INVESTIGATION OF THE REACTION OF 4-METHYL-7-AZAINDOLINE WITH ACETIC AND TRIFLUOROACETIC ACIDS IN METHYLENE CHLORIDE BY PMR AND IR SPECTROSCOPY

G. G. Dvoryantseva, T. N. Ul'yanova,
Yu. N. Sheinker, D. M. Krasnokut-skaya,
and L. N. Yakhontov

UDC 547.759.3:543.422.25.4

The relative position of the equilibria of proton transfer via a hydrogen bond and dissociation of the H complexes to give solvated ions was determined on the basis of a study of the dependence of the chemical shifts and the spin–spin coupling constants of aromatic protons in the PMR spectrum of 4-methyl-7-azaindoline on the acetic and trifluoracetic acid concentrations in methylene chloride. The protolytic equilibrium in the amine–CF_3COOH system is shifted completely to favor H complexes of the ion pair type when the reagent ratio is nearly equimolar. A molecular complex ⇄ ion pair equilibrium is observed in the reaction with CH_3COOH under the same conditions. The results were confirmed by measurement of the IR spectra of the investigated systems. The enthalpy ($-\Delta H = 2.9 \pm 0.7$ kcal/mole) and entropy ($-\Delta S = 8.0 \pm 2$ kcal/mole·deg) of proton transfer via a hydrogen bond were determined from the PMR spectra measured at +25° to −50°.

The great significance of protonation processes in the mechanism of the action of various medicinal preparations is well known. Thus, for example, the pharmacological activity of tertiary amines – cholinomimetics and cholinolytics – changes as the pH changes in a manner parallel to the degree of ionization of the substances; similar relationships are also observed for preparations that affect adreno- and serotonin-reactive systems [1]. Acid–base reactions in aqueous and nonaqueous media in many respects determine the penetration of biologically active substances through cell membranes [2].

According to modern concepts, an acid–base reaction in the general case proceeds through a series of successive equilibria in which solvent molecules participate:

$$B + HA \underset{1}{\rightleftharpoons} B\ldots HA \underset{2}{\rightleftharpoons} B^+H\ldots A^- \underset{3}{\rightleftharpoons} B^+H + A^-$$

In recent papers, data on the dipole moments and IR spectra (for example, see [3, 4]) of acid–amine systems are discussed from the point of view of the effect of the donor–acceptor properties of the interacting components on the position of equilibrium (2). It is assumed that in media of low polarity the dissociation of ion pairs does not make an appreciable contribution to the constant of proton transfer via a hydrogen bond [4]. It follows from data on the electrical conductivities and dissociation constants of H complexes [5] that this assumption is valid for protolytic reactions that occur in nonionizing media ($\varepsilon < 4$). As the polarity of the solvent increases, the role of equilibrium (3) may increase substantially. In this connection, in studying the transfer of a proton via a hydrogen bond in media with $\varepsilon > 4$ it is necessary to estimate the relative positions of equilibria (2) and (3). The solution of this problem within the framework of the most practicable method (IR spectros-

---

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 76-82, January, 1976. Original article submitted November 25, 1974.

TABLE 1. PMR Spectral Parameters of 4-Methyl-7-azaindoline in Various Solvents

Medium	ε	Chemical shifts, δ, ppm					SSCC, J, Hz	
		2-H	3-H	4-H	5-H	6-H	23*	56
$CDCl_3$	4,8	3,59	2,96	2,14	6,32	7,70	16,7	5,6
CH_2Cl_2	8,9	3,58	2,97	2,16	6,31	7,63	16,7	5,5
$(CD_3)_2CO$	21,5†	3,55	2,92	2,06	6,25	7,58	16,7	5,5
CD_3OD	33,6†	3,56	2,95	2,14	6,32	7,51	16,7	5,6
80% CD_3OD		3,57	2,95	2,15	6,37	7,55	16,7	5,6
CH_3CN	37,5	3,52	2,93	— †	6,29	7,59	16,6	5,5
CH_3COOH	6,1	3,89	3,06	— ‡	6,43	7,51	16,7	6,8
CF_3COOH	8,4	4,05	3,25	2,37	6,62	7,36	16,9	6,8

---

*$J_{23} = J_{cis} + J_{trans}$.

