SEMICARBAZONES AND THIOSEMICARBAZONES OF THE HETEROCYCLIC SERIES.
43.* SPECTRA AND STRUCTURE OF ISATIN 2-THIOXOHYDRAZONES

A. B. Tomchin, K. N. Zelenin,
and G. A. Shirokii

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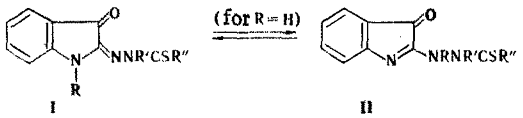
Isatin 2-thioxohydrazones formed in the reaction of isatin O-methyl ether with thioxohydrazines can be isolated in iminohydrazine and aminohydrazone tautomeric forms. The effect of the structure of the hydrazone fragment and the medium on the interconversions of the tautomers was investigated.

It has been previously established that the structure of isatin 2-thiosemicarbazone, for which tautomerism of the aminohydrazone–iminohydrazine type (Ia ⇄ IIa) is possible, in solution corresponds to formula IIa [2]. In the present research we investigated the structure and tautomeric transformations of isatin 2-thioxohydrazones in the crystalline state and in solution as a function of the nature of the thioxo fragment. To solve this problem we synthesized, in addition to I-IIa-h [2], I-IIi-o, and, for comparison, carbonylhydrazones III-IV [3].



I II

I, II a R=R'=H, R''=NH$_2$; b R=CH$_3$, R'=H, R''=NH$_2$; c R=H, R'=CH$_3$, R''=NH$_2$; d R=R'=H, R''=NHCH$_3$; e R=H, R'=CH$_3$, R''=NHCH$_3$; f R=R'=H, R''=N(CH$_3$)$_2$; g R=CH$_3$, R'=H, R''=N(CH$_3$)$_2$; h R=CH$_3$, R'=H, R''=NHCH$_3$; i R=R'=H, R''=NHPh; j R=CH$_3$, R'=H, R''=NHPh; k R=CH$_3$, R'=H, R''=NHC$_6$H$_4$OCH$_3$-*p*; *l* R=CH$_3$, R'=H, R''=NHC$_6$H$_4$COOC$_2$H$_5$-*p*; m R=R'=H, R''=Ph; n R=R'=H, R''=C$_6$H$_4$Cl-*m*; o R=R'=H, R''=SCH$_3$; III, IV a R''=NH$_2$; b R''=Ph

III IV

For comparison, we also synthesized compounds with fixed structures Ib,g,h,j-*l* and IIb. The fixed aminohydrazones differ from iminohydrazine IIb with respect to the lower frequency of the carbonyl group in the IR spectra, both in the crystalline state and in solution (Table 1), as a consequence of the formation of an intramolecular hydrogen bond. In addition, they are characterized by a bathochromic shift of the long-wave absorption band in the electronic spectra due to a longer conjugation chain (Table 2). Similar differences are also observed between the tautomers of the remaining compounds (Tables 1 and 2).

In the case of Ii-IIi we were able to isolate both tautomeric forms in the crystalline state. They have different melting points and IR spectra: the carbonyl band is found at 1679 cm^{-1} in the IR spectra of the first form, whereas it is found at 1707 cm^{-1} in the IR spectra of the second form (Table 1). An aminohydrazone structure should evidently be assigned to the first form, whereas an iminohydrazine structure should apparently be assigned to the second form. A similar phenomenon is observed for I-IId,e,f. Each of them was isolated in the form of two differently colored samples, of which one is a mixture of two forms, and the second contains only one of them – Ie, If, IId. Tautomers II predominate in the crystalline state in the case of I-IIa,c,o,p, whereas tautomers I predominate in the crystalline state in the case of I-IIf,m,n. Thus, depending on the conditions used in the preparation and recrystallization, isatin 2-thioxohydrazones may have a different

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*See [1] for communication 42.

S. M. Kirov Military Medical Academy, Leningrad 195009. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 355-359, March, 1979. Original article submitted July 18, 1978.

