IR SPECTRA AND STRUCTURE OF 4-THIOBARBITURIC ACID DERIVATIVES

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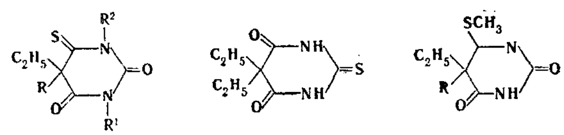
On the basis of data from the IR spectra of 4-thiobarbituric acid derivatives, and their deutero analogs, and similarly constructed model compounds, it was established that the investigated substances exist in the thione lactam form and form two types of associates through intermolecular hydrogen bonds.

During a study of the structures of barbituric acid derivatives – an important class of medicinal compounds – it was established that in the crystalline state and in solutions they can exist in two tautomeric forms [1-8] and are also capable of forming associates through two types of hydrogen bonds [6, 9].

The 4-thiobarbituric acids that we obtained displayed high pharmacological activity. In order to study the relationship between the structure and the activity in the present paper we discuss the IR spectra and structure of 5,5-disubstituted 4-thiobarbituric acids I-IV in comparison with model compounds V-XI. The spectra of the crystalline compounds and chloroform solutions of them were recorded (Figs. 1 and 2, Table 1). The mass spectral investigation of these compounds is described in [10].



I–IV; IX–XI   V   VI–VIII

I $R=C_2H_5$; II $R=n\text{-}C_3H_7$; III $R=i\text{-}C_4H_9$; IV $R=C_6H_5$; I–IV $R^1=R^2=H$; VI $R=C_2H_5$; VII $R=n\text{-}C_3H_7$; VIII $R=C_6H_5$; IX–XI $R=C_2H_5$; IX $R^1=H$; $R^2=CH_3$; X $R^1=CH_3$; $R^2=H$; XI $R^1=R^2=CH_3$

4-Thiobarbituric acid derivatives are potentially capable of lactim–lactam and thione–thiol tautomerism. A comparison of the spectra of the investigated and model compounds in the region of multiple bond vibrations (Fig. 1) makes it possible to form a judgment regarding the position of the tautomeric equilibrium, since the intense absoprtion bands corresponding to $\nu_{C=O}$ and $\nu_{C=N}$ vibrations are situated here. In analogy with the assignment of the frequencies made on the basis of calculations of the normal vibrations of barbituric acid derivatives [6, 7], the intense bands in the spectra of I-IV at 1750 and 1680 cm^{-1} can be assigned to $\nu_{C(2)=O}$ and $\nu_{C(6)=O}$. As expected, the shift of the $\nu_{C=O}$ bands when the compounds are deuterated is only slight. The assignment of the frequencies of the ring C = N bond in the thiol and lactim forms is more complex. On the basis of a comparison of the investigated spectra with one another and with the spectra of a series of compounds containing a ring C = N bond [11] and with the results of calculation of the normal vibrations of 2-thiobarbituric acid [7], the intense band at 1550 cm^{-1} evidently can be assigned to the pyrimidine ring $\nu_{C=N}$ frequency or, in any case, to the vibrations of the pyrimidine ring itself with the participation of the C = N bond.

A comparison of I-IV and 2-thiobarbital from the point of view of their tautomerism seems of interest. Distinct bands in the ν_{SH} region [12] at 2600 and 2560 cm^{-1}, which are observed at high concentrations of the compound, are observed in the spectrum of crystalline acid V, along with intense absorption bands of carbonyl

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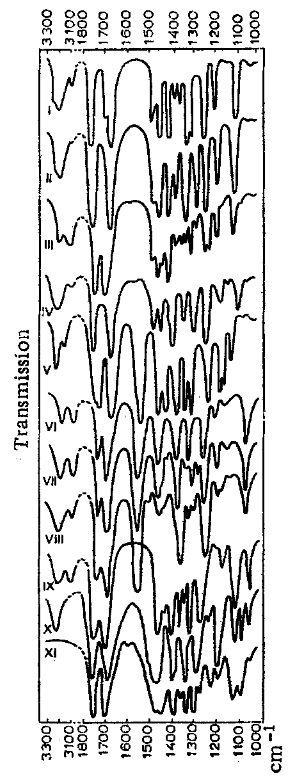


Fig. 1

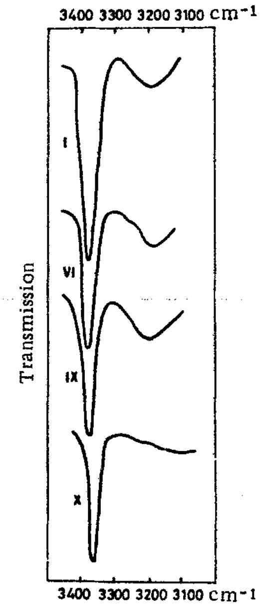


Fig. 2

Fig. 1. IR spectra of mineral oil suspensions of crystalline samples of I–XI.

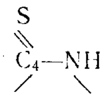
Fig. 2. IR spectra of I, VI, IX, and X in chloroform (c 0.01 M, l 0.25 mm).

