1,3-THIAZINEDIONES AND PYRIMIDINEDIONES

I. STRUCTURE AND TAUTOMERISM OF 2-SUBSTITUTED 4,6-DIOXODIHYDRO-1,3-THIAZINES

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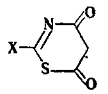
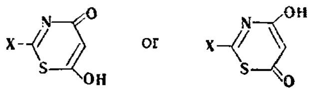
2-Methyl- and 2-alkoxy-4,6-dioxodihydro-1,3-thiazines were synthesized. A comparative examination of the IR and PMR spectra of 2-substituted thiazinediones and their O-methyl ethers and sodium derivatives was made. It is shown that a change in the character of the substituent has a substantial effect on the structure of the β-dicarbonyl fragment.

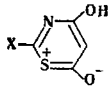
2-Phenyl-4,6-dioxodihydro-1,3-thiazine (I) was obtained for the first time in 1960 [1]. Methods for the synthesis of other 2-substituted 1,3-thiazinediones were developed soon thereafter (for example, see [2, 3]). Despite the fact that the first studies revealed the practical value of thiazinedione derivatives [4-6], a systematic study of the chemistry of these compounds was not made, whereas even a superficial knowledge of the spectral characteristics of 2-substituted 4, 6-dioxodihydrothiazines – potentially tautomeric heterocyclic β-diketones – showed that a change in the character of the substituents may have a substantial effect on the structure of the β-dicarbonyl fragment [1,7] and should therefore be reflected in the reactivity of the entire system. One might have assumed the presence of the following principal tautomeric form for 2-substituted thiazinediones:



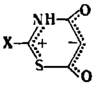
II



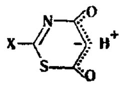
III



IVa



IVb



IVc

Thus the absence of absorption above 1600 cm^{-1} in the IR spectrum of I in the crystalline phase was explained in [1] by the possibility of its existence in dipolar form IVa. The spectral characteristics of thiazinedione I and its p-chloro derivative [8] confirmed the assumption of the existence in the solid form of an ionized form, for which structure IVb was proposed. However, it is not yet possible to form a preference for any one of the proposed ionized forms of IV on the basis of the IR spectra of solid samples.

Diketone form II was assigned to the 2-(alkylthio)thiazinediones that we synthesized in [3], particularly to benzylthio derivative V from the IR spectral data (two absorption bands at 1675-1715 cm^{-1}).

2-Methyl- and 2-alkoxythiazinediones, obtained by malonation of thioacetamide and O-alkylthiocarbamates with carbon suboxide, represented a third group of compounds:

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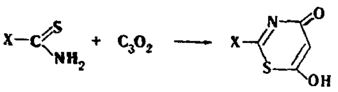

VI-XI

VI X=CH_3; VII X=$C_6H_5CH_2O$; VIII X=CH_3O;
IX X=C_2H_5O; X X=C_3H_7O; XI X=iso-C_3H_7O

The IR spectra of crystalline samples of these compounds, except for VIII ($\nu_{C=O}$ 1735, 1700 cm^{-1}), are characterized by a single intense absorption band at 1628-1650 cm^{-1}; this constitutes evidence that they exist in the III form.

This difference in the spectral characteristics of 2-substituted thiazinediones served as a basis for the further study of this problem. The IR and PMR spectra of dimethyl sulfoxide (DMSO) solutions of the compounds of all three groups and of some model compounds were recorded. It was found that the IR spectrum of solid thiazinedione I is similar to the spectrum of its sodium derivative (XII) (Table 1). Intense absorption at ~ 1600 cm^{-1} was also observed for the sodium salts of VI-XIII. This absorption may be considered to be one of the bands of the conjugate enolate anion, which is also characteristic for other cyclic β-diketones (for example, see [9]). Absorption at 1645 cm^{-1} that constitutes evidence for the existence of enol form III in solution appears in the spectrum of a DMSO solution of thiazinedione I. Similar absorption in the carbonyl region is also observed for O-methyl ethers XIV-XVI, obtained by methylation of I, VI, and VII with diazomethane.

Only a small shift of the bands of carbonyl absorption characteristic for transition from the solid phase to solution was observed in the IR spectrum of a DMSO solution of benzylthio derivative V, whereas the character itself of the spectrum did not change. 2-Substituted 5,5-dimethylthiazinediones XVII and XVIII, which served as models of keto form II, also have two absorption bands at 1700-1730 cm^{-1} (Table 1).

