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Synthesis of Substituted 3-[(4-Oxocyclohexa-2,5-dien-1-ylidene)-hydrazinylidene]-1,3-dihydro-2*H*-indol-2-ones and Their Reactions with Hydrogen Chloride

B. V. Murashevich, N. A. Nichik, A. K. Zamyatina, N. V. Toropin, and K. S. Burmistrov

Ukrainian State University of Chemical Technology, pr. Gagarina 8, Dnepropetrovsk, 49005 Ukraine
e-mail: murashevich@yahoo.com

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Abstract—4-Hydroxyphenylhydrazones of isatin derivatives were synthesized and oxidized with lead compounds to the corresponding azines. The introduction of isatin fragment in a quinoid system increases the redox potential of the system compared with 1,4-benzoquinone thus presumably resulting in the prevalence of 1,4-addition process. By an example of the reaction of *N*-methylisatins with hydrogen chloride it was shown that the reaction proceeded in keeping with the theoretically predicted direction. Azines, derivatives of isatin unsubstituted at the nitrogen atom, do not react with hydrogen chloride because of the presence of a strong intramolecular hydrogen bond.

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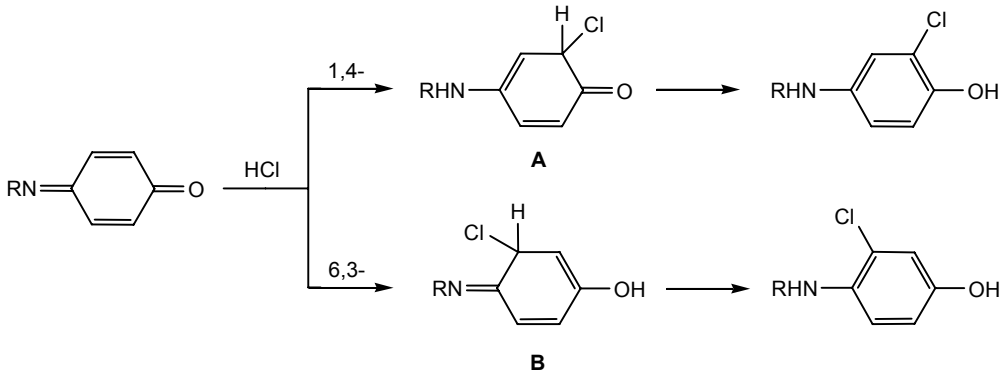
Quinone imines are nitrogen analogs of quinones and like quinones take part in metabolic processes of living organisms exhibiting a high biologic activity. Among quinone imine derivatives found in natural objects compounds are present with anticancer and antibacterial action [1]. In the human body these compounds undergo diverse transformations, and some of intermediates may be very toxic. For instance, the metabolite of paracetamol considered as endowing the drug with hepatotoxicity is *N*-acetyl-1,4-benzoquinone imine [2]. The most characteristic reactions of quinone imines are redox processes and addition of reagents of HX type. HCl is one of these reagents. *N*-Substituted quinone imines are known to react readily with hydrogen chloride and bromide along the scheme of 1,4- or 6,3-addition [3–6]. The direction of addition (1,4- or 6,3-) is governed by relative feasibility of the quinoid intermediate **A** or **B** (Scheme 1).

In its turn the energy advantage of structures **A** and **B** may be estimated from the comparison of the redox potentials of the quinone imines. If the replacement of the carbonyl group C=O in quinone by an imino group C=NR results in increased redox potential, then the scheme of 1,4-addition is operating due to the relative

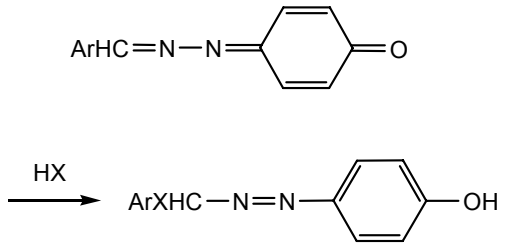
Scheme 1.