†These are the ε values for the corresponding nondeuterated solvents.

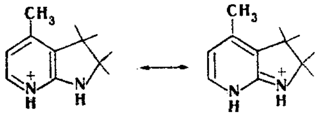
‡The signal of the methyl group is overlapped by the signal from the solvent.

copy) is difficult because of the closeness of the optical properties of H complexes of the ion pair and dissociated ion types. In an investigation of the protonation of 5-azaindole derivatives in nonaqueous media by PMR spectroscopy [6] we observed anomalies in the character of the curves of the dependence of the chemical shifts of the protons of the heteroaromatic ring on the acid concentration. The results made it possible to assume that the PMR method may prove to be effective in a study of the individual steps of the protonation of such systems.

In order to determine the possibility of the application of PMR spectroscopy to the study of the relative positions of equilibria (2) and (3), in the present research we investigated the dependence of the chemical shifts of the protons and spin–spin coupling constants of 4-methyl-7-azaindoline on the trifluoroacetic and acetic acid concentrations in methylene chloride. The results are compared with IR spectroscopic data for these systems.

The parameters of the PMR spectra of 4-methyl-7-azaindoline in various media are presented in Table 1.

As seen from Table 1, the proton in the α position relative to the nitrogen atom of the pyridine ring (6-H) in the neutral molecule displays the maximum sensitivity to the effects of the medium and, consequently, to the formation of hydrogen bonds. On passing from the neutral molecule to the cation, the changes in the parameters of the PMR spectrum, particularly, the shift of the 6-H signal to weak field, are similar to those observed on protonation under similar conditions of 5-azaindoline [6] and correspond to the addition of a proton to the pyridine nitrogen atom to give a conjugate ion of the amidinium type:



In contrast to the chemical shifts, the J_{56} spin–spin coupling constant (SSCC) in both the neutral and protonated forms is practically independent of solvation effects and is sensitive only to proton transfer. The dependences of the chemical shifts of the protons of the two-ring system and the J_{56} constant on the molar CF_3COOH concentration in CH_2Cl_2 are presented in Fig. 1. The linear portions of the $\nu_i = f(C_{AH})$ graphs observed in this system for $C_{AH} \geqslant$ 10 mole% correspond to a shift of the protolytic equilibrium to the right and characterize the parameters of the spectrum of the monocation. A distinct minimum is observed near an equimolar reagent ratio ($C_{AH} \approx 2$ mole%) on the curve for the proton in the α position relative to the cationoid center (6-H). The character of the $\nu_6 = f(C_{AH})$ curve does not correspond to a simple protolytic equilibrium and can be explained by the formation of an acid–amine H complex in which the change in the shielding of the α proton ($\Delta\nu_6$) exceeds the difference between the chemical shift of this proton in the neutral molecule and in the

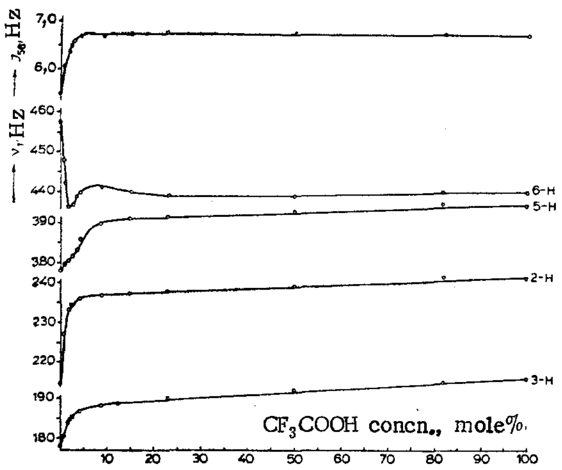


Fig. 1. Dependence of the J_{56} constant and the chemical shifts (ν_i) of the protons of 4-methyl-7-azaindoline on the CF_3COOH concentration in CH_2Cl_2.

