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SEMICARBAZONES AND THIOSEMICARBAZONES OF THE HETEROCYLIC SERIES

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

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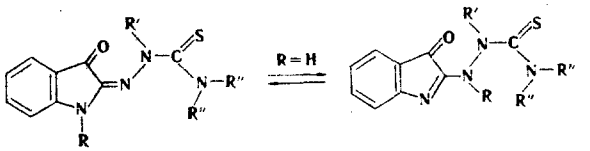
Isatin 2-thiosemicarbazone and its derivatives with one methyl group attached to the nitrogen atoms of the side chain exist in solution primarily in the iminohydrazine tautomeric form. Further substitution of the hydrogen atoms attached to the nitrogen atom in the primary thioamide group or replacement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

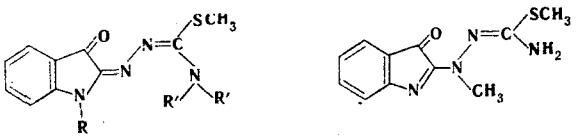
The structure of isatin 2-thiosemicarbazone has not been studied. Structure Ia with a six-membered chelate ring was assigned to it without proof [2], whereas isatin 2-thiosemicarbazone does not have antivirus activity, a necessary condition for which has been assumed to be the formation of a structure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

I—II a R=R′=R″=H; b R=CH_3, R′=R″=H; c R=R″=H, R′=CH_3; d R=R″=CH_3, R′=H; e R=R′=H, R″=H, CH_3; f R=R′=H, R″=CH_3, CH_3; g R=H, R′=CH_3, R″=H, CH_3



III IV

III a R=R′=H; b R=H, R′=CH_3, CH_3; c R=R′=CH_3

*See [1] for communication XXXVII.

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TABLE 1. Isatin 2-Thiosemicarbazone and Its Methyl Derivatives

Compound	mp, °C	Crystallization solvent	Empirical formula	Found, %		Calc., %		UV spectral data (alcohol solutions)		TLC data on activity II Al_2O_3		Yield, %
				N	S	N	S	λ_{max}, nm	lg ε	R_f	eluent	
IIb	217	Ethanol	$C_{10}H_{10}N_4OS$	23,5	13,4	23,9	13,7	267 344 456	4,38 4,11 3,96	0,44	Chloroform—methanol 95 : 1	11*
Ic—IIc	266	†	$C_{10}H_{10}N_4OS$	23,5	13,9	23,9	13,7	257 295 340 456	4,47 3,82 3,83 3,85	0,34	Chloroform—methanol 98 : 1	15*
Id	195	Ethanol	$C_{12}H_{14}N_4OS$	21,7	12,6	21,4	12,2	275 342 522	4,28 4,13 3,79	0,93 0,83	Benzene—ethanol, 7,5 : 1; benzene—ethanol 10 : 1	53
Ie—IIe	211	n-Propyl alcohol	$C_{10}H_{10}N_4OS$	23,7	13,3	23,9	13,7	242 267 340 460	4,12 4,27 4,13 3,99	0,71	Benzene—methanol 5 : 1	60
If—IIf	182	Decomposed during crystallization	$C_{11}H_{12}N_4OS$	22,2	12,9	22,6	12,9	242 265 337 460 500	4,27 4,23 4,06 3,61 3,61	0,54	Benzene—ethanol 10 : 1	56* 63 ‡
Ig—IIg	186	Ethanol	$C_{11}H_{12}N_4OS$	22,5	12,7	22,6	12,9	261 336 476	4,47 4,06 3,69	0,75 0,40	Benzene—ethanol 10 : 1; Chloroform—methanol 99 : 1	40*
IIIb	178,5	n-Propyl alcohol	$C_{12}H_{14}N_4OS$	21,6	12,5	21,4	12,2	237 272 358 481	4,09 4,12 4,07 4,15	0,58	Benzene—ethanol 10 : 1	46
IIIc	118	Reprecipitated from benzene solution with ether	$C_{13}H_{16}N_4OS$	20,2	12,0	20,3	11,6	236 279 360 507	4,16 4,14 4,05 3,96	0,49	Benzene—methanol 1 : 1	14
IV	209	Ethanol	$C_{11}H_{12}N_4OS$	22,8	13,2	22,6	12,9	268 335 410 478	4,69 4,06 3,48 3,22	0,29	Benzene—ethanol 7,5 : 1	87

*With respect to the silver salt of isatin.
†A triazine ring formed during crystallization.
‡From VI.

