fore depend to a lesser extent on the character of the hybridization of the ring nitrogen atom, can be considered to be more expedient. The coincidence of δ (5-CH_2) in the PMR spectra of tautomeric Ia and model derivatives IIa (Table 2) indicates the amine structure of 2-arylamino-5,6-dihydro-4H-1,3-thiazines Ia.

It follows from the PMR spectra of TFA solutions of I-III that bases I-III are protonated at the nitrogen atom attached to the C=N double bond, but the positive charge is delocalized over the amidine system. The coincidence of the chemical shifts of the signals of all of the methylene groups of I-III (Table 2) indicates an identical structure for the resulting cations. At the same time, on passing from the bases to the cations the weak-field shifts of the signals of these groups ($\Delta\delta_{CH_2}$) of amine models II and substituted I are found to be close and differ markedly from the corresponding values of models of imine structure III, and the differences between the $\Delta\delta_{CH_2}$ values of the latter (III) and the $\Delta\delta_{CH_2}$ values of tautomeric derivatives I are close to the differences in the chemical shifts of the methylene groups of bases II and III (Table 2). This once again indicates that aryl- and alkylaminothiazines Ia and Ib exist in the amine form.

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SYNTHESIS OF 2-HYDRAZINO- AND 2-AMINO-1,3,4-THIADIAZINES CONTAINING POLYHYDRIC PHENOL RESIDUES IN THE 5 POSITION

I. Ya. Postovskii, A. P. Novikova,
L. A. Chechulina, and L. P. Sidorova

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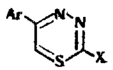
2-Hydrazino-1,3,4-thiadiazines containing polyhydric phenol residues in the 5 position were obtained by reaction of 3,4-dihydroxy-, 2,5-dihydroxy-, and 2,3,4-trihydroxyphenacyl ω-halides with thiocarbohydrazide. 2-Amino-1,3,4-thiadiazines were obtained by reaction of 3,4-dihydroxy- and 2,5-dihydroxyphenacyl ω-halides with thiosemicarbazide in acidic and alcoholic media. In contrast to the dihydroxy derivatives, 2,3,4-trihydroxyphenacyl halide forms a 2-amino derivative only in strongly acidic media, whereas the isomeric thiazole compound with a hydrazine group in the 2 position of the thiazole ring is formed in alcoholic media.

In order to obtain new inhibitor-antioxidants we synthesized a series of 2-hydrazino- and 2-amino-1,3,4-thiadiazines containing polyhydric phenol (pyrocatechol, hydroquinone, and pyrogallol) residues in the 5 position.

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1051-1055, August, 1976. Original article submitted August 5, 1975.

TABLE 1. 2-Hydrazino- and 2-Amino-1,3,4-Thiadiazines Containing Polyhydric Phenol Residues in the 5 Position



Compound	Ar	X	mp, °C*	Empirical formula	Found, %				Calculated, %				UV spectra, λ_{max}, nm ($\varepsilon \cdot 10^4$)	Yield, %
					C	H	N	S	C	H	N	S		
I	3,4-$(OH)_2C_6H_3$	$NHNH_2$	185—186	$C_9H_{10}N_4O_2S$	45,1	4,4	23,2	13,3	45,4	4,2	23,5	13,4	222 †, 327 (1,6)	70
II	2,5-$(OH)_2C_6H_3$	$NHNH_2$	175—176	$C_9H_{10}N_4O_2S \cdot H_2O$	42,6	4,7	21,9	12,2	42,2	4,7	21,9	12,5	238 †, 359 (1,2)	80
III	2,3,4-$(OH)_3C_6H_2$	$NHNH_2$	203—204	$C_9H_{10}N_4O_3S$	43,0	4,1	21,8	12,5	42,5	4,0	22,0	12,6	216 †, 333 (1,1)	60
IV	3,4-$(OH)_2C_6H_3$	NH_2	194—195	$C_9H_9N_3O_2S$	48,3	4,1	18,6	14,3	48,4	4,0	18,8	14,3	238 †, 331 (1,7)	96
V	2,5-$(OH)_2C_6H_3$	NH_2	196—197	$C_9H_9N_3O_2S$	48,5	4,1	18,7	14,5	48,4	4,0	18,8	14,3	250 (1,2) 367 (1,0)	70
VI	2,3,4-$(OH)_3C_6H_2$	NH_2	185—186	$C_9H_9N_3O_3S$	44,7	3,8	17,6	13,6	45,2	3,8	17,6	13,3	217 (2,0), 344 (1,6)	90

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*All of the substances melted with decomposition.