cation ($\Delta\nu_6^{B+H}$). Inasmuch as this sort of effect is not observed on the curve for the protons remote from the protonation center, it may be assumed that it is due mainly to the steric effect of the electrical field and the magnetic anisotropy of the carboxyl group in the H complex. This effect falls rapidly as the distance between the proton under consideration and the center of the magnetic and electrical dipole increases. The dissociation of H complexes to give solvated ions therefore leads to a decrease in the relative chemical shift ($\Delta\nu_6$) to ($\Delta\nu_6^{B+H}$). The position of the extreme point on the $\nu_6 = f(C_{AH})$ curve determines, to a first approximation, the maximum concentration of acid at which equilibrium (3) is shifted more to the left to a considerable degree.

The problem of the type of complex formed, i.e., regarding the position of equilibrium (2), can be examined on the basis of a comparison of the dependence of the $\Delta\nu_6$ and ΔJ_{56} values on the reagent molar ratio (C_{AH}/C_B). Inasmuch as the steric effects of polar and magnetically anisotropic groups do not affect the SSCC of aromatic protons, the J_{56} values should not change on passing from complexes of the ion pair type to dissociated ions. Consequently, regardless of the position of equilibrium (3), the linear portion of the $\Delta J_{56} = f(C_{AH}/C_B)$ graph, where ΔJ_{56} = const, determines the range of C_{AH}/C_B values over which equilibrium (2) is shifted completely to the left. If the position of the minimum on the $\Delta\nu_6 = f(C_{AH}/C_B)$ curve corresponds to ΔJ_{56} = const, this constitutes evidence for a shift in the system of the equilibria of the protolytic reaction primarily to favor the formation of an ion pair. Precisely this situation occurs in the 4-methyl-7-azaindoline–CF_3COOH system (Fig. 2). The J_{56} constant reaches a constant value (ΔJ_{56} = const) at the same reagent ratio ($C_{AH}/C_B \approx 1.1$) at which a minimum is observed on the $\Delta\nu_6 = f(C_{AH}/C_B)$ curve. The dependence of the relative chemical shift on the acid–amine molar ratio for $1.1 < C_{AH}/C_B < 2.5$ is determined by the position of equilibrium (3). Linear extrapolation of this dependence to $C_{AH}/C_B = 1$ makes it possible to evaluate the chemical shift of the α proton of the investigated heterocycle in the H complex of the ion pair type ($\Delta\nu_6^{pt}$).

An increase in the distance between the atoms of the proton donor and proton acceptor may be observed not only during dissociation but also on passing from complexes of the ion pair type to acid–amine molecular complexes [7]. Consequently, a shift in equilibrium (2) should lead to a decrease in the $\Delta\nu_6$ relative chemical shift. In the case of a fixed proton acceptor, equilibrium (2) should be shifted to the left as the proton-donor strength decreases [3, 4]. In fact, on passing from CF_3COOH to CH_3COOH the minimum on the $\Delta\nu_6 = f(C_{AH}/C_B)$ curve is shifted to the higher-acidity region ($C_{AH}/C_B \approx 1.5$), and its depth decreases sharply (Fig. 2). The linear portion of the $\Delta J_{56} = f(C_{AH}/C_B)$ graph is also observed at higher acid concentrations (ΔJ_{56} = const when $C_{AH}/C_B \geq 3$). The results constitute evidence for the presence in the 4-methyl-7-azaindoline–CH_3COOH system of two types of H complexes in equilibrium (2). This conclusion is confirmed by the change in the dependence of $\Delta\nu_6$ and ΔJ_{56} on the acid–amine molar ratio at various temperatures (Fig. 2). A decrease in the temperature to –50° shifts the minimum on the $\Delta\nu_6 = f(C_{AH}/C_B)$ curve to the lower-acidity region, during which its depth increases. Both dependences approach the corresponding curves measured for the amine–CF_3COOH system. Consequently, a decrease in the temperature shifts equilibrium (2) to favor the H complex with proton transfer. A similar effect of the temperature on the position of equilibrium (2) was also observed in other acid–amine systems from IR spectra [4].