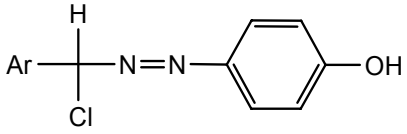
advantage of intermediate **A**. When this replacement leads to the reduced redox potential, intermediate **B** becomes more feasible and the reaction takes the path of 6,3-addition. The efficiency of this approach was decisively demonstrated by examples of reactions *N*-aryl-1,4-benzoquinone imines with HCl and HBr [4–6].

It was recently found that arenalazines of quinones containing in the molecule an azomethine fragment reacted with the reagents of the HX type along the scheme of 1,8-addition [7, 8] (Scheme 2).

Scheme 2.



Evidently the reaction of 1,8-addition occurs due to the energy advantage of intermediate **C** having aromatic nature.



C

The aim of this study was the synthesis and reactivity investigation of azines with the structure free of CH=N moiety. We selected as such structures isatin derrivatives, 3-[(4-oxocyclohexa-2,5-dienylidene)hydrazinylidene]-1,3-dihydro-2*H*-indol-2-ones **1a–1d** that were synthesized by the reaction of 4-hydroxyphenylhydrazine with the corresponding isatins followed by oxidation by procedure described before [9].

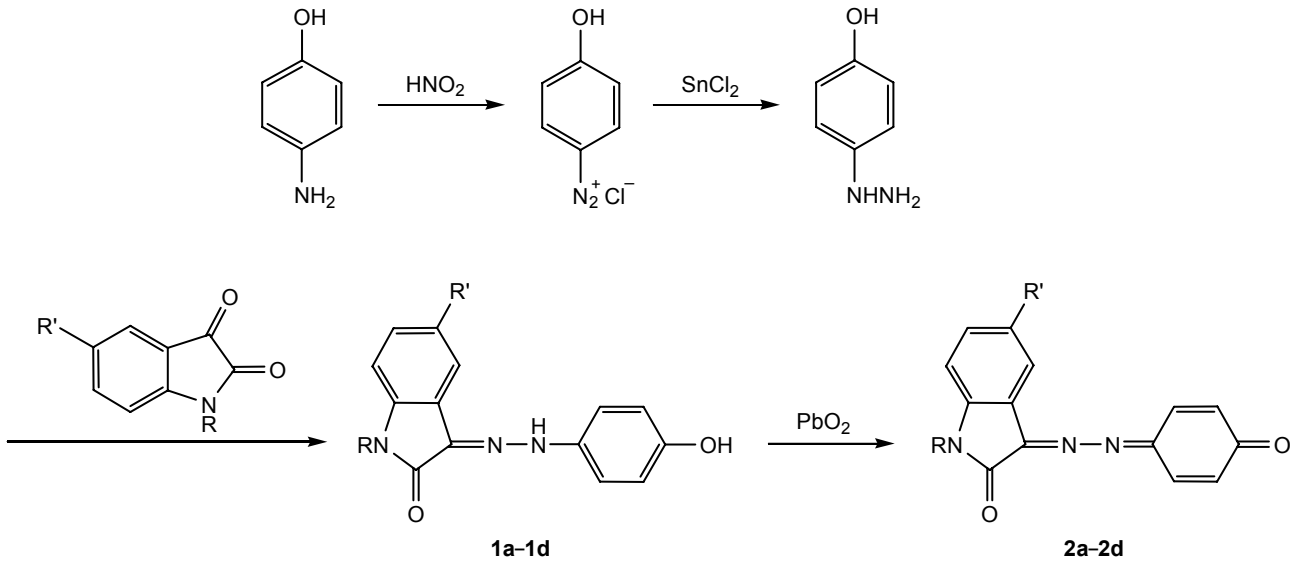
The reaction was carried out without isolation of 4-hydroxy-phenylhydrazine, and hydrazones **1a–1d** were obtained in 60–85% yields. Their subsequent oxidation with lead dioxide in dichloroethane afforded the target azines **2a–2d** in a fair yield (Scheme 3).

