1,3-THIAZINEDIONES AND PYRIMIDINEDIONES.

3.* 5-SUBSTITUTED 2-PHENYL-1,3-THIAZINEDIONES

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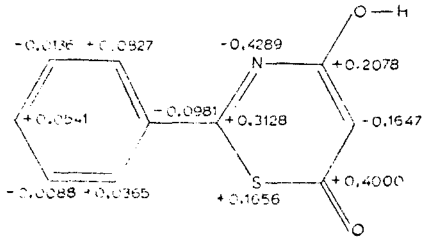
2-Phenyl-4-hydroxy-1,3-thiazin-6-one was subjected to electrophilic substitution reactions, and its 5-nitro, 5-bromo-, 5-iodo, 5-sulfo, and 5-arylazo derivatives were obtained. The effect of the substituent attached to $C_{(5)}$ on the tautomerism of the β-dicarbonyl fragment of the heteroring is examined.

Very little study has been devoted to the preparation of derivatives of 2-phenyl-4-hydroxy-1,3-thiazin-6-one (I) with a functional group in the 5 position [2, 3], whereas I, which is a heteroaromatic system [4] with an activated 5 position, is a convenient substrate for the preparation of such compounds by means of electrophilic substitution reactions.

In the present research we studied the nitration, bromination, iodination, sulfonation, and diazo coupling of thiazinone I. In the selection of the reaction conditions one must take into account the tendency of the thiazinedione ring to undergo cleavage and the possibility of substitution in the phenyl ring. Of course, the available spectral [4] and calculated [the calculation by the Pariser—Parr—Pople (PPP) method with the Dewar σ,π parametrization [5] was performed by B. Ya. Simkin] data constitute evidence for a decrease in the electron density in the benzene ring (see the molecular diagram below) and activation of the 5 position for electrophilic attack. Nevertheless, equimolar amounts of the reagents were used, and relatively mild reaction conditions were selected.



Nitration was carried out in organic solvents at 0-60°C with nitric acid solutions with various concentrations. The best results were obtained in the case of nitration with nitric acid (sp. gr. 1.42) in glacial acetic acid containing catalytic amounts of acetic anhydride at 40-50°C. The use of a nitrating mixture or higher concentrations of nitric acid led to pronounced resinification of the reaction mixture. Under the conditions that we selected, protonated acetyl nitrate [6] is evidently a mild nitrating reagent.

The bromination of I in organic solvents (dioxane, acetic acid, and CCl_4) also proceeded satisfactorily in all cases, but the highest yield of bromo derivative III was obtained in glacial acetic acid; this is probably associated with the higher solubility of I in it. The ease of bromination and nitration confirms the high activity of I with respect to electrophilic reagents. Polarization of the bromine molecules and the formation of a σ complex in this case do not require the participation of a catalyst — a "halogen carrier." However, we were able to carry out iodination only when we used iodine monochloride. Compound IV is unstable when it is stored in air and loses iodine quite rapidly.

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*See [1] for communication 2.

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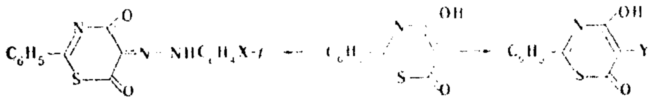


VI-VIII I II-V

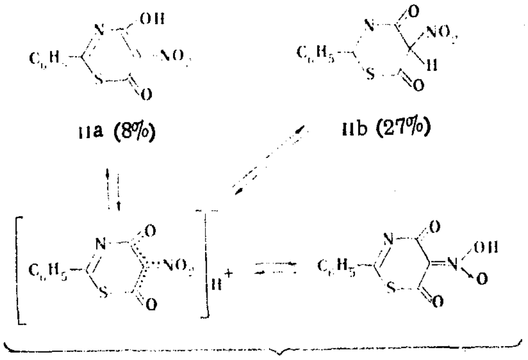
II Y=NO$_2$; III Y=Br, IV Y=I; V Y=SO$_3$H, VI X=H; VII X=Br; VIII X=NO$_2$

We were unable to isolate reaction products in the case of sulfonation with sulfuric acid (sp. gr. 1.835). The most convenient sulfonating reagent was a solution of sulfur trioxide in dichloroethane. Sulfonic acid V is very hygroscopic, and it was therefore converted to the disodium (Va) or bis(isobutylammonium) (Vb) salt, which were analyzed.