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TABLE 1. C=O Absorption Frequencies in the IR Spectra of Isatin 2-Acylhydrazones

Compound	$\nu_{C=O}$, cm^{-1} (KBr)	Compound	$\nu_{C=O}$, cm^{-1} KBr	$\nu_{C=O}$, cm^{-1} DMSO
Ib	1682[a]	IIa	1697	1710
Id	1679	IIb	1698	1712
Ie	1683	IIc	1696	1729
If	1662	IId	1702	—
Ig	1676	IIe	1708	1723
Ih	1660	IIf	1706	—
Ii	1679[b]	IIi	1707	1719
Ij	1680	IIn	—	1716
Ik	1680	IIo	1695	1716
Il	1680[c]	IVa	1703[d]	—
Im	1685	IVb	1725	—
In	1680			
Io	1670			
IIIb	1670[e]			

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a) At 1679 cm^{-1} in the case of DMSO. b) At 1660 cm^{-1} in the case of DMSO. c) The ν_{CO} band of the carbethoxy group is found at 1705 cm^{-1}. d) The ν_{CO} band of the side chain is found at 1735 cm^{-1}. e) The ν_{CO} band of the side chain is found at 1700 cm^{-1}.

TABLE 2. Long-Wave Absorption Maxima in the Electronic Spectra of Isatin 2-Hydrazones

Compound	λ_{max}, nm chloroform	λ_{max}, nm alcohol	λ_{max}, nm DMSO	Compound	λ_{max}, nm chloroform	λ_{max}, nm alcohol	λ_{max}, nm water[a]	λ_{max}, nm DMSO
Ia	—	—	524	IIa	456	462	460	462
Ib	522	525	525	IIb	455	457	460	460
If	528	—	528	IIc	—	456	—	—
Ig	532	532	532	IId	—	460	462	—
Ih	—	532	—	IIe	—	472	—	—
Ii	530	—	530	IIf	458	460	—	458
Ij	535	536	537	IIi	460	466	466	463
Ik	—	545	—	IIo	463	465	—	—
Il	—	538	—	IIp	440	445	—	445
Im	525	520[a]	522	IIq	—	—	—	442
In	525	508	540					
Io	—	516	535					
Iq	490	—	—					

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[a] In an aqueous buffer solution (pH 7.0).

structure in the crystalline state, and recrystallized samples of thiosemicabazones usually contain primarily tautomer I. As a rule, a yellow, orange, or reddish color of the crystals corresponds to predominance of form II, whereas a dark-cherry-red or crimson color corresponds to predominance of form I.

The I $\rightleftarrows$ II interconversions of the tautomers proceed readily at room temperature. For example, the electronic spectra of solutions of Ii and IIi in DMSO change in the course of 1.5 h up to establishment of equilibrium (Fig. 1). The presence in these spectra of isosbestic points, the linear relationship between the optical densities at two wavelengths, and the TLC data indicate that the investigated transformation occurs without the formation of any other products. The equilibrium concentrations of the tautomers were calculated from the optical densities at 463 and 530 nm (Table 3). Since the Ii $\rightleftarrows$ IIi transformation takes place too rapidly under these conditions for calculation, for Ii we used the optical density of fixed aminohydrazone Ij. Calculation at two wavelengths gives results that coincide.

Iminohydrazine tautomers II predominate in solutions of isatin 2-thiosemicarbazones.

In DMSO or in a mixture of DMSO with chloroform the transition from 2-semicarbazones IIIa-IVa or isatin 2-benzoylhydrazones IIIb-IVb to I-II leads to an increase in the equilibrium percentage of the aminohydrazone tautomer. Replacement of the terminal amino group in the 2-semicarbazone by a phenyl group affects the position of the tautomeric equilibrium in the same way. These data, as well as a comparison of the data for thioxohydrazones in DMSO, indicate that an increase in the electron-acceptor effect of the substituent attached to the terminal nitrogen atom shifts the equilibrium to favor aminohydrazone tautomer I. This tendency is particularly appreciable when the polarity of the solvent is sufficient. This conclusion is in agreement with the effect of acyl groups on the position of the tautomeric equilibrium in heterocyclic amines [4] and with data on the effect of structural factors on the stability of the "amidrazone" form for hydrazones of phthalazones [4]. In addition, in the compounds that we investigated the influence of C(X)R" groups on the strength of the intramolecular hydrogen bond [6] does not have a decisive effect on the tautomerism.