† The maximum was expressed as a shoulder.

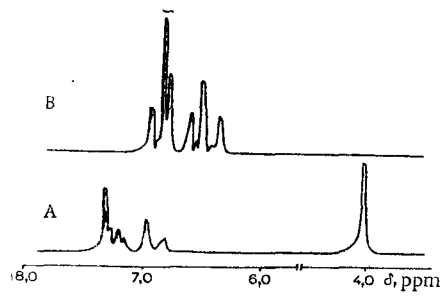


Fig. 1

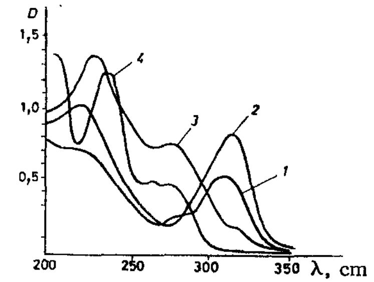
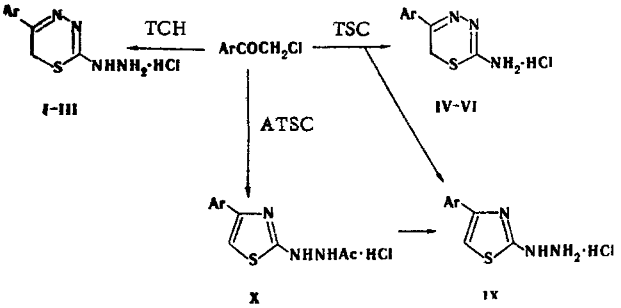


Fig. 2

Fig. 1. PMR spectra (in CF_3COOH): A) 2-hydrazino-5-(3,4-dihydroxyphenyl)-1,3,4-thiadiazine (I); B) 2-hydrazino-4-(2,3,4-trihydroxyphenyl)thiazole (IX).

Fig. 2. UV spectra (in ethanol): 1) 2-hydrazino-5-(2,3,4-trihydroxyphenyl)-1,3,4-thiadiazine (III); 2) 2-amino-5-(2,3,4-trihydroxyphenyl)-1,3,4-thiadiazine (VI); 3) 2-hydrazino-4-(2,3,4-trihydroxyphenyl)-thiazole (IX); 4) 2-hydrazino-4-phenylthiazole (VIII).

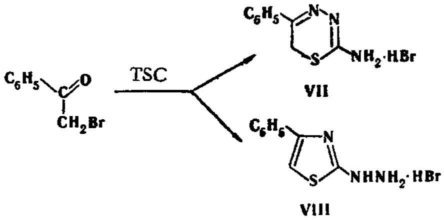
2-Hydrazino-1,3,4-thiadiazines I-III were obtained in the hydrohalide form by condensation of the corresponding hydroxyaryl ω-halo ketones with thiocarbohydrazide (TCH) in acetic acid or in ethanol. Bases I-III were isolated in the crystalline state in the usual manner by neutralization of the aqueous solution to pH 6-7. Alkaline solutions of thiadiazines I-III have an intense yellow color and darken in air; I-III give a green coloration with Fe^{3+} in aqueous solutions.



I, IV Ar = 3,4-dihydroxyphenyl II, V Ar = 2,5-dihydroxyphenyl III, VI, IX, X Ar = 2,3,4-trihydroxyphenyl

The PMR spectra of thiadiazines I-III (Fig. 1, spectrum A) have a multiplet at 6.8-7.5 ppm, the integral intensity of which makes it possible to assign it to the aromatic protons of the polyhydric phenol residue, and a two-proton singlet in the stronger-field region (3.9 ppm), corresponding to the methylene group of the thiadiazine ring. The UV spectra of I-III contain two maxima at 220-240 and 330-360 nm.

Another group of compounds – 2-amino-1,3,4-thiadiazines (IV-VI) – was obtained by condensation of hydroxyaryl ω-halo ketones with thiosemicarbazides (TSC). In [1], Bose isolated two reaction products – 2-amino-5-phenyl-1,3,4-thiadiazine (VII) and 2-hydrazino-4-phenylthiazole (VIII) – by heating phenacyl bromide with TSC in methanol.