Diazo coupling was carried out in a 10% solution of sodium carbonate, since NaOH solutions partially decompose the thiazinedione ring. Compounds VI-VIII are only slightly soluble in organic solvents and water but are quite soluble in alkalis to give intensely red solutions.

The problems of the tautomerism of 2,5-disubstituted thiazinediones have not been previously examined, whereas the spectral characteristics of II-VIII, obtained in this study, show that the introduction of a substituent in the 5 position may affect the state of the tautomeric equilibrium, particularly if the substituent itself is capable of participating in fixation of the enolic proton (nitro and phenylazo groups).

In contrast to the spectrum of I (1640 cm^{-1}), there are three absorption bands corresponding to enol form II (1640 cm^{-1}) and diketo form IIb (1690-1730 cm^{-1}) in the carbonyl region of the IR spectrum of nitro derivative II in DMSO. The signal of five phenyl protons and three signals, the sum of the integral intensities of which corresponds to one proton, are observed in the PMR spectrum of II in d$_6$-DMSO (see Fig. 1). These data constitute evidence that II exists in three tautomeric forms under these conditions.



IIa (8%) IIb (27%)

IIc (65%)

Signal b (δ 5.93 ppm) is related to the methylidyne proton of diketo form IIb, the existence of which is also confirmed by the IR spectrum. A close position of the proton signal was also noted in the spectra of the diketo form of nitroacetylacetone [7] and nitroacetoacetic ester [8] (6.05 and 6.13 ppm). We assigned the a and c signals at weak field to structures IIa and IIc. The position of the a signal (11.87 ppm) is comparable to the position of the signal of the enolic proton solvated by DMSO in the spectra of I and III (11.62 and 11.82 ppm). Signal c (15.16 ppm) was assigned to one of the other two possible tautomeric forms. In [7] the position of the signal of the enolic proton of nitroacetylacetone (16.86 ppm) is linked with the formation of a strong intramolecular O-H...O= bond in the cis-chelate structure. In the case of cyclic β-diketones (trans-enols) this may be either the form of the conjugate anion or, which one cannot exclude, a solvated aci-nitro form, the existence of which has been substantiated, for example, for 2-nitroindanedione [9, 10].

The UV spectra of III and IV in ethanol [λ_{max} 248 nm (log ε 4.33 and 4.21)] are similar to the spectrum of starting I [λ_{max} 246 nm (log ε 4.38)], for which an enol structure has been proved [4]. The IR spectra of crystalline samples of I, III, and IV are also similar (absorption above 1600 cm^{-1} is absent). Consequently, a strongly polarized enol form is characteristic for III and IV.

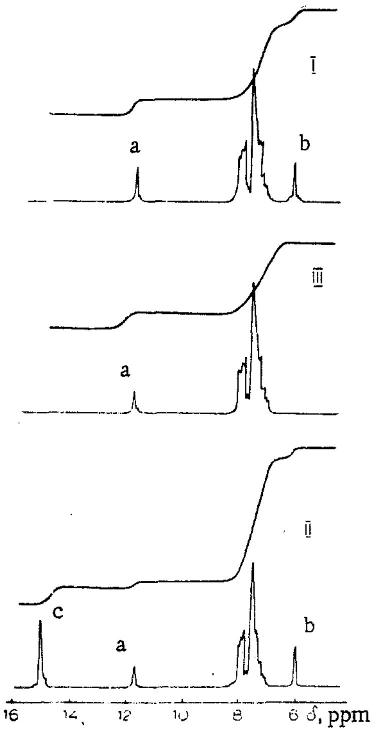
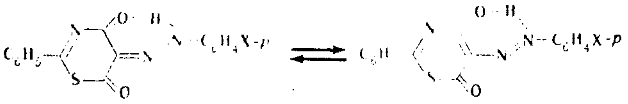


Fig. 1. PMR spectra of I-III.

To prove the structure of the sulfonation product we recorded the PMR spectrum of its bis(isobutylammonium) salt Vb. The PMR spectrum of salt Vb does not contain the signal of an olefinic proton attached to $C_{(5)}$ at 5.5-6.5 ppm, and the signals of the aromatic protons remain unchanged; this is in agreement with substitution in the 5 position. As in the case of the spectra of salts of I, the IR spectrum of salt Vb does not contain absorption in the carbonyl region above 1600 cm^{-1}.