TABLE 2. PMR Chemical Shifts of the Protons Attached to Nitrogen Atoms

Compound	Solvent	Concn., M	Temp., °C	NH, δ, ppm		
				H-2′	H-1, H-1′	H-4′
Ia—IIa	DMSO	0,8	26	10,75	10,65	8,82; 8.09
			58		10,62	8,22
			85		10,30	7,86
Ib	DMSO	0,1	26	12,07	—	8,77; 8,44
			58	12,24	—	8,55
			85	12,16	—	8,26
IIb	DMSO	0,15	39	10,44	—	8,38
Ic—IIc	DMSO	0,5	39	—	10,52	7,66—7,01*
Id	DMSO	0,3	39	—	10,42	—
IIIa	Hexamethylphosphoric triamide	0.35	39	—	10,58	7,52—7,01*
IIIb	Hexamethylphosphoric triamide	0,15	39	—	10,60	—

*Overlapped by the signals of aromatic protons.

To solve the problem of the structure of isatin 2-thiosemicarbazone we compared it with fixed structures Ib [6] and IIb and also with Ic-IIc in which an IHB is excluded. In addition, we studied isatin 2-thiosemicarbazone derivatives I-IId-g, which are substituted at the terminal nitrogen atom, and S-methyl derivatives IIa-c [6] and IV, obtained by methylation of the corresponding thiosemicarbazones (Table 1).

The electronic spectrum of isatin 2-thiosemicarbazone [λ_{max}, nm (log ε): 248 (4.05), 2.74 (4.26), 348 (4.02), and 462 (3.97)] in polar and nonpolar solvents is similar to the spectrum of homologs IIb,c but differs from the spectrum of derivative Ib [λ_{max}, nm (log ε): 282 (4.28), 365 (3.90), and 525 (3.69)] with respect to a hypsochromic shift of the longwave absorption band. The PMR spectrum of isatin 2-thiosemicarbazone contains two close NH signals, the positions of which depend markedly on the temperature, whereas in the spectrum of Ib the chemical shift of the single NH proton is appreciably lower, and its position remains almost constant as the temperature changes, i.e., it corresponds to a proton participating in the formation of an IHB (Table 2). Thus unsubstituted isatin 2-thiosemicarbazone in solution exists completely in iminohydrazine form IIa, which does not contain a quasiaromatic chelate structure, in contrast to isatin 2-benzoylhydrazones, which we previously investigated in [4]. This difference may be explained by the fact that in the latter compounds the substituent attached to the imine nitrogen atom of the hydrazone fragment reduces the electron density on this atom more markedly and reinforces the IHB, which stabilizes the aminohydrazone tautomer.

According to the spectral data, predominance in solution of the iminohydrazine tautomeric form is characteristic for all of the isatin 2-thiosemicarbazones with unsubstituted indole nitrogen atoms. Only the dimethyl derivative of isatin 2-thiosemicarbazone (If-IIf), the electronic spectrum of which contains longwave absorption bands of both forms — in DMSO at 466 (If) and 500 nm (IIf) (their intensity ratio depends on the nature of the solvent) — constitutes an exception to this. The shift in the tautomeric equilibrium here is probably explained by stabilization of the IHB of the hydrazone structure by stubstitution of both hydrogen atoms in the primary thioamide group. As in the case of isatin 3-thiosemicarbazones [7], the effect of the substituent in this position is nonadditive and is evidently due to steric factors. In fact, only iminohydrazine tautomers IIe and IIg are observed in solutions of compounds with only one methyl group attached to the primary thioamide nitrogen atom.

A comparison of the electronic spectra of S-methyl derivatives IIIa [λ_{max}, nm (log ε): 264 (4.47), 336 (4.06), and 476 (3.69)] and IIIb with fixed tautomeric structures IIIc and IV provides evidence that indole-nitrogen-atom unsubstituted IIIa and IIIb predominate in solution in the aminohydrazone form, the fraction of which increases as the polarity of the solvent increases.

In addition to the above-examined tautomerism of S-methyl derivative IIIa, tautomerism of the thioamide fragment of the hydrazone $-N=C(SCH_3)-NH_2 \rightleftarrows -NH-C(=NH)SCH_3$ is also

possible. Inasmuch as the signal of the NH proton at weak field is absent in the PMR spectrum of IIIa in hexamethylphosphoric triamide, whereas the chemical shift of the indole NH proton is close to the corresponding value in the spectrum of fixed tautomer IIIb, an amino structure is more likely.

We also recorded the electronic spectra of the investigated compounds in alkaline media. The spectrum of IIa under these conditions is similar to the spectra of derivatives IIb and If-IIf and differs from the spectrum of a neutral solution with respect to a bathochormic shift of the longwave absorption band; this is apparently due to ionization with splitting out of the =N—NH proton. However, the spectrum of IIc, in which this hydrogen atom is replaced by a methyl group, undergoes a hypsochromic shift in alkaline media, and this is due to its rapid cyclization to give 2-methyl-3-thioxo-2,3-dihydro-1,2,4-triazino[6,5-b]indole [6].

EXPERIMENTAL

The method used to measure the spectra was presented in [7]. The individuality of all of the substances was monitored by thin-layer chromatography (TLC[7]) and other methods.

1-Methylthiosemicarbazide [8] was obtained by reduction of 1-ethoxymethylenethiosemicarbazide [9].