TABLE 3. Concentration of Aminohydrazone Form I in I $\rightleftarrows$ II Equilibrium Mixtures ($4 \cdot 10^{-5}$ M Solutions)

Compound	Concn., %		
	chloroform	chloroform–DMSO (3:1)	DMSO
Ia—IIa	0	16	25
If—IIf	28	30	30
Ii—IIi	30	45	47
Im—IIm	100	100	100
Io—IIo	0	20	100
Ip—IIp	0	0	0
Iq—IIq	100	49	0

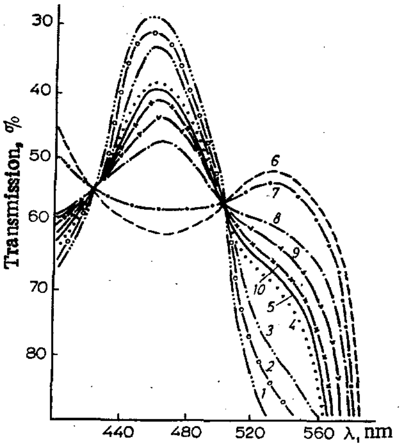

Fig. 1. Electronic spectra of $4 \cdot 10^{-5}$ M solutions of isatin 2-(4-phenyl)thiosemicarbazones Ii–IIi in DMSO at a layer thickness of 1 cm: 1) IIi after 3 min; 2)–5) after 15, 30, 60, and 90 min, respectively; 6) spectrum of fixed aminohydrazone Ij; 7) Ii 3 min after dissolving; 8), 9), 10), and 5) the same solution after 15, 30, 60, and 120 min, respectively.

The effect of the solvent on the position of the tautomeric equilibrium depends ambiguously on the structure of the hydrazone fragment. Thus, in contrast to benzoylhydrazones IIIb–IVb, in the thioxohydrazone series the percentage of aminohydrazone form I increases as the polarity of the solvent increases.

According to the data from the IR and PMR spectra, the percentage of the aminohydrazone tautomer is lower than the value from electronic spectral data. This discrepancy is due to the fact that the position of the I $\rightleftarrows$ II equilibrium depends markedly on the concentration of the solutions. According to the electronic spectral data for Ii–IIi, the equilibrium percentages of the aminohydrazone for $1.6 \cdot 10^{-5}$ and $4 \cdot 10^{-5}$ M solutions in chloroform are 42 and 30%, as compared with 87, 47, and 33% for $1.6 \cdot 10^{-5}$, $4 \cdot 10^{-5}$, and $1.6 \cdot 10^{-4}$ M solutions in DMSO. The equilibrium percentages of tautomer If are 49 and 35% for $4 \cdot 10^{-5}$ and $1.7 \cdot 10^{-4}$ M solutions of If–IIf in DMSO. Thus the equilibrium is shifted to favor the formation of iminohydrazine form II as the concentration of the solutions increases. This can be explained by its stabilization as a result of the formation of intermolecular hydrogen bonds. However, the ability of tautomers I to associate is reduced because of the formation in them of the intramolecular hydrogen bond characteristic for structures of a similar type [7].

EXPERIMENTAL

The method for the measurement of the spectra was presented in [8]. The yields, TLC data, and the results of elementary analysis of the new compounds are presented in Table 4.

For the measurement of aminohydrazone form I in the equilibrium mixture of tautomers I and II, the substances were dissolved rapidly in DMSO, the resulting $5 \cdot 10^{-3}$ M solutions were immediately diluted with the appropriate solvent to the above-indicated concentration, and the optical densities were measured with an SF-10 spectrophotometer until changes with time ceased. The optical densities of the $1.6 \cdot 10^{-4}$ M solutions were measured at a layer thickness of 0.5 cm, as compared with a layer thickness of 1 cm for $4 \cdot 10^{-5}$ M solutions and 5 cm for $1.6 \cdot 10^{-5}$ M solutions. The spectra of fixed tautomers Ib and IIb were used to calculate the percentage of the hydrazone form in solutions of Ia–IIa, and the spectra of Ij and IIb were used to calculate the percentage of the hydrazone form in solutions of If–IIf. In the case of I–IIm the solutions contain, in addition to tautomer Im, the product of its cyclization with the formation of a thiadiazine ring [8]; the amount of the latter increases with time and as the polarity of the solvent increases. Tautomer IIm is not observed in the solutions. In the calculation of the percentage of the hydrazone tautomer in a solution of Ii–IIi in a mix-

TABLE 4. Isatin 2-Thioxohydrazones

Compound	mp, °C	R_f[a]	Found, %		Empirical formula	Calc., %		Yield, %
			N	S		N	S	
Ih	183[b]	0,79 (A)	22,7	12,8	$C_{11}H_{12}N_4OS$	22,6	12,9	35
Ii	189[c]	0,07 (B)[d]	18,7	10,5	$C_{15}H_{12}N_4OS$	18,9	10,8	56
IIi	176	0,40 (B)	18,6	10,6	$C_{15}H_{12}N_4OS$	18,9	10,8	66
Ik	197[e]	0,91 (C)	16,8	9,4	$C_{17}H_{16}N_4O_2S$[f]	16,5	9,4	76

