SEMICARBAZONES AND THIOSEMICARBAZONES OF THE HETEROCYCLIC SERIES

XXVII.* SPECTRA AND STRUCTURE OF ISATIN β-THIOSEMICARBAZONES

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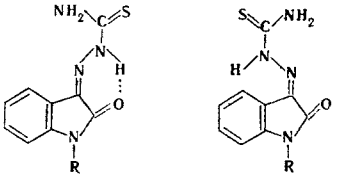
Isatin β-thiosemicarbazone and its alkyl derivatives containing a hydrogen atom attached to $N_{(2')}$ exist primarily in the form of the syn isomer stabilized by intramolecular hydrogen bonding in solutions and in the crystalline state. The strength of this hydrogen bond increases when both hydrogen atoms in the primary thioamide group are replaced by alkyl groups.

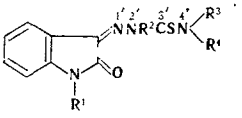
Isatin β-thiosemicarbazones (I) and N-methylisatin β-thiosemicarbazones (II) ("methisazone") can exist as syn (a) and anti (b) isomers



I-II a I-II b

I R=H; II R=CH_3

To solve the problem of the structures of I and II we compared them with III-IV, in which an intramolecular hydrogen bond (IHB) is excluded by substitution of the hydrogen atom attached to $N_{(2')}$. We also studied derivatives V-XIV, which are substituted at $N_{(4')}$ (Table 1).



I-XIV

According to the results of thin-layer chromatography (TLC) (Table 1), II-IV, IX, XIII, and XIV, even after repeated recrystallization, are mixtures of two substances with close R_f values. We were unable to separate these substances, inasmuch as they are readily interconverted. According to the data in [2], I and II are anti isomers in polar solvents. This conclusion is based on the fact that the chemical shifts of the 2'-H proton and the proton attached to the indole nitrogen in the PMR spectra in dimethyl sulfoxide (DMSO) depend on the concentration, and 2'-H consequently participates in the formation of an intermolecular hydrogen bond rather than an intramolecular hydrogen bond. To verify this, we recorded the PMR spectra of I and II in solutions with concentrations ranging from 3.5 to 20% and, for comparison with them, the PMR spectra of benzaldehyde thiosemicarbazone (XV) [7], acetone thiosemicarbazone (XVI) [8], and benzaldehyde

*See [1] for Communication XXVI.

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TABLE 1. Isatin β-Thiosemicarbazones

Compound	R_1	R_2	R_3	R_4	mp, °C	Crystallization solvent	Empirical formula	Found, %		Calc., %		Yield, %	TLC data (activity II Al_2O_3) j	
								N	S	N	S		eluent[k]	R_f [l]
I	H	H	H	H	255[a]	Aqueous alcohol	$C_9H_8N_4OS$					82,0	B	0,415
II	CH_3	H	H	H	243[b]	Butyl alcohol	$C_{10}H_{10}N_4OS$					98,8	A	0,50; 0,614
III	H	CH_3	H	H	195[c]	Butyl alcohol	$C_{10}H_{10}N_4OS$					88,0	B	0,316; 0,389
IV	CH_3	CH_3	H	H	177[d]	Alcohol	$C_{11}H_{12}N_4OS$	22,8	13	22,6	12,9	89,0	A	0,615; 0,693
V	H	H	CH_3	H	258[e]	Alcohol	$C_{10}H_{10}N_4OS$					93,5	B	0,414
VI	CH_3	H	CH_3	H	198,5	Acetic acid	$C_{11}H_{12}N_4OS$	22,5	13,2	22,6	12,9	96,7	C	0,52
VII	H	H	CH_3	CH_3	230[f]	Butyl alcohol	$C_{11}H_{12}N_4OS$					72,8	B	0,473
VIII	CH_3	H	CH_3	CH_3	200[g]	Alcohol	$C_{12}H_{24}N_4OS$	21,8	11,8	21,4	12,2	82,0	A	0,81
IX	H	H	H—C_4H_9	n-C_4H_9	153[h]	Alcohol	$C_{17}H_{24}N_4OS$					96,0	A	0,554; 0,62
X	CH_3	H	H—C_4H_9	n-C_4H_9	120,5[i]	Acetonitrile	$C_{18}H_{26}N_4OS$	16,4	9,5	16,2	9,3	80,6	C	0,593
XI	H	CH_3	CH_3	H	168,5	Alcohol	$C_{11}H_{12}N_4OS$	22,7	12,7	22,6	12,9	73,2	A	0,436
XII	CH_3	CH_3	CH_3	H	169	Alcohol	$C_{12}H_{14}N_4OS$	21,3	12,2	21,4	12,2	91,5	C	0,32
XIII	H	CH_3	CH_3	CH_3	196,5	Butyl alcohol	$C_{12}H_{12}N_4OS$	21,4	12,5	21,4	12,2	92,0	A	0,487; 0,599
XIV	CH_3	CH_3	CH_3	CH_3	155	Alcohol	$C_{13}H_{16}N_4OS$	20,5	11,9	20,3	11,6	66,1	B	0,524; 0,62