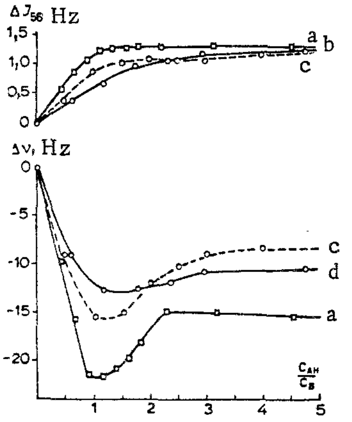


Fig. 2. Dependence of the relative chemical shift $\Delta\nu_6$ and the relative ΔJ_{56} constant on the 4-methyl-7-azaindoline–trifluoroacetic acid molar ratio at 25° (a) and on the 4-methyl-7-azaindoline–acetic acid molar ratio at 25° (b) and –50° (c) in CH_2Cl_2.

The data obtained by the PMR method are in complete agreement with the results of a measurement of the IR spectra of the systems under consideration at various reagent molar ratios in CH_2Cl_2 (Fig. 3). In the investigation of the acid–base reaction, the 1450-1800 cm^{-1} region, in which bands of stretching vibrations of the carbonyl group of the acids, bands of the skeletal vibrations of the pyridine ring in azaindoles [8] and aminopyridines [9], and bands of the corresponding ionic forms are observed, was most significant.

A comparative examination of the protonation curves and the IR spectra of the individual components and of acid–amine systems makes it possible to isolate, in this region, the vibrational frequencies that are sensitive only to proton transfer and are sufficiently characteristic for the molecular and ionic forms of the H complexes (Table 2). The presence of three absorption bands at 1490-1497, 1588-1592, and 1620-1626 cm^{-1} is characteristic for the spectrum of the neutral 4-methyl-7-azaindoline molecule. Neither solvation effects nor the formation of molecular complexes with the investigated acids has any practical effect on the position of these bands. A spectral sign of the formation of a molecular complex is the presence in the spectrum of the system when $C_{AH}/C_B \leq 1$ of a band of stretching vibrations of the carbonyl group of an acid, which is usually close in frequency to the band of the acid dimer in the same solvent. The bands of skeletal vibrations of a protonated heterocycle (at $\sim$ 1540, 1630, and 1650 cm^{-1}) were identified from spectra measured for a C_{AH}/C_B value corresponding, with respect to the $\Delta\nu_6 = f(C_{AH}/C_B)$ curve, to a complete shift of the protolytic equilibrium to the right. The assignment was confirmed by measurement of the spectra of acid–amine systems in CD_3OD and 80% CD_3OD.

Absorption in the region of $\nu_{C=O}$ vibrations of the free acid (1780-1810 cm^{-1}) is absent in the spectrum of the 4-methyl-7-azaindoline–trifluoroacetic acid system in CH_2Cl_2 when $C_{AH}/C_B \leq 1$, and an intense band of a carboxylate ion (ν_{as}) appears at 1679 cm^{-1}. An increase in the acid concentration is accompanied by a decrease in the intensity of the bands of the base at 1494, 1592, and 1623 cm^{-1}, which disappear completely in excess acid. The intensity of the band of a protonated heterocycle at 1543 cm^{-1} increases simultaneously. Two other bands of the cation (1637 and 1653 cm^{-1}) are overlapped to a considerable degree by the band at 1676 cm^{-1} and are observed as inflections on its low-frequency wing. In conformity with the protonation curve (Fig. 2), these data constitute evidence that the protolytic equilibrium is shifted completely to favor an H complex of the ion pair type during reaction of the investigated base with CF_3COOH in methylene chloride when $C_{AH}/C_B \leq 1$. The presence of weak bands of the base in the IR spectrum of this system in the case of an equimolar reagent ratio and the small shift in the minimum on the $\Delta\nu_6 = f(C_{AH}/C_B)$ curve to the $C_{AH}/C_B > 1$ region may be explained by the formation of complexes of the $(AHA^-)B^+H$ composition, in addition to complexes of the A^-HB^+ composition.