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a) Activity II aluminum oxide. The solvent systems are indicated in parentheses: A) chloroform–petroleum ether (7 : 1); B) benzene; C) benzene–methanol (10 : 1). b) From butanol. c) From propanol. d) Undergoes tautomeric conversion under TLC conditions. e) From DMF–water (2 : 1). f) Found: C 60.3; H 5.1%. Calculated: C 60.0; H 4.7%.

ture of chloroform and DMSO, the spectra of this compound in the indicated individual solvents were regarded as the spectra of the pure tautomers, since the absorption band of the other tautomer was not detected in them.

1-Methylisatin 2-(4-Methyl)thiosemicarbazone (Ih). Boiling solutions of 2.46 g (23 mmole) of 4-methylthiosemicarbazide in 30 ml of water and 5.45 g (23 mmole) of 1-methyl-2-phenylimino-3-oxindole in 75 ml of alcohol were mixed, and heating was continued for 2.5 h. The mixture was then cooled and filtered, and the filtrate was evaporated in vacuo to two-thirds of its original volume. The liberated reaction product was triturated with hexane (four 6-ml portions), and the precipitate was removed by filtration, washed with boiling water (three 6-ml portions) and alcohol (two 3-ml portions), dried in vacuo over phosphoric anhydride, reprecipitated from acetonitrile by the addition of hexane (the yield from reprecipitation was 64%), and crystallized from butanol to give Ih in the form of dark-cherry-red crystals.

Isatin 2-(4-Phenyl)thiosemicarbazone (Ii). A suspension of 12.4 g (79 mmole) of finely ground 4-phenylthiosemicarbazide in 150 ml of water and a solution of isatin O-methyl ether (obtained from 22.4 g of the silver salt of isatin) in 200 ml of benzene were mixed, and the mixture was shaken for 1 h. It was then filtered, and the solid material was washed with boiling water (three 10-ml portions), benzene (10 ml), and hexane (15 ml), and dried in vacuo to give the iminohydrazine tautomer of Ii in the form of fine orange crystals. A suspension of 15.4 g of this substance in 85 ml of benzene was heated to the boiling point, and the hot solution was filtered. The precipitate was washed with boiling benzene (10 ml) and pentane and dried in vacuo to give the aminohydrazone tautomer of Ii in the form of reddish crystals. According to the data from TLC and the UV and PMR spectra, these tautomers rapidly undergo interconversion in solution.

1-Methylisatin 2-[4-(p-Methoxyphenyl)]thiosemicarbazone (Ik). A solution of 1.64 g (7 mmole) of 1-methyl-2-phenylimino-3-oxindole and 1.37 g (7 mmole) of 4-(p-methoxyphenyl)thiosemicarbazide [9] in 30 ml of alcohol was refluxed for 45 min, after which it was allowed to stand overnight. It was then filtered, and the precipitate was washed with alcohol (5 ml) and dried. The reaction product (1.8 g) was crystallized successively from propanol–butanol (2.6 : 1) and dimethylformamide–water (2 : 1), washed with alcohol, and dried at 90 deg C to give Ik in the form of dark-cherry-red crystals.

LITERATURE CITED

1. A. B. Tomchin and G. A. Shirokii, Zh. Org. Khim., 14, 855 (1979).
2. A. B. Tomchin, G. A. Shirokii, and V. S. Dmitrukha, Khim. Geterotsikl. Soedin., No. 1, 83 (1976).
3. A. B. Tomshin, V. S. Dmitrukha, T. N. Timofeeva, and P. S. Pel'kis, Zh. Org. Khim., 10, 1519 (1974).
4. Yu. N. Sheinker, E. M. Peresleni, N. P. Zosimova, and Yu. I. Pomerantsev, Zh. Fiz. Khim., 33, 2096 (1959).
5. N. N. Bystrykh, "Synthesis, structure, and some properties of hydrazone and hydrazino derivatives of phthalazine," Author's Abstract of His Master's Dissertation, Kazan (1978).
6. N. B. Sokolova, "Synthesis and reactivities of some five-membered heterocyclic systems based on pyrrole, thiophene, and furan," Author's Abstract of Her Master's Dissertation, Lensovet Leningrad Technological Institute, Leningrad (1975).
7. A. B. Tomchin, I. S. Ioffe, A. I. Kol'tsov, and Yu. V. Lepp, Khim. Geterotsikl. Soedin., No. 4, 503 (1974).