[a]According to [3], mp 252°. [b]According to [3], mp 243°. [c]According to [4], mp 195°. [d]According to [4], mp 172.5°. [e]According to [5], mp 260°. [f]According to [6], mp 232°. [g]According to [6], mp 196°. [h]According to [3], mp 153°; according to [6], mp 151°. [i]According to [6], mp 110°. [j]Layer thickness 1 mm, applied in methanol; compounds II and III were applied in acetone. [k]The symbol A indicates chloroform–methanol (95 : 1), B indicates benzene–alcohol (10 : 1), C indicates benzene–methanol (10 : 1). [l]The R_f values of those substances that predominate in the mixture are given in boldface.

4,4-dimethylthiosemicarbazone (XVII) [9] as models in which participation of 2'-H in the formation of an IHB is excluded (Table 2).

Despite the data in [2], the signals of all of protons including 2'-H are independent of concentration. The low values of the chemical shifts of the 2'-H protons in derivatives I and II and their constancy as the temperature changes demonstrate that I and II exist in solution primarily in form **a**, which is stabilized by an IHB.

The 2'-H chemical shifts in the spectra of 4',4'-dialkyl derivatives VII-IX are considerably lower than those observed for I and II (compare the spectra of XV and XVI). The syn form therefore also predominates in VI-IX, and the IHB in them is even stronger. The effect of groupings in the 4' position is not additive (Tables 2 and 3) and is apparently primarily due to the steric contraction of the chelate ring.

The conclusion presented in [2] regarding the predominance of isomer **b** in solutions of I and II was also substantiated by the fact that the frequencies of the carbonyl group for solutions of these substances in DMSO differ from the frequencies of the carbonyl group in the crystalline state, in which, in the opinion of the authors, this substance is isomer **a**. Data from the IR spectra of I-XIV in DMSO and chloroform are presented in Table 4. Substitution of the hydrogen atom attached to $N_{(2')}$ by a methyl group leads to an increase in the frequency of the carbonyl group (> 30 cm^{-1}). This confirms that the syn form corresponds to compounds in which the hydrogen atom attached to $N_{(2')}$ is not substituted (I-II and V-X). Since the shift in the frequency of the carbonyl group on passing from chloroform to carbon tetrachloride is insignificant, it can be assumed that this conclusion is also valid for nonpolar solvents.

A comparison of the UV spectra of derivatives I-XIV (Table 3) shows that replacement of the hydrogen atom attached to $N_{(2')}$ changes the spectrum to a considerably greater extent than for the previously investigated thiosemicarbazones and 2-methylthiosemicarbazones of other carbonyl compounds [10]. Thus, on the basis of the PMR, IR, and UV spectral data, it can be concluded that I-XIV in solutions are actually the syn isomers.

It is interesting that two bands of carbonyl absorption are present in the IR spectra of solutions of some of the compounds and that their relative intensities depend on the solvent. The observed phenomenon can hardly be explained by association. In the case of XIV, in which the formation of hydrogen bonds is excluded, both bands correspond to a free carbonyl group. Splitting of the

TABLE 2. Chemical Shifts of the Protons Attached to the Nitrogen Atoms in Dimethyl Sulfoxide Solutions

Compound	Conc., %	Temp., °C	NH (δ, ppm)		
			2'H	1-H	4'-H
I		26	12,58	11,20	9,04 8,64
	13,8	59	12,55	11,04	8,61
		81	12,56	10,93	8,55
	6,9	26	12,58	11,20	9,03 8,64
	3,5	26	12,58	11,23	9,03 8,64
II	13	26	12,43	—	8,90 8,60
		81	12,46	—	8,57
	6,5	26	12.44	—	9,04 8,65
	3,8	26	12,44	—	9,04 8,67
III	11	26	—	10,90	8,70 8,38
IV	18	26	—	—	8,74 8,40
V	12,2	26	12,65	11,22	9,23
VI	4	26	12,55	—	9,17 9,10
VII	14	26	13,40	11,23	—
VIII	3,9	26	13,44	—	—
IX	14,5	26	13,62	11,27	—
XV		26	11,51	—	8,1
	20	59	11,30	—	7,9
		81	11,20	—	7,8
	10	26	11,47	—	8,1
	5	26	11,44	—	8,1
XVI		26	9,89	—	7,94 7,51
	14,1	59	9,66	—	7,54
		81	9,58	—	7,50
	9,4	26	9,90	—	7,96 7,52
	4,7	26	9,90	—	7,96 7,52
XVII	20	26	11,05	—	—
XVIII	15,2	26	—	9,50	8,30 7,83
XIX	8,6	26	—	—	8,1—6,8 (+Ar)