When VI-XI were dissolved in DMSO, in addition to a small increase in the absorption frequency of the carbonyl group, the absorption of a weak double bond appeared at 1710-1730 cm^{-1} in the IR spectra; this could be a reflection of a keto-enol equilibrium.

Data from the PMR spectra of solutions of the investigated compounds and some models (Table 2) confirmed the above-expressed assumptions.

In the case of I the equilibrium is shifted entirely to favor the enol form, as evidenced by the absence of signals of the protons of the methylene group of the keto form at ~3.5 ppm and of the anionic form at 4.7 ppm. On the other hand, V exists only in diketo form II. In the case of VI and VII it was found to be possible to observe a keto-enol equilibrium under these conditions.

The effect of various factors on the position of the equilibrium and the character of the PMR spectra was examined in greater detail in the case of VI, in the PMR spectrum of which the signals of the methyl groups of the keto and enol forms have different chemical shifts – 2.12 and 2.58 ppm. Signals of only the enol form were observed in the spectra of samples prepared in a dry box with thoroughly dried d_6-DMSO* in the course of 3-4 h, after which extremely weak signals of the keto form appeared. Further observation was complicated by processes involving the decomposition of thiazinedione VI. In the case of spectra of samples prepared with a

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*The position of the keto-enol equilibrium is retained in the case of samples prepared in air, but the signal of the enol proton is broadened considerably and shifted to the strong-field region.

TABLE 1. $\nu_{C=O}$ Frequencies in the IR Spectra of 2-Substituted Thiazinediones and Their Derivatives

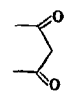
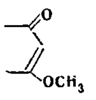
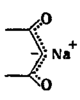
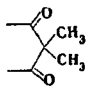
Compound	X	$\nu_{C=O}$, cm^{-1} (in mineral oil)			
					
I	C_6H_5	1600	1662	1600	1700,1730
V	$C_6H_5CH_2S$	1710,1675	—	—	1700,1730
VI	CH_3	1628	1668	1616	—
VII	$C_6H_5CH_2O$	1650	1663	—	—

TABLE 2. PMR Spectra of 2-Substituted 4,6-Dioxodihydro-1,3-thiazines and Their Derivatives (δ, ppm)

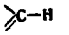
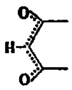
Compound	X		>CH$_2$		O–H	O–CH$_3$	X
I	C_6H_5	5,85	—	—	11,62	—	7,43—8,03
XIV		5,95	—	—	—	3,88	7,23—7,83
XII		—	—	4,75	—	—	7,43—8,03
V	$C_6H_5CH_2S$	—	3,53	—	—	—	4,42; 7,31
VI	CH_3	5,40	3,68	—	10,66	—	2,58 (enol) 2,12 (ketone)
XV		5,77	—	—	—	3,97	2,60
XIII		—	—	4,67	—	—	2,30
VII	$C_6H_5CH_2O$	5,34	3,42	—	11,78	—	7,38; 5,49
XVI		5,52	—	—	—	3,85	7.4; 5,52

TABLE 3. 2-Substituted 4,6-Dioxodihydro-1,3-thiazines and Their Derivatives

Compound	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
			N	S	N	S	
VI	130—132[a, b]	$C_5H_5NO_2S$	9,7	22,0	9,8	22,4	55
VII	107—108[b, c]	$C_{11}H_9NO_3S$	6,0	13,4	6,0	13,6	65
VIII	116,5—117[b, c]	$C_5H_5NO_3S$	8,9	20,3	8,8	20,1	44
IX	127—128[b, c]	$C_6H_7NO_3S$	8,2	18,8	8,1	18,7	75
X	106—107[b, c]	$C_7H_9NO_3S$	7,4	17,2	7,5	17,1	49
XI	111—112[b, c]	$C_7H_9NO_3S$	7,6	17,4	7,5	17,1	65
XII	270[b]	$C_{10}H_7NNaO_2S$	5,9	13,1	6,2	14,1	86
XIII	190[b]	$C_5H_4NNaO_2S$	8,4	18,3	8,5	19,3	99
XIV	91—92[d]	$C_{11}H_9NO_2S$	6,4	14,1	6,4	14,6	96
XV	79—80[e]	$C_6H_7NO_2S$	8,9	19,9	8,9	20,4	85
XVI	69—70,5[e]	$C_{12}H_{11}NO_3S$	5,4	12,4	5,6	12,8	89
XVII	62—63[e]	$C_{13}H_{13}NO_2S_2$	5,1	22,8	5,0	22,9	62
XVIII	53—55[e]	$C_{12}H_{11}NO_2S$	6,3	14,0	6,0	13,7	66