8. A. B. Tomchin and G. A. Shirokii, Zh. Org. Khim., 13, 404 (1977).
9. M. Tishler, Croat, Chem. Acta, 28, 147 (1956).

BENZINDOLES.

17.* VILSMEIER REACTION IN THE ANGULAR TETRAHYDROBENZINDOLE SERIES

L. B. Shagalov, G. M. Ostapchuk,
A. D. Zlobina, V. N. Eraksina,
T. A. Babushkina, A. M. Vasil'ev,
and N. N. Suvorov

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The behavior of tetrahydro[4,5]- and tetrahydro[6,7]benzinodoles in the Vilsmeier reaction was investigated. It was established that the steric hindrance created by the cyclohexane ring condensed in the 4 and 5 positions has a substantial effect on the character of the reaction of tetrahydrobenzindoles with various N,N-disubstituted amines. A case of N-acylation in the investigated reactions is described. 3-Formyl-4,5,6,7-tetrahydro[4,5]- and 6,7,8,9-tetrahydro[6,7]-benzindoles were converted to the corresponding tryptamines.

The study of the Vilsmeier reaction in the case of angular benzindoles and their tetrahydro derivatives has made it possible to ascertain the effect of a condensed benzene ring on the reactivity of the 3 position. It has been previously established [2] that the yields of 3-acyl[4,5]- and 3-acyl[6,7]-benzindoles in the Vilsmeier reaction with various dimethylacylamines depend on both the electrophilicity of the attacking complex and on the distribution of electron density in the benzindole molecule. The electron density in the 3 position of [6,7]-benzindole is somewhat higher than in the case of the [4,5] isomer [3]. It follows from Table 1 that the yields of 3-acyl[6,7]benzindoles are somewhat higher than the yields of 3-acyl[4,5] isomers: this was manifested particularly clearly in the reaction with the least reactive compound, N,N-dimethylacetamide: in the case of [4,5]benzindole no reaction at all occurred. On the basis of the different reaction times for the isomeric benzindoles with dimethylbenzamide (Table 1), it was concluded that in the case of attack by a bulky complex the benzene ring condensed in the 4 and 5 positions evidently creates steric hindrance.

This conclusion is confirmed by the results of a study of the Vilsmeier reaction with tetrahydro[4,5]- and tetrahydro[6,7]-benzindoles, which differ little with respect to the magnitude of the electron density in the 3 position. For example, 6,7,8,9-tetrahydro[6,7]benzindole therefore reacts with N,N-diethylchloroacetamide under conditions similar to those for indole itself, and the yield of the corresponding 3-chloroacetyl derivatives is 60% in both cases. However, the yield of 3-chloroacetyl-4,5,6,7-tetrahydro[4,5]benzindole (V) falls to 42%, and this constitutes evidence for steric hindrance created by the hydrogenated benzene ring condensed in the 4 and 5 positions, as in the [4,5]benzindole series.

We have established that the reaction of tetrahydro[4,5]benzindole with N,N-dimethylbenzamide leads to two substances. Treatment of the reaction mixture with water precipitates IX, the IR spectrum of which does not contain absorption bands in the region of NH vibrations. When it was hydrolyzed with alcoholic alkali, it gave the starting tetrahydro[4,5]benzindole and benzoic acid. This enabled us to assign the N-benzoyl-4,5,6,7-tetrahydro[4,5]benzindole structure to IX. The PMR spectrum does not contain the signal of protons of an NH group but does contain signals of 2-H (7.26 ppm) and 3-H (6.64 ppm) protons with characteristic spin-spin coupling constant (SSCC) $J_{2,3} = 4.1$ Hz, as well as signals of 8-H and 9-H protons, which form an AB system with 7.00 ppm for 6-H and 7.90 ppm for 7-H, $J_{3,9} = 0.6$ Hz, $J_{8,9} = 8.00$ Hz, similar to what is observed for unsubstituted benzindole and its derivatives [3]. The considerable deshielding of the 7-H proton of the N-

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*See [1] for communication 16.

Institute of Biophysics of the Ministry of Public Health of the USSR, Moscow 123182. D. I. Mendeleev Moscow Institute of Chemical Technology, Moscow 125047. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 360–365, March, 1979. Original article submitted March 14, 1978.