TABLE 3. Positions and Intensities of the Absorption Maxima in the UV Spectra of Isatin β-Thiosemicarbazones in Alcohol

Compound	λ_{max}, nm	log ε	Compound	λ_{max}, nm	log ε
I	247,5	4,10	IX	246; 257,3	4,23; 4,22
	274	4,03		278	3,84
	370	4,31		361	4,33
II	242,5	3,96	X	245	4,24
	277	3,99		282,5	4,02
	367	4,31		353	4,26
III	255	4,28	XI	247,5; 253	4,30; 4,30; 4,25
	309	3,81		259	
	393	4,08		291	3,90
				385	4,03
IV	248	4,33	XII	246,5; 254	4,33; 4,32
	303	3,58		390	4,07
	393	3,95			
V	242, 248	4,11; 4,12	XIII	255	4,41
	279	3,97		410	3,81
	370	4,37			
VI	240	3,91	XIV	260	4,42
	281	3,85		400	3,80
	368	4,19			
VII	240	4,17	XVIII	250	4,21
	277, 279	3,95; 3,95		360	4,32
	352	4,18			
VIII	240	4,19	XIX	256,5	4,05
	280, 287	4,01; 4,01		364	4,30
	355	4,21			

TABLE 4. Absorption Frequencies of the C=O and N–H Groups in the IR Spectra of Isatin β-Thiosemicarbazones

Compound	CO, cm^{-1}[a]				NH, NH_2, cm^{-1}	
	in the crystalline state		in solutions		in mineral oil	in KBr pellets
	in mineral oil	in KBr pellets	in DMSO	in chloroform		
I	1682, 1710	1684[b] **1674**, 1699[c]	1694 1694	1710 1710	3180, 3274, 3346, 3428, 3530	3149, 3189, 3239, 3420 3158, 3262, 3327, 3418
II	1686	1679	1686	1698	3158, 3258, 3430	3145, 3249 3423
III	1737	1725	1734	[d]	3170, 3354	3167, 3243 3336
IV	1710, 1750	1689, 1740[e]	**1701**, 1737	1714, 1722	3220, 3380 3505	3328, 3449
V		1671, **1693**	1694	1706		3236
VI		1692	1685	1693		3223
VII	1707	1694	1694	1701	—	3167, 3193
VIII	1715	1692	1684	1684	—	—
IX		1682, **1695**	1694	1706		3153
X		1689	1683	1689		—
XI		1685, **1711**	1729	1725		3140, 3357
XII		**1688**, 1733	**1701**, 1723[e]	1715		3361
XIII		1697, **1725**	1727	1738		3297
XIV		**1701**, 1730[e]	**1702**, 1731	1703, 1722		—
XVIII	1715	1704	1711	[d]		3148, 3266, 3387
XIX	1729	1712	1700	1692		3473

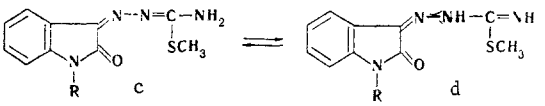
[a]The frequencies of the more intense bands are singled out by boldface numbers. [b]For a sample with mp 255°. [c]For a sample with mp 250°. [d]The substance did not dissolve in chloroform. [e]The band is of low intensity and appears as a shoulder.

carbonyl band is detected only for 2'-methyl derivatives, in which, according to data from three-dimensional models, the grouping attached to $N_{(2')}$ hinders the formation of the anti isomer. Hence, it can be assumed that this splitting is caused by the presence of conformers that possibly differ by rotation about the $N_{(1')}$–$N_{(2')}$ bond.

The structure of thiosemicarbazones I and II in the crystalline state also had to be reliably ascertained. The participation of the NH groups in the hydrogen bonds, according to the IR spectral data (Table 3), increases in the order 1-NH < 4'-NH_2 < 2'-NH. The syn form is probably also characteristic in the crystalline state for compounds in which the hydrogen atom in the 2' position is not substituted.