The structure of hydrazones **1a–1d** and azines **2a–2d** was confirmed by the data of ^{1}H NMR spectra. In the spectra of azines **2a–2d** a nonequivalence of the protons of the quinoid ring was observed because of hindered isomerization near the nitrogen atom.

By the method of potentiometric titration of solutions of hydrazones **1a–1d** with lead tetraacetate in 0.5 M sodium acetate solution in acetic acid we measured the redox potentials of the systems **1a–1d/2a–2d**. The values of redox potentials of compounds **1a–1d** are 0.614, 0.611, 0.602, 0.615 V.

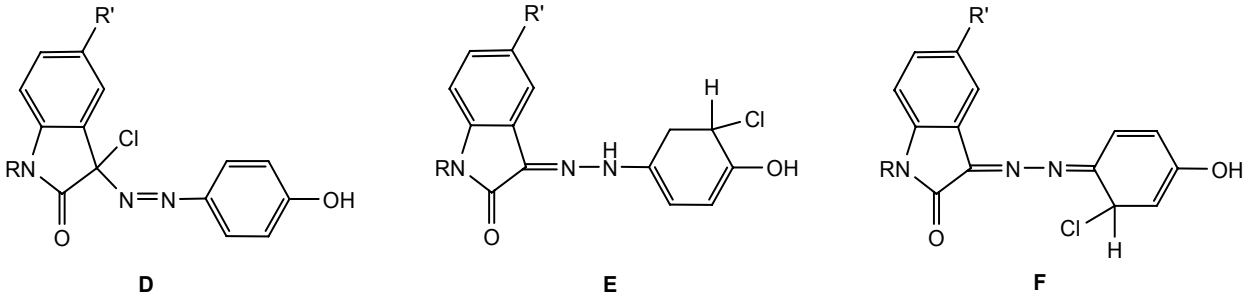
The reactivity of obtained azines **2a–2d** we studied by an example of the reaction with hydrogen chloride. In this case evidently intermediates **D–F** may arise.

Scheme 3.



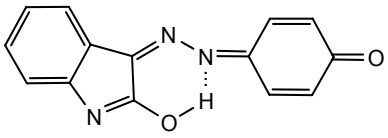
1a–1d **2a–2d**

R = R' = H (**a**); R = Me, R' = H (**b**), Br (**c**), NO_2 (**d**).



D E F

Since the redox potential of the systems **1/2** insignificantly exceeds the redox potential of the system quinone–hydroquinone (0.583 V [10]), the addition of hydrogen chloride most probably would occur by the scheme of 1,4-addition. The substrates, isatin derivatives having the CONH moiety, in particular, compound **2a**, did not react with hydrogen chloride. The low reactivity apparently is due to the prevailing existence of compound **2a** in tautomeric imidol form with an intramolecular hydrogen bond.

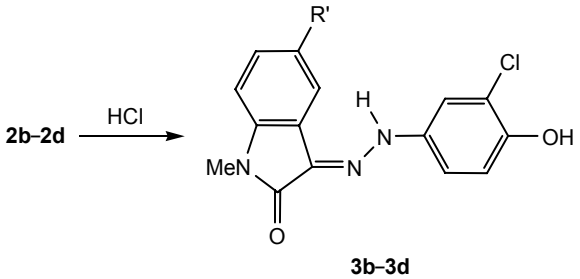


2a

This assumption is confirmed by the IR spectrum of compound **2a**, which contains a strong absorption band in the region 3432 cm^{-1} corresponding to the stretching vibrations of the imidol OH group involved in the formation of the hydrogen bond, whereas the absorption band of the stretching vibrations of the C=O group of the imide isatin fragment in the region 1730 cm^{-1} is very weak.

The presence of a hydrogen bond with the exocyclic nitrogen atom of the quinoid system reduces its basicity thus impeding the protonation which is the primary act of the hydrogen halide addition [6].

Scheme 4.



3b–3d

In order to exclude the possible influence of the hydrogen bond on the reactivity we studied HCl addition to azines **2b–2d**. In contrast to compound **2a**, the IR spectrum of compound **2b** contains a strong absorption band in the region 1727 cm^{-1} confirming the existence of the substance in the amide form. Actually, these compounds as has been predicted from the values of redox potentials readily add hydrogen chloride in 1,4-positions.