Bands of skeletal vibrations of the base at 1502, 1592, and 1622 cm^{-1} and of stretching vibrations of the carbonyl group of the acid at 1705 cm^{-1}, which can be assigned to the acid–amine molecular complex, are observed in the spectrum of the 4-methyl-7-azaindoline–acetic acid system in CH_2Cl_2 in excess amine in the case of an equimolar reagent ratio. In addition, bands of the cation at 1545 and 1634 cm^{-1} and of the anion at 1672 cm^{-1} in the H complex of the ion pair type appear. A change in the acid concentration does not lead to a shift in the frequencies of the vibrations of the base bonded to it but brings about a change in the ratio of the intensities of the bands of the molecular and ionic forms. In conformity with

TABLE 2. Characteristic Frequencies in the IR Spectra of H Complexes of 4-Methyl-7-azaindoline with Acetic and Trifluoroacetic Acids at 1450-1800 cm^{-1}

Medium	B	CF_3COOH		CF_3COOH		
		A—H	$B^+H...A^-(B^+H+A^-)$	AH	B...HA	$B^+H...A^-(B^+H+A^-)$
$CDCl_3$	1490 m	1783 s	1541	1714s	1490	1543*
	1590 s	1803 sh	1636sh	1758m	1590	1635
	1621 s		1654sh		1621	1655 sh
			1676		1705	1671
CH_2Cl_2	1494 m	1783 s	1543	1717 s	1502	1545*
	1592 s	1805 s	1637 sh	1764 m	1592	1636
	1623 s		1653 sh		1622	1672
			1676		1705	
CH_3CN	1492 m	1751 sh	1555	1730 m	1492	1535
	1588 s	1797 s	1635 sh	1757 s	1590	1631
	1620 s		1654		1620	1670
			1678		1712	
CD_3OD	1497 m	1776 s	1540	1713s		1540 sh
	1588 s	1793 s	1629			1571
	1626 s		1656			1627
			1676			1652
80% CD_3OD	1495 m	1679 s	1540	1687 sh		1540 sh
	1588 s	1772 m	1624	1712 s		1562
	1625 s		1652 sh			1625
			1672			1650

---

*In excess acid the band is overlapped with the ν_{as} (COO^-) band of dissociated acetate ions.