1-Methyl-2-phenylimino-3-oxoindoline (V). This compound was obtained by the method in [10]. An increase in the amount of methyl iodide by a factor of 1.5 and in the amount of 5% sodium ethoxide by a factor of three made it possible to increase the yield to 60%. The product had mp 129° [10].

2-Phenylimino-3-oxoindoline (VI). The method used to prepare the O-methyl ether of isatin (VII) [11] was refined. A solution of 24 g (0.14 mole) of $AgNO_3$ in 66 ml of water was added to a solution of 36 g (0.265 mole) of $CH_3COONa \cdot 3H_2O$ in 85 ml of water, and the resulting precipitate was removed by filtration, washed with water (three 30-ml portions), and squeezed. The resulting silver acetate was dissolved rapidly in 900 ml of boiling water, and the solution was filtered immediately. The filtrate was added to a solution of 20.4 g (0.14 mole) of isatin in 490 ml of refluxing methanol. Heating was continued for 5 min, after which the hot mixture was filtered, and the solid material was washed with 50% methanol (100 ml) and dried at 105° to give 20 g of dull cherry-red crystals of the silver salt of isatin (VIII).

After thorough drying and grinding, VIII was mixed with 36 ml of anhydrous ether and 9 ml (0.14 mole) of methyl iodide, and the mixture was allowed to stand with periodic shaking without access to light and moisture for 4 days. A yellow mass of AgI impregnated with bright-red needles of isatin O-methyl ether (VII) was formed. It was extracted with anhydrous benzene (three 58-ml portions). The resulting freshly prepared solution of VII (84%) in 174 ml of benzene was mixed with a solution of 6.05 ml (0.066 mole) of aniline in 10 ml of benzene, and the mixture was allowed to stand at —20° for 1 h. Petroleum ether (1900 ml) was added gradually with stirring, and the mixture was allowed to stand for 24 h. The resulting precipitate was removed by filtration, washed with petroleum ether and pentane, and dried in a vacuum desiccator over paraffin to give a product with mp 125° (from benzene) in 63% yield. The product was identical to 2-phenylimino-3-oxoindoline (VI) obtained from hydrocyanocarbodiphenylimide [12].

1-(3-Oxo-2-indolyl)-1-methylthiosemicarbazide (IIb), Isatin 2-(2'-Methyl)thiosemicarbazone (IIc), 2-(4'-Methyl)thiosemicarbazone (IIe), 2-(4'-4'-Dimethyl)thiosemicarbazone (If-IIf), and 2-(2',4'-Dimethyl)thiosemicarbazone (IIg). These compounds were obtained by the following method. A solution of ether VII (obtained from 40 mmole of the silver salt of isatin) in 140 ml of benzene was shaken with a supersaturated solution of 33.6 mmole of the appropriate thiosemicarbazide in water previously cooled to room temperature. The amount of water necessary to dissolve the thiosemicarbazide was 113, 200, 85, 78, and 126 ml and the reaction times were 4.5, 2.5, 1.0, 0.17, and 4.0 h, respectively. The resulting precipitate was removed by filtration, washed with boiling water and alcohol, and dried at 105° to give IIb, IIe, and If-IIf as red crystals and IIc* and IIg as orange crystals.

*We were previously unable to obtain IIc by condensation of 2-methylthiosemicarbazide with 2-phenylimino-3-oxoindoline (VI), inasmuch as this reaction proceeds only at high temperatures, and this leads to cyclization of IIc to give 2-methyl-3-thioxo-2,3-dihydro-1,2,4-triazino[6,5-b]indole [6].

1-Methylisatin 2-(4',4'-Dimethyl)thiosemicarbazone (Id). This compound was obtained from 1-methyl-2-phenylimino-3-oxoindoline (V) by the method previously presented for the preparation of Ib [6].

Isatin 2'-(4',4'-Dimethyl)thiosemicarbazone (If-IIf). This compound was also obtained from 2-phenylimino-3-oxoindoline VI by the method used to prepare IIa [13].

Isatin 2'-(S',4',4'-Trimethyl)isothiosemicarbazone (IIb) and 2-(1',S'-Dimethyl)isothiosemicarbzone (IV). These compounds were obtained from If-IIf and IIb in analogy with the preparation of IIIa [6]. In the case of IV the reaction was carried out room temperature for 4.5 h.

1-Methylisatin 2'-(S',4',4'-Trimethyl)isothiosemicarbazone (IIIc). A 0.6-g (2.29 mmole) sample of Id was methylated by the method used to methylate Ia-IIa [6]. The reaction mixture was filtered, the filtrate was vacuum evaporated, and the residue was triturated with anhydrous ether. The solid material was removed by filtration and washed with ether. It was then extracted with boiling benzene (three 20-ml portions), the benzene extract was vacuum evaporated to 5 ml, and IIIc was precipitated as dark cherry-red crystals by the addition of 50 ml of ether.

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