TABLE 1. Frequencies (cm^{-1}) of the Maxima of the Absorption Bands of 2- and 4-Thio Derivatives of Barbituric Acid in the Crystalline State (a) and in Chloroform Solutions (0.001 M) (b)

I		II	III	IV	V	VI		VII	VIII	IX		X		XI		Assignment
a	b	a	a	a	a	a	b	a	a	a	b	a	b	a	b	
3210 3080	3380 3200	3200 3070	3210 3110	3230 3075	3243 3155	3182 3080	3380 3180	3200 3080	3210 3080	3220 3080	3380 3200	3210	3365	—	—	$\nu_{N_{(1,3)}H}$
1760 1698 1678	1750 1730	1765 1677	1740 1700	1762 1680	1740 1720 1670	1732 1692	1735 1710	1730 1692	1732 1688	1740 1690	1745 1725	1740 1670	1742 1693	1738 1690	1732 1685	$\nu_{C_{(2)}=O}$ $\nu_{C_{(4,6)}=O}$
	—	—	—	—	1543	1550	1550	1552	1542	—	—	—	—	—	—	Ring ν with the participation of C=N
1483	—	1480	1485	1475	—	—	—	—	—	—	—	1495	—	—	—	ν of the $\overset{S}{\overset{\Vert}{C_4}}$—NH group

groups. Absorption is not observed in this region in the spectra of I–IV under similar conditions. This fact and the presence of a $\nu_{C=N}$ band at 1540 cm^{-1} indicate the probable existence of acid V in the form of a mixture of thione and thiol forms.

It follows from the data in Fig. 1 and Table 1 that the spectra of I–IV practically coincide with the spectra of fixed thione lactam models IX–XI. On the other hand, as in the case of V, an intense $\nu_{C=N}$ band at 1550 cm^{-1} is present in the spectra of thiol forms VI–VIII, in addition to absorption bands of carbonyl groups. The development of a double bond in the pyrimidine ring of S-methyl analogs VI–VIII leads to a decrease of more than 30 cm^{-1} in the $\nu_{C=O}$ frequency because of the developing conjugation.

The presence in the spectra of I-IV of a band at ~ 1480 cm^{-1}, which is absent in the spectra of other derivatives of barbituric acid [6, 7], can also be explained by the thione structure. A similar frequency observed in the spectra of thioureides [12] was interpreted by the authors as the band of an R−NH−C = S grouping. Since the band at 1480 cm^{-1} is too high to be able to be assigned to vibrations of the C = S bond and since a shift in the band is observed when the compound is deuterated, we assigned it to the vibrations of the bonds in the  fragment of the pyrimidine ring. The results provide evidence in favor of the fact that 4-thiobarbituric acid derivatives I-IV, in contrast to analogous compounds from the 2-thiobarbiturate series, have a thione lactam structure. This is confirmed by the mass spectral behavior of these compounds [10].

The lactam forms of 4-thio-substituted barbituric acids can participate in the formation of hydrogen bonds. In the high-frequency region of the spectra the investigated compounds are characterized by two bands at ~ 3210 and ~ 3080 cm^{-1}, which are very sensitive to deuteration (f = 1.33). In the spectra of solutions (Fig. 2) these frequencies vanish, and a distinct intense band at 3380 cm^{-1}, which is due to the vibrations of free NH groups, appears. Both bands in the spectra of crystalline 4-thio derivatives are close to the analogous bands in the spectra of barbituric analogs and can be assigned to the vibrations of the NH groups linked by hydrogen bonds of two types; the abilities of the $N_{(1)}H$ and $N_{(3)}H$ groups to form hydrogen bonds differ. Thus two ν_{NH} bands are present in the spectra of crystalline S-methyl derivatives VI-VIII and IX, and this constitutes evidence for the presence of two types of associates through the $N_{(1)}H$ group. Similar bands are observed in the spectrum of 1-methylbarbital [3] and were assigned by the authors to $\nu_{NH...O}$ bands of two different types of hydrogen bonds. The $N_{(3)}H$ group is evidently capable of forming only one type of hydrogen bond, since only one band at 3210 cm^{-1} is present in the spectrum of X (Fig. 2, Table 1). All of this makes it possible to conclude that the thioamide grouping to the pyrimidine ring of the investigated compounds can, in contrast to the amide grouping, form only one type of hydrogen bond.

Thus the fact that the IR spectra of 4-thiobarbituric acid derivatives coincide with the spectra of 2-thiobarbital and the S- and N-methyl analogs shows that the investigated compounds exist in the thione lactam form and that in the crystals the molecules are linked by two types of intermolecular hydrogen bonds.

EXPERIMENTAL

Thio derivatives of barbituric acid obtained by thiolysis of imino acids with the appropriate structures by the method described in [13] were used in the research. The deuterium analogs were obtained by heating the substances at 90°C for 2 h in excess deuteromethanol and subsequent removal of the solvent by vacuum distillation. The IR spectra of mineral oil suspensions and solutions of the compounds in chloroform (0.01 M), purified by the method in [14], were recorded with a Perkin−Elmer 577 spectrometer. Dismountable cuvettes with a thickness of 0.25 mm were used.

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