The 2-phenyl-5-phenylazo-4-hydroxy-1,3-thiazin-6-one structure has been assigned [3] to the product of diazo coupling of I with benzenediazonium chloride; however, no proof whatsoever was presented. It follows from the literature data [11] that a hydrazone structure is more likely for compounds of this sort. Three absorption maxima at ~250, 294, and 430 nm (log ε 4.5) are observed in the UV spectra of VI and VII. According to the data in [12], the two intense maxima at ~240 and 400 nm (log ε 4.4) correspond to the hydrazone form with an intramolecular C=O...H-N hydrogen bond. The fixed azo diketo form is characterized by maxima at 244 and 286 nm (log ε 4.3). Thus the three maxima in the UV spectra of VI and VII can be linked with the absorption of two tautomeric forms. The IR spectra of VI and VII



VI a VII a VI b, VII b

(solid samples) also confirm the existence of forms VIa and VIIa. In contrast to the spectra of I and its derivatives with a fixed enol form ($\nu_{C=O}$ 1669 cm^{-1}), absorption at 1679 and 1723 cm^{-1}, which is characteristic for a dicarbonyl structure, also appears in the spectra. From a comparison of the spectrum of a compound that models the diketone form [4], the low-frequency shift of one of the bands may be a reflection of the formation of an intramolecular C=O...HN bond.

EXPERIMENTAL

The IR spectra of mineral oil suspensions and DMSO solutions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of 15% (10% for I) solutions of the compounds in d_6-DMSO were recorded at 35°C with an EM-360 (60 MHz) spectrometer. The UV spectra of ethanol solutions of the compounds were recorded with an SF-4A spectrophotometer. Chromatog-

TABLE 1. 5-Substituted 2-Phenyl-4-hydroxy-1,3-thiazin-6-ones

Compound	Dec. tem., °C	R_f	Found, %		Empirical formula	Calc., %		Yield, %
			N	S		N	S	
II	136—137	0,63[a]	11,1	12,6	$C_{10}H_6N_2O_4S$	11,2	12,8	75
III	156—157	0,42[b]	4,9	11,3	$C_{10}H_6BrNO_2S$	4,9	11,3	75
IV	136—138	0,44[a]	4,0	10,2	$C_{10}H_6INO_2S$	4,2	9,7	40
V	53—55[c]	—	—	—	$C_{10}H_7NO_5S_2$	4,9	22,5	95
Va	300	0,70[d]	4,1	20,3	$C_{10}H_5NNa_2O_5S_2$	4,2	19,5	85
Vb	105—107	0,62[d]	7,5	12,2	$C_{26}H_{45}N_3O_5S_2$	7,7	11,8	65
VI	196—198	0,68[e]	13,4	10,5	$C_{16}H_{11}N_3O_2S$	13,6	10,4	90
VII	216—218	0,73[e]	10,5	8,6	$C_{16}H_{10}BrN_3O_2S$	10,8	8,3	90
VIII	220—222	0,79[e]	15,5	9,1	$C_{16}H_{10}N_4O_4S$	15,8	9,0	75

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a) Dichloroethane—acetone—dibutyl ether (4:1:1). b) Dibutyl ether—acetone (1:1). c) Melts without decomposition. d) Dichloroethane—dibutyl ether (4:1). e) Benzene—chloroform—acetone (2:3:1).

raphy was carried out on Silufol UV-254 plates with detection in UV light. The characteristics of the compounds obtained are presented in Table 1.

2-Phenyl-5-nitro-4-hydroxy-1,3-thiazin-6-one (II). A solution of 0.45 ml (7.4 mmole) of nitric acid (sp. gr. 1.42) in 2 ml of glacial acetic acid was added with stirring at 40-50°C to a suspension of 1 g (4.9 mmole) of I in 8 ml of glacial acetic acid containing 0.1 ml of acetic anhydride, and the mixture was stirred for 20 min. The precipitate was removed by filtration and recrystallized from acetone or glacial acetic acid.

2-Phenyl-5-bromo-1,3-thiazin-6-one (III). A solution of 0.33 ml of bromine in 5 ml of glacial acetic acid was added with stirring to a suspension of 1 g (4.9 mmole) of I in 15 ml of glacial acetic acid, and the mixture was stirred at 40-50°C for 20 min. The precipitate was removed by filtration and recrystallized from dichloroethane.