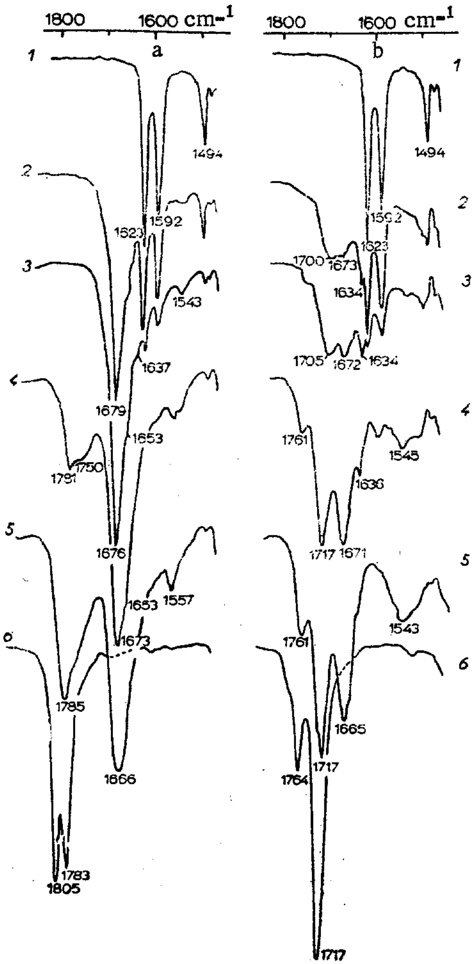


Fig. 3. IR spectra of solutions of 4-methyl-7-azaindoline systems with trifluoroacetic (a) and acetic (b) acids in CH_2Cl_2. The amine concentration (C_B) was 0.13 mole/liter, and the acid concentrations (C_{AH}) were as follows: 1) 0; 2) 0.065; 3) 0.13; 4) 0.26; 5) 0.30 mole/liter; 6) $C_B = 0$; $C_{AH} = 0.26$ mole/liter. The cuvette was a CaF_2 cuvette, and the layer thickness was 0.05 mm.

TABLE 3. Equilibrium Constant and Enthalpy and Entropy of Proton Transfer via a Hydrogen Bond

Temperature °C	$\Delta\nu_6^{H}$, гц	$\Delta\nu_6^{pt}$ гц	K_{pt}	$-\Delta H$, mole/kcal	$-\Delta S$, mole • deg
+25	11,9	18,6	1,8±0,2	2,9±0,7	8,0±2
−50	16,8		9,4±2,0		

the PMR data, this indicates the existence of equilibrium (2). At acid concentrations corresponding, with respect to the protonation curve, to a shift in equilibrium (3) to the right, the intensity of the absorption at 1540-1550 cm^{-1} in the IR spectra of the systems increases, and this is associated with the appearance of dissociated acetate ions [in CD_3OD and 80% CD_3OD the ν_{as} (CH_3OO^-) band is observed at 1560-1570 cm^{-1}]. The band of protonated heterocycles that appears in the same region is characterized by a substantially smaller width and lower intensity (Fig. 3). A comparison of the intensities of the bands at 1672 and 1540 cm^{-1} when $C_{AH}/C_B \leq 1$ (Fig. 3, spectrum b), in agreement with the PMR data, makes it possible to disregard the contribution of equilibrium (3).

The equilibrium constant and the enthalpy and entropy of proton transfer via a hydrogen bond were calculated from the chemical shifts of the α proton of the heterocycle in the PMR spectra of an equimolar mixture of the amine and CH_3COOH at +25° to −50° (Table 3).

The percentage of the H complex with proton transfer (X) was calculated from the equation

$$\nu_6^H = X\nu_6^{pt} + (1 - X)\nu_6^M,$$

where ν_6^H is the chemical shift (in Hz) observed in the spectrum of the complex at a given temperature, ν_6^M is the chemical shift of the molecular form determined from the spectrum of a 0.3 M solution of the free base in CH_2Cl_2, and ν_6^{pt} is the chemical shift in the ion pair estimated from the spectrum of the amine—CF_3COOH system when $C_{AH}/C_B = 1$ in the same medium with allowance for a correction for the effect of the anion. The correction was calculated as the difference in the chemical shifts of the cation in CH_2Cl_2/CF_3COOH and CH_2Cl_2/CH_3COOH solutions on the linear portions of the $\Delta\nu_6 = f(C_{AH}/C_B)$ graphs. The enthalpy found ($-\Delta H$ = 2.9 ± 0.7 kcal/mole) is in reasonable agreement with the value obtained from the IR spectra of the pyridine—dichloroacetic acid system ($-\Delta H$ = 3.6 ± 0.8 kcal/mole [10].

EXPERIMENTAL

4-Methyl-7-azaindoline was synthesized and characterized as described in [11]. The PMR spectra of 0.3 M solutions of the compounds were measured with a C-60 HL spectrometer with tetramethylsilane as the internal standard. Within the limits of the approximation adopted for evaluation of the ν_6^M and ν_6^{pt} values, the accuracy in the determination of the proton transfer constants is limited by the accuracy in the measurement of the resonance frequencies (± 0.2 Hz). The errors in the determination of the thermodynamic functions were calculated from standard formulas [12]. The IR spectra of solutions of the compounds were measured with a Perkin—Elmer 457 spectrometer.