We have previously detected the presence of two carbonyl bands in the IR spectrum of I in the crystalline state [4]. However, a sample displaying only one carbonyl band was obtained under different crystallization conditions [2]. On the basis of these data, the first sample was considered to be a mixture of syn and anti isomers (**a**, **b**) [2, 11], and the second sample was considered to be the pure syn isomer (**a**) [2]. We have shown that, depending on the rate of crystallization, I and VII can be isolated as two samples that differ with respect to melting point and IR spectra in the crystalline state but are identical in solutions. Splitting of the carbonyl band is also observed in the crystalline state for IV, V, IX, and XI-XIII. A comparison of all the presented data makes it possible to assume that the presence of two carbonyl bands in the solid state is due not to isomerism but rather to the peculiarities of the crystal lattice and the formation of intermolecular hydrogen bonds. The decrease in the melting point when the hydrogen atoms in the NH groups are replaced by methyl groups also attests to the presence of these bonds.

In a previous study of the tautomerism of thiosemicarbazones I and II we used their S-methyl derivatives, XVIII and XIX, which are capable of existing in two tautomeric forms **c** and **d**, as fixed thiol forms.



XVIII R=H XIX R=CH_3

At the same time, the spectral characteristics of I-XIV make it possible to solve the problem of the tautomerism of XVIII and XIX when they are compared with the corresponding characteristics of the latter. Since the signal of the 2'-H proton at weak field is absent in the PMR spectra of the S-methyl derivatives in DMSO (Table 2), but the spectra do contain signals characteristic for the 4'-NH_2 group, structure **c** is more likely. When the polarity of the solvent decreases, the UV spectrum of XIX, in contrast to the spectra of I-XIV, undergoes a hypsochromic shift; this is possibly due to the formation of form **d**.

The presence in the IR spectrum of crystalline XIX of a distinct band above 3400 cm^{-1}, which according to our data is characteristic for the primary thioamide group of the thiosemicarbazone chain, makes it possible to assume that XIX exists in form **c** under these conditions.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in DMSO were recorded with a C-60 HI spectrometer with hexamethyldisiloxane (HMDS) as the external standard. The chemical shifts were measured on the δ scale with an accuracy up to 0.01 ppm. The IR spectra of 0.1 M solutions in DMSO (layer thickness 0.07 mm) and of $3 \cdot 10^{-4}$ M solutions in chloroform (layer thickness 14.4 mm) were recorded with a UR-10 spectrometer; in both cases, compensation was made for the absorption of the solvent. The DMSO was purified according to the specifications in [12], and its homogeneity was monitored by PMR spectroscopy. The UV spectra of alcohol solutions were recorded with an SF-8 spectrophotometer.

4-Methylthiosemicarbazide [13] and 2,4-dimethylthiosemicarbazide [13] were obtained from methyl methyldithiocarbamate [14], while 2,4,4-trimethylthiosemicarbazide [13] was obtained from tetramethylthiuramdisulfide [15].

Benzaldehyde 4,4-Dimethylthiosemicarbazone (XVII). A solution of 1.4 g (12 mmole) of 4,4-dimethylthiosemicarbazide [14] in 11 ml of 1 N HCl was added to a solution of 1.47 g (12 mmole) of benzaldehyde in 11 ml of alcohol. A greenish-white precipitate formed, and the temperature rose to 33°. After 0.5 h, the mixture was filtered, washed with 50% aqueous alcohol (three 1.5-ml portions), and dried at 105° to give 65.5% of silvery-white needles with mp 159° (from 40% aqueous alcohol) (mp 162° [9]).

Isatin β-Thiosemicarbazones. The synthesis of I, II [16], V [5], VII-X [6], and XVIII [5, 4, 11] was previously described; we presented the method for the preparation of III, IV, and XIX in [4] (also see [11]). Depending on the conditions of crystallization from aqueous alcohol, compound I was obtained as cotton-like crystals with mp 255° or needles with mp 250°. According to the IR spectra (KBr pellets), the two samples were identical to those described in [2]. Compound VII was similarly obtained as crystals with mp 230 or 217°.

N-Methylisatin 4-Methylthiosemicarbazone (VI), Isatin and N-Methylisatin 2,4-Dimethylthiosemicarbazones (XI, XII), and Isatin and N-Methylisatin 2,2,4-Trimethylthiosemicarbazones (XIII, XIV). These compounds were obtained via the following method. Aqueous solutions of equimolecular amounts of isatin (or N-methylisatin) and the appropriate thiosemicarbazide derivatives were mixed while boiling, 0.1 N HCl (0.08-0.31 ml per gram of diketone) was added, and heating was continued for 10-15 min. The mixtures were filtered, and the precipitates were washed with water and dried at 105°. The results of elementary analysis and the R_f values are presented in Table 1.

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