2-Phenyl-5-iodo-4-hydroxy-1,3-thiazin-6-one (IV). An equimolar amount of iodine monochloride in 10 ml of glacial acetic acid was added with stirring and cooling to 5°C to a suspension of 1 g (4.9 mmole) of I in 10 ml of glacial acetic acid, and the mixture was stirred for 10 min. The precipitate was removed by filtration and recrystallized from dichloroethane.

2-Phenyl-5-sulfo-4-hydroxy-1,3-thiazin-6-one (V). A solution of 1.2 g (15 mmole) of sulfur trioxide in 10 ml of dichloroethane was added dropwise to a suspension of 3 g (15 mmole) of I in 20 ml of dichloroethane, and the mixture was stirred with cooling for 20 min. The precipitate was removed by filtration and washed with dichloroethane. Disodium salt Va. A solution of sodium ethoxide prepared from 0.65 g of sodium in 15 ml of alcohol was added with stirring to a suspension of 4 g (14 mmole) of sulfonic acid V in 15 ml of anhydrous alcohol, and the mixture was stirred for 30 min until a homogeneous green-yellow suspension was obtained. The solid was removed by filtration and washed with anhydrous alcohol and ether. Bis(isobutylammonium) salt Vb. A 2.28-ml sample of dry diisobutylamine was added dropwise to a suspension of 2 g (7 mmole) of V in 10 ml of toluene, and the mixture was stirred at room temperature for 3 h. The precipitate was removed by filtration and recrystallized from benzene or ethyl acetate.

2-Phenyl-5-phenylazo-4-hydroxy-1,3-thiazin-6-one (VI). An equimolar amount of a solution of benzenediazonium hydrosulfate was added at 0°C to a solution of 1 g (4.9 mmole) of I in 10 ml of 10% sodium carbonate solution, and the mixture was stirred for another 40 min. The resulting precipitate was removed by filtration and recrystallized from ethanol.

2-Phenyl-5-(p-bromophenylazo)-4-hydroxy-1,3-thiazin-6-one (VII). A 1-g sample of sodium acetate was added to 15 ml of a solution of p-bromobenzenediazonium chloride (5 mmole), and a solution of 1 g (4.9 mmole) of I in 10 ml of a 10% sodium carbonate solution was added to the mixture at 0°C. The resulting precipitate was removed by filtration, washed on the filter with sodium chloride solution, dried in vacuo, and recrystallized from dichloroethane.

2-Phenyl-5-(p-nitrophenylazo)-4-hydroxy-1,3-thiazin-6-one (VIII). This compound was obtained by the procedure used to prepare VII and was recrystallized from nitrobenzene.

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STRUCTURE OF THE CATIONIC FORMS OF PYRIMIDO[4,5-b][1,4]THIAZINES — A NEW TYPE OF FOLIC ACID ANTAGONIST

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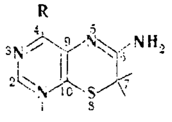
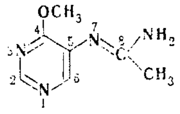
The protonation of 4-methoxy-, 4-amino-, and 4-dimethylamino-6-aminopyrimido[4,5-b][1,4]thiazines and N-(4-methoxy-5-pyrimidinyl)acetamidine was studied by ^{1}H and ^{13}C NMR spectroscopy. It is shown that the addition of a proton in the first three compounds takes place at the N_5 atom of the thiazine ring, whereas in the case of N-(4-methoxy-5-pyrimidinyl)acetamidine primary protonation is observed at the nitrogen atom of the amidine group, and the second proton adds to the N_1 atom of the pyrimidine ring.

Previous research on pyrimido[4,5-b][1,4]thiazine derivatives has led to the detection of a new type of folic acid antagonist that has antitumorigenic activity [1]. 4-Methoxy-6-aminopyrimido[4,5-b][1,4]thiazine hydrochloride (tomizin) has been selected from this group of substances for clinical study [2]. The participation of an acid–base reaction in the mechanism of inhibition of dihydrofolatereductase (DFR) has been established for a number of previously known folic acid antagonists [3]. In this connection, it seemed of interest to study the structure of the protonated forms of pyrimido[4,5-b][1,4]thiazines and to establish the possible centers of bonding of compounds of this type with the acidic functions of the active centers of DFR. With this end in mind, we investigated the protonation of I-IV by



I–III



IV

I R = OCH_3; II R = NH_2; III R = $N(CH_3)_2$

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