 1730
XIId	210 (4,18), 252 (4,26)	1400, 1440, 1560, 1595, 1670, 1690, 1730
XIIIa	223 (4,13), 268 (3,40), 305 (2,88)	1420, 1440, 1530 sh., 1555, 1639 sh, 1660, 1680
XIIId	210 (4,25), 250 (4,30)	1420, 1450, 1550, 1590, 1630, 1680
XV	207 (4,21), 256 (4,25), 323 (4,02), 362 (3,62)	1400, 1440, 1500, 1540, 1560, 1590, 1620, 1660
XVI	210 (4,19), 258 (4,45)	1420, 1440, 1470, 1570, 1585, 1630, 1670

*In H_2SO_4.

The conversion of azinylcyanoacetic esters Ia-VIa to monoamides, in analogy with other nitriles [5], evidently takes place via protonation and subsequent hydration of the cyano group of the side chain of cations Ib-VIb, which is more reactive in 95% H_2SO_4 than the ester group [6]. The signals of the carbon atoms of the CN groups in solutions of cations Ib-VIb in sulfuric acid are shifted to strong field by 4-10 ppm as compared with solutions of Ia-VIa in neutral solvents (the effect of protonation of the CN group in HCN in the ^{13}C NMR spectra is –12 ppm [7], but, as was demonstrated, benzonitriles undergo ~50% protonation in 98% H_2SO_4 [8]). The greater stability of solutions of ylidene cations IIIb-VIb in H_2SO_4 as compared with Ib and IIb is evidently associated with the decrease in the electrophilicity of the C atom of the CN group in the delocalized conjugated cation and, because of this, the lower rate of the reaction with nucleophiles (H_2O). An increase in the acidity of the medium (transition to 100% H_2SO_4 and HSO_3F) makes the hydrolysis reaction less selective. Judging from the ^{13}C NMR spectrum of Ia-IIIa in these acids, transformations at both groups (the cyano and ester groups) take place simultaneously very rapidly at room temperature to give complex mixtures of products.

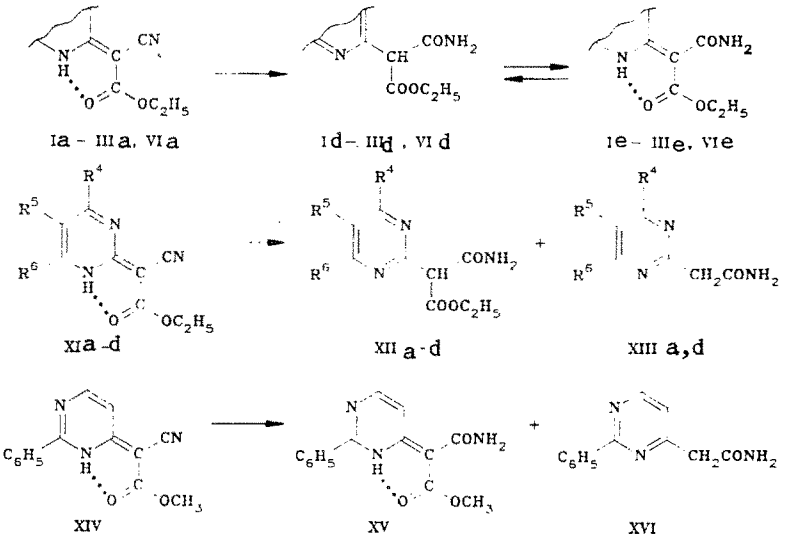
Thus, it was demonstrated by UV and ^{13}C NMR spectroscopy that in solutions in concentrated sulfuric acid dihydroazinylidenecyanoacetic esters with two or three heteroatoms in the ring form primarily cations IIIb-VIb with an ylidene structure; dihydropyridazine IIa, which gives aza aromatic cation IIb, constitutes an exception. It follows from the dependence of the tautomeric equilibrium constants on the basicities of the tautomers [9] that the shift of the tautomeric equilibrium to favor the formation of protonated aromatic tautomer IIb for pyridazine derivative IIa is associated with the substantially greater basicity of the aromatic tautomer as compared with the ylidene tautomer. To confirm this assumption, we examined data on the basicities of the fixed tautomeric forms (the O- and N-methyl derivatives) of hydroxy diazines VII-X, which are topologically similar to the investigated esters IIa and IIIa.