We obtained 2-amino-1,3,4-thiadiazines IV and V in 70-80% yields by reaction of 3,4-dihydroxyphenacyl chloride and 2,5-dihydroxyphenacyl bromide with TSC in alcoholic media. Compounds IV and V are formed in higher yields up to 96% in acidic media (acetic acid and concentrated hydrochloric and hydrobromic acids). The absence of thiazole isomers with a hydrazine group (compounds of the VIII type) in the reaction products was shown chromatographically (on Silufol).

The UV and PMR spectral data indicate the structural similarity between 2-amino compounds IV and V and the above-described 2-hydrazino-1,3,4-thiadiazines. The UV spectra of IV and V, like those of I-III, contain two maxima at 220-250 and 330-360 nm (Fig. 2). The δ_{CH_2} singlet at 3.9 ppm characteristic for the thiadiazine ring is observed in the PMR spectra.

In contrast to IV and V, 2-amino-1,3,4-thiadiazine VI with a pyrogallol residue in the 5 position is formed only in concentrated hydrochloric acid. The condensation of 2,3,4-trihydroxyphenacyl chloride with TSC in butanol and acetic acid gives isomeric thiazole IX containing a hydrazine group in the 2 position.

To confirm the structure of IX, we also obtained it by a different method, which, according to [2], is known to lead to the formation of a thiazole derivative – condensation of 1-acetylthiosemicarbazide (ATSC) with 2,3,4-trihydroxyphenacyl chloride in absolute ethanol. A compound identical to IX with respect to its properties and spectral characteristics was obtained as a result of hydrolysis of the acetyl group of the resulting 2-hydrazinoacetyl-4-(2,3,4-trihydroxyphenyl)thiazole.

The UV and PMR spectral data emphasize the structural differences between the 2-hydrazinothiazole obtained (IX) and 2-amino-1,3,4-thiadiazine VI and 2-hydrazino-1,3,4-thiadiazine III, which contain a pyrogallol residue in the 5 position. The UV spectrum of thiazole IX contains intense absorption maxima at 225 and 276 nm, but the long-wave maximum at 330-360 nm that is characteristic for thiadiazine derivatives is absent (Fig. 2). The δ_{CH_2} signal is absent in the PMR spectrum of 2-hydrazinothiazole IX, and a signal that can be assigned to the 5-H proton of the thiazole ring appears in the aromatic proton region (Fig. 1, spectrum B).

A study of the reason for the difference in the condensation of 2,3,4-trihydroxyphenacyl chloride with TSC and the condensation with dihydroxyphenacyl chloride, as well as the difference in the mechanisms of the formation of the isomeric compounds, will be the subject of future research.

The antioxidant activity on a fatty-acid model (oleic acid) was studied for I-IX by the method in [3]. All of the compounds inhibit the oxidation of oleic acid.

EXPERIMENTAL*

The PMR spectra of trifluoroacetic acid solutions of the compounds were recorded with a Perkin-Elmer R 12B spectrometer with hexamethyldisiloxane as the internal standard. The UV spectra of 0.05-cm-thick layers of ethanol solutions ($1 \cdot 10^{-3}$ M) of the compounds were recorded with a Specord spectrophotometer. Thin-layer chromatography (TLC) was carried out with Silufol UV-254 plates with an n-butanol-acetic acid-water (4:1:5) system.

3,4-Dihydroxyphenacyl chloride, with mp 169-170° (literature mp 172°), was obtained by the method in [4]. 2,5-Dihydroxyphenacyl bromide, with mp 113-115° (literature mp 112-113°), was obtained by the method in [5]. 2,3,4-Trihydroxyphenacyl chloride, with mp 163-165° (literature mp 166°), was prepared by the method in [6].

Model compounds: 2-amino-5-phenyl-1,3,4-thiadiazine (VII), with mp 126° (literature mp 126°), was obtained by the method in [1], and 2-hydrazino-4-phenylthiazole (VIII), with mp 168-169° (literature mp 169°), was obtained by the method in [2].

2-Hydrazino-5-(3,4-dihydroxyphenyl)-1,3,4-thiadiazine (I). Hydrochloride. A 1.06-g (10 mmole) sample of thiocarbohydrazide was added to a solution of 1.86 g (10 mmole) of 3,4-dihydroxyphenacyl chloride in 20 ml of acetic acid, and the mixture was refluxed for 10 min. The resulting precipitate was removed by filtration and washed successively with a small amount of acetic acid and alcohol to give 1.9 g (70%) of a product with mp 212-213° (dec.). Found: C 39.7; H 4.1; N 20.4%. $C_9H_{10}N_4O_2S \cdot HCl$. Calculated: C 39.3; H 4.0; N 20.4%.