LITERATURE CITED

1. I. V. Komissarov, Elements of the Theory of Receptors in Molecular Pharmacology [in Russian], Moscow (1969), pp. 147 and 169.
2. A. Albert, Selective Toxicity. The Physico-Chemical Basis of Therapy, Halsted Press, New York (1973).
3. L. Sobczyk and Z. Pawelka, Rocz. Chem., 47, 1523 (1973).
4. G. V. Gusakova, G. S. Denisov, and A. L. Smolyanskii, Zh. Prirodn. Soedin., 16, 320, 503 (1972).
5. L. I. Derevyanko and M. N. Tsarevskaya, Zh. Obshch. Khim., 42, 36 (1972).
6. G. G. Dvoryantseva, T. N. Ul'yanova, Yu. N. Sheinker, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., 767 (1973).
7. P. Shuster, Z. Chem., 13, 41 (1973).

8. R. E. Willette, Advances in Heterocyclic Chemistry, 9, 27 (1968).
9. E. Spinner, J. Chem. Soc., 3119 (1962).
10. G. V. Gusakova, G. S. Denisov, A. L. Smolyanskii, and V. M. Shraiber, Dokl. Akad. Nauk SSSR, 193, 1065 (1970).
11. L. N. Yakhontov, M. Ya. Uritskaya, and M. Ya. Rubtsov, Zh. Obshch. Khim., 34, 1449 (1964).
12. A. Hammett, Physical Organic Chemistry, McGraw-Hill, New York (1940).

SEMICARBAZONES AND THIOSEMICARBAZONES OF THE HETEROCYLIC SERIES

XXXVIII.* AMINOHYDRAZONE–IMINOHYDRAZINE TAUTOMERISM OF ISATIN 2-THIOSEMICARBAZONE AND ITS ALKYL DERIVATIVES

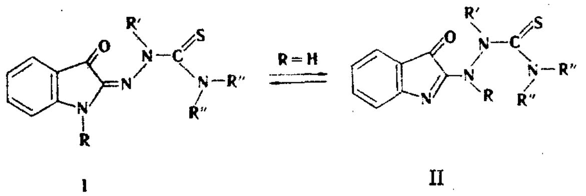
A. B. Tomchin, G. A. Shirokii,
and V. S. Dmitrukha

UDC 547.754.756:543.422.6:541.621

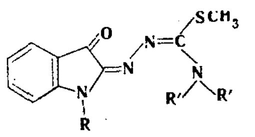
Isatin 2-thiosemicarbazone and its derivatives with one methyl group attached to the nitrogen atoms of the side chain exist in solution primarily in the iminohydrazine tautomeric form. Further substitution of the hydrogen atoms attached to the nitrogen atom in the primary thioamide group or replacement of the hydrogen atom attached to the sulfur atom by a methyl group promotes the formation of the aminohydrazone tautomer.

The structure of isatin 2-thiosemicarbazone has not been studied. Structure Ia with a six-membered chelate ring was assigned to it without proof [2], whereas isatin 2-thiosemicarbazone does not have antivirus activity, a necessary condition for which has been assumed to be the formation of a structure with an intramolecular hydrogen bond (IHB) [3].

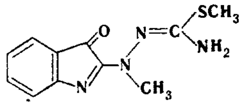
In analogy with isatin 2-benzoylhydrazones [4], aminohydrazone–iminohydrazine tautomerism Ia⇄IIa is possible in isatin 2-thiosemicarbazone [5].



I–II a R=R′=R″=H; b R=CH₃, R′=R″=H; c R=R″=H, R′=CH₃; d R=R″=CH₃, R′=H; e R=R′=H, R″=H, CH₃; f R=R′=H, R″=CH₃, CH₃; g R=H, R′=CH₃, R″=H, CH₃



III



IV

III a R=R′=H; b R=H, R′=CH₃, CH₃; c R=R′=CH₃

---

*See [1] for communication XXXVII.

Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 83-88, January, 1976. Original article submitted February 7, 1975.