	VII	VIII	IX	X
pK_a, H_2O (20°C)	2,52	–2,10	< 1	2,50

It is apparent from the pK_a values presented that a tendency for a decrease in the basicity is observed for 3-hydroxypyridazine derivatives VII and VIII on passing from aromatic derivative VII to ylidene derivative VIII, while the pattern is reversed in series of substituted pyrimidines: N-methyldihydro-2-pyrimidinone (X) is more basic than 2-methoxypyrimidine (IX).

Hydrolysis products, viz., the corresponding azinylmalonic ester monoamides Id-IIId and VId, were obtained in high yields when solutions of Ia-IIIa and VIa in 95% H_2SO_4 were allowed to stand with subsequent neutralization. The preparative hydrolysis conditions were also found for a number of alkyl(aryl)- and bromo-substituted dihydro-2-pyrimidinylidene- (XIa-d) and dihydro-6-pyrimidinylidenecyanoacetic esters (XIV). The reaction products were also monoamides XIIa-d and XV (Table 3).



Ia,d,e – 2-pyridyl; IIa,d,e – 3-pyridazinyl; IIIa,d,e – 2-pyrimidinyl; VIa,d,e – 4,6-diphenyl-s-triazinyl; XI, XII, XIIIa $R^4 = R^6 = H$, $R^5 = Br$; b $R^4 = R^6$ H, $R^5 = CH_3$; c $R^4 = CH_3$, $R^5 = R^6 = H$; d $R^4 = R^6 = H$, $R^5 = C_6H_5$

Judging from the time required for the hydrolysis reaction for various substituted dihydropyrimidine derivatives XIa-d at 70°C (see Table 3), the effect of substituents on the reaction rate is small. Nevertheless, the reaction is facilitated appreciably by acceptor substituents in the pyrimidine ring (for example, by a factor of approximately three by a bromine atom). In the case of several XI and XIV derivatives we showed that the corresponding azinylacetic acid amides XIII and XVI, respectively, can be obtained when the reaction conditions are changed (with an increase in the temperature and the time). The compositions and structures of the compounds obtained are confirmed by the results of elementary analysis and the IR and UV spectral data (Tables 4 and 5). It should be noted that azinylmalonic ester monoamides can exist in both the aromatic forms Id, IId, and VId and in the ylidene forms Ie, IIe, and VIe, but the tautomerism of these compounds was not studied in detail in the present research; only spectral data for their identification are presented. 2-Pyrimidinylmalonic ester monoamide IIId exists virtually only in the aromatic tautomeric form (a long-wave absorption maximum is absent in the UV spectrum, and the IR spectrum contains bands of ν_{CO} vibrations in an unconjugated ester group at 1740 cm^{-1}; see Table 5). Ring-substituted 2-pyrimidinylmalonic ester monoamides XIIa-d which, according to the IR and UV spectral data, probably also exist in aromatic tautomeric forms (see Table 5), have the same properties. The presence of signals of a CH_2 group in the PMR spectra (~4 ppm) is also characteristic for azinylacetamides XIII and XVI.

Thus it was established that the hydrolysis of dihydroazinylidenecyanoacetic esters in 95% H_2SO_4 proceeds selectively and leads to azinylmalonic ester monoamides or to azinylacetamides in high yields; the ratio of these products can be varied by changing the reaction conditions.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra (10^{-4} mole/liter in ethanol and analytical-grade concentrated H_2SO_4) were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of 7-10% solutions were obtained with a Varian A-56/60 spectrometer. The ^{13}C NMR spectra were recorded with a Bruker WP-200 SY spectrometer at room temperature.

The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in a $CHCl_3$–C_2H_5OH system (10:1).

The synthesis of 1,6-dihydro-6-pyridazinylidenecyanoacetic ester IIa was accomplished in conformity with the method in [10] (80% yield).

The results of elementary analysis for C, H, N, and Br for Id, e, IId, e, IIId, Va, VIa, d, e, XIIa-d, XIIIa-d, XV, and XVI were in agreement with the calculated values.