Base.† A 0.5-g sample of the hydrochloride of I was dissolved in 30 ml of water, and the solution was filtered with charcoal. The filtrate was cooled to 30°, and dilute ammonium hydroxide was added to pH 6-7. The resulting precipitate was removed by filtration, washed on the filter with water, crystallized from aqueous ethanol (25:5), and vacuum dried at 80°.

Thiadiazines II and III were obtained by the method used to prepare I.

2-Amino-5-(3,4-dihydroxyphenyl)-1,3,4-thiadiazine (IV). Hydrochloride. A 1.86-g (10 mmole) sample of 3,4-dihydroxyphenacyl chloride was added to a colorless solution of 0.93 g (10 mmole) of thiosemicarbazide in 20 ml of concentrated HCl, and the mixture was refluxed for 10 min. It was then cooled, and the resulting precipitate was removed by filtration, washed with cold water, and crystallized from water with the addition of activated charcoal to give 2.5 g (96%) of light-yellow plates with mp 232-233° (dec.). Found: C 41.9; H 3.7; N 16.7%. $C_9H_9N_3O_2S \cdot HCl$. Calculated: C 41.6; H 3.8; N 16.1%.

Base. A 1-g (3.8 mmole) sample of the hydrochloride of IV was dissolved in 20 ml of water, and the solution was neutralized carefully to pH 6-7 with dilute ammonium hydroxide. The mixture was cooled, and the resulting precipitate was removed by filtration and crystallized from water with the addition of activated charcoal to give a product with R_f 0.47 on Silufol in an n-butanol-acetic acid-water (4:1:5) system.

Thiadiazines V and VI were similarly obtained by the method used to prepare IV.

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*The PMR spectra were recorded by E. O. Sidorov. The elementary analyses were performed by T. G. Kostrikina and co-workers.

†The characteristics of the base are presented in Table 1.

2-Hydrazino-4-(2,3,4-trihydroxyphenyl)thiazole (IX). A) Hydrochloride. A 2.02-g (10 mmole) sample of 2,3,4-trihydroxyphenacyl chloride was dissolved by heating in 20 ml of n-butyl alcohol, and the solution was refluxed with the addition of charcoal and filtered. A 0.93-g (10 mmole) sample of thiosemicarbazide was added to the filtrate, and the mixture was heated to the boiling point, whereupon a brown precipitate began to form immediately. Heating was continued on a boiling-water bath for 10 min, after which the precipitate was removed by filtration, washed with n-butanol and ether, and crystallized from 2 N HCl to give 2.0 g (70%) of a product with mp 219° (dec.). Found: C 39.6; H 3.7; Cl 13.1%. $C_9H_9N_3O_3S \cdot HCl$. Calculated: C 39.9; H 3.7; Cl 12.9%.

B) Hydrochloride. A 1.33-g (10 mmole) sample of 1-acetylthiosemicarbazide was added to 2.02 g (10 mmole) of 2,3,4-trihydroxyphenacyl chloride in 25 ml of absolute ethanol, and the mixture was heated on a water bath. After 10 min, the formation of a precipitate was observed. Heating was continued for 1.5 h, after which the mixture was cooled, and the precipitated X was removed by filtration. It was then dissolved in 50 ml of ethanol, and the solution was treated with 1 ml of concentrated HCl and heated on a water bath for 2 h. It was then cooled, and the precipitated hydrochloride of IX was removed by filtration and crystallized from 2 N HCl to give 1.5 g (55%) of a product with mp 215-216° (dec.). No melting-point depression was observed for a mixture of this product with the compound obtained in butanol.

Base. A solution of 0.5 g (1.8 mmole) of the hydrochloride of IX in 30 ml of water was refluxed with the addition of charcoal, after which it was filtered, and the filtrate was cooled to 30° and treated with σ saturated sodium acetate solution to pH 7. The resulting yellow precipitate was removed by filtration and purified by recrystallization from nitromethane. It was vacuum dried at 80° to give 0.35 g (70%) of a product with mp 196° (dec.). Found: C 45.1; H 4.0; N 17.4; S 13.6%. $C_9H_9N_3O_3S$. Calculated: C 45.2; H 3.8; N 17.6; S 13.3%; λ_{max}, nm ($\varepsilon \cdot 10^4$): 225 (2.7), 276 (1.5).

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