[a] From ethyl acetate. [b] Melts with decomposition. [c] From benzene. [d] From CCl_4. [e] From hexane.

solvent containing traces of water, the equilibrium initially (1 h after dissolving) is shifted practically completely to favor the enol form (≥ 95-97%), but the amount of the keto form reaches ~25% in 1.5 h. An increase in the water content in the solvent leads to rapid establishment of the equilibrium and sharply increases the percentage of the keto form (~60% 1.5 h after dissolving). The addition of traces of triethylamine accelerates the ketoenol transformation process, particularly in the case of samples containing traces of water.

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% solutions of the compounds in DMSO and d_6-DMSO were recorded with an EM-360 spectrometer (60 MHz) at 35°. The UV spectra of ethanol solutions were recorded with an SF-4A spectrophotometer. Chromatography was carried out on Silufol UV-254 plates. The characteristics of the compounds are presented in Table 3.

2-Methyl-4,6-dioxodihydro-1,3-thiazine (VI). A small excess of carbon suboxide gas was passed through a solution of 3 g (0.04 mole) of thioacetamide in 130 ml of ethyl acetate, and the resulting precipitate was removed by filtration and recrystallized from ethyl acetate to give a product with R_f 0.34 [dibutyl ether – ethanol – water (6 : 6 : 1)]. UV spectrum, λ_{max}: 238 and 305 nm (log ε 4.00 and 3.35).

2-Benzyloxy-4,6-dioxodihydro-1,3-thiazine (VII). A 4.8-g (0.012 mole) sample of liquid C_3O_2 was added to a cooled (to −10°) solution of 8 g (0.048 mole) of O-benzylthiocarbamate in 200 ml of ethyl acetate, and the mixture was gradually heated to room temperature, after which the solvent was removed in vacuo. The solid material was recrystallized from benzene to give a product with R_f 0.64 [dibutyl ether – ethanol (1 : 1)]. UV spectrum; λ_{max}: 225 and 267 nm (log ε 4.26 and 4.09).

Compounds VIII-XI were similarly obtained.*

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*Compound IX was previously described in [2].

2-Phenyl-4,6-dioxodihydro-1,3-thiazine Sodium Salt (XII). A 15-g (0.074 mole) sample of I was added with stirring to a solution of 5.02 g (0.074 mole) of sodium ethoxide in 200 ml of absolute ethanol, and the mixture was stirred for 3 h. The solid material was removed by filtration and washed with hot absolute ethanol to give a product with R_f 0.46 [dibutyl ether – ethyl acetate (1 : 1)]. UV spectrum: λ_{max} 247 nm (log ε 4.47).

2-Methyl-4,6-dioxodihydro-1,3-thiazine Sodium Salt (XIII). This compound was similarly obtained.

2-Phenyl-4-oxo-6-methoxy-1,3-thiazine (XIV). A total of 30 ml of an ether solution containing 0.8 g (0.02 mole) of diazomethane was added gradually with stirring to a cooled (to –3°) suspension of 2 g (0.01 mole) of I in 40 ml of ethyl acetate, after which the mixture was allowed to stand overnight. The solvent was removed, and the solid material was recrystallized successively from hexane and CCl_4 to give a product with R_f 0.75 [ethanol – dibutyl ether (1 : 1)].

Compounds XV and XVI were similarly obtained.

2-Benzylthio-5,5-dimethyl-4,6-dioxodihydro-1,3-thiazine (XVII). An 8.25-g (0.049 mole) sample of dimethylmalonyl dichloride was added to a solution of 3.6 g (0.019 mole) of S-benzyldithiocarbamate in 150 ml of CCl_4, after which the mixture was refluxed for 5 h. The solvent was removed, and the residue was fractionated. The fraction with bp 163-164° (1 mm) was collected. UV spectrum (in hexane): λ_{max} 270 nm (log ε 4.3).

2-Phenyl-5,5-dimethyl-4,6-dioxodihydro-1,3-thiazine (XVIII). This compound was obtained by the method in [10].

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