1,2-Dihydro-2-pyrazinylidenecyanoacetic ester Va was synthesized starting from 2-chloropyrazine [11] (70% yield) by the method in [2]. The IR spectrum (KBr) coincided with the spectrum described in [12]. PMR spectrum ($CDCl_3$): 8.68 (1H, s, 3-H), 7.69 (1H, d, J = 5.0 Hz, 5-H), 7.30 (1H, d, J = 5.0 Hz, 6-H), 4.26 (2H, q, OCH_2CH_3), 1.34 ppm (3H, t, OCH_2CH_3).

4,6-Diphenyl-1,2-dihydro-2-s-triazinylidenecyanoacetic ester VIa was obtained from 4,6-diphenyl-2-chloro-s-triazine [13] (80% yield) by the method in [2]. IR spectrum (KBr): 1660, 1680 (C=O), 2205 cm^{-1} (C≡N). PMR spectrum ($CDCl_3$): 7.50-8.90 (10H, m, CH_{arom}), 4.28 (2H, q, OCH_2CH_3), 1.24 ppm (3H, t, OCH_2CH_3).

The synthesis of the substituted 1,2-dihydro-2-pyrimidinylidene- (XIa-d) and 1,6-dihydro-6-pyrimidinylidenecyanoacetic esters (XIV) was accomplished in accordance with the methods in [9, 14].

General Method for the Hydrolysis of Dihydroazinylidenecyanoacetic Esters in 95% Sulfuric Acid. A solution of 5 mmoles of Ia-IIIa, VIa, XIa-d, and XIV in 2.5 ml of H_2SO_4 (analytical grade) was maintained at room temperature or heated on an oil bath (the temperature in the flask, the reaction times, and the yields of the compounds obtained are presented in Table 3) with monitoring of the course of the reaction by means of TLC data. At the end of the reaction the solution was poured over ice (~20 g), and the aqueous mixture was neutralized with solid $NaHCO_3$. The resulting precipitate was removed by filtration, washed with water (three 5-ml portions), dried in a vacuum desiccator, and recrystallized from ethanol. This procedure gave monoamides Id-IIId, VId, XIIa-d, and XV or acetamides XIIIa, d and XVI, the physicochemical characteristics of which are presented in the tables.

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SYNTHESIS AND PROPERTIES OF DERIVATIVES OF 7-AROYLALKYLXANTHINYL-8-THIOACETIC ACID

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When 7-aroylalkyl-8-bromo-3-methyl- and 1,3-dimethylxanthines are boiled with an excess of thioglycolic acid, a reductive dehalogenation takes place, while reaction with an equimolar amount of thioglycolic acid in DMFA leads to 7-aroylalkyl-3-methyl- and 1,3-dimethylxanthinyl-8-thioacetic acids. Cyclization of the latter with acetic anhydride in the presence of anhydrous sodium acetate results in the formation of 3-aryl-1,4-dihydro-9-methyl- and -7,9-dimethylthiazino[3,2-f]xanthine.

7-Aroylalkyl-8-bromoxanthines are known as convenient synthones for the synthesis of annelated imidazo- [1], oxazolo- [2, 3], thiazolo[f]azoloxanthines [4], or azinoxanthines [5].

In the present work we obtained thiazinoxanthine derivatives from these synthones.

The reaction of 7-aroylalkyl-8-bromoxanthines (VI-X) with an equimolar amount of thioglycolic acid in DMFA results in the formation of derivatives of 7-aroylalkylxanthinyl-8-thioacetic acid (XI-XV). It should be noted that on boiling compounds VI-X in an excess of thioglycolic acid, a reductive dehalogenation of the substrates takes place with the formation of compounds III-V.

This process is most probably related to the reducing properties of thioglycolic acid. Compounds III-V can also be obtained by direct alkylation of the potassium salts of 3-methyl- or 1,3-dimethylxanthine by α-haloketones in DMFA. Samples of compounds III-V obtained by the two methods do not give a mixed melting point depression.

When compounds XI-XV were boiled in acetic anhydride in the presence of anhydrous sodium acetate, we obtained 3-aryl-1,4-dihydro-9-methyl- and -7,9-dimethylthiazino[3,2-f]xanthines (XVI-XIX) (Table 1). It is clear that, in the course of the reaction, after cyclization with the formation of an annelated thiazine ring, a decarboxylation of the intermediately formed acids takes place.

In the IR spectra of acids XI-XV intense absorption bands of the stretching vibrations of the OH group are observed in the 3475-3375 cm^{-1} region and the absorption bands of stretching vibrations of the NH fragment appear in the 3165-3150

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