The addition is accompanied by a partial reduction of azines **2b–2d** to hydrazones **1b–1d**, thus somewhat decreasing the yield of the reaction products. The reason of the partial reduction of azines is the fact that the introduction of chlorine in the quinoid ring caused the decrease in the redox potential, namely, the mesomeric effect of chlorine dominates over the inductive effect evidently because of the long conjugation chain of the quinoid ring with the isatin fragment. Therefore the initial azines **2b–2d** partially oxidize in the course of the reaction the addition products **3b–3d** (Scheme 4). The structure of addition products **3b–3d** is confirmed by the ^1H NMR spectra, and for compound **3b** also by an independent synthesis from 4-hydroxy-2-chlorophenylhydrazine.

EXPERIMENTAL

^1H NMR spectra were registered on a spectrometer Varian Gemini 2000 (400 MHz), internal reference TMS. IR spectra were recorded on a spectrophotometer Perkin Elmer Spectrum BX II from pellets with KBr. The mixtures were separated by column chromatography on silica gel ROCC, fraction 60–200 μm, eluent chloroform–2-propanol, 1 : 9. The qualitative analysis of reaction mixtures was performed by TLC using plates with fixed layer of silica gel Kieselgel 60 F254 (Merck) on a polymer sublayer and Sorbfil (IMID) on an aluminum sublayer, eluent chloroform or mixtures chloroform–2-propanol in various ratios.

4-Hydroxyphenylhydrazones of substituted isatins 1a–1d. General procedure. A solution of 6 g (0.05 mol) of 4-aminophenol in a mixture of 50 mL of water and 15 mL of 32% hydrochloric acid was cooled on an ice bath to 0°C. At continuous stirring maintaining the temperature below 5°C a solution was added of 4 g (0.055 mol) of sodium nitrite in 15 mL of water. The obtained solution of a diazonium salt was stirred for 40 min. It was then added to a cooled to –5°C solution of tin(II) chloride obtained by dissolving 30 g of tin in a mixture of 50 mL of water and 100 mL of 32% hydrochloric acid. After stirring for 2 h to the reaction mixture was added a solution of 0.05 mol of an appropriate isatin in a sufficient amount of 2-propanol, also a solution was added of 6 g (0.07 mol) of sodium acetate in 35 mL of water. The mixture obtained was stirred for 2 h, heated to 50°C, and left standing for crystallization. The separated precipitate was filtered off and several times washed with water on the filter. The filtrate was additionally diluted with water, the separated precipitate was filtered off, washed with water on the filter, the precipitates were combined and dried.

3-[2-(4-Hydroxyphenyl)hydrazinylidene]-1,3-dihydro-2*H*-indol-2-one (1a). Yield 84%, yellow crystals, mp 220°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.80 d (1H, C_6H_4OH, *J* 8.8 Hz), 6.91 d (1H, C_6H_4, *J* 7.8 Hz), 7.03 t (1H, C_6H_4, *J*.8 Hz), 7.20 t (1H, C_6H_4, *J* 6.3 Hz), 7.27 d (1H, C_6H_4OH, *J* 8.8 Hz), 7.50 d (1H, C_6H_4, *J* 6.3 Hz), 9.29 s (1H, NH-Ar), 10.91 s (1H, NH), 12.78 s (1H, OH). Found, %: C 66.40; H 4.36; N 16.59. $C_{14}H_{11}N_3O_2$. Calculated, %: C 66.40; H 4.35; N 16.60.

3-[2-(4-Hydroxyphenyl)hydrazinylidene]-1-methyl-1,3-dihydro-2*H*-indol-2-one (1b). Yield 60%, orange crystals, mp 214–216°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.26 s (3H, CH_3), 5.74 d (1H, C_6H_4, *J* 7.1 Hz), 6.79 d.d (2H, C_6H_4OH, *J* 8.8 Hz), 7.10 t (1H, C_6H_4, *J* 6.6 Hz), 7.10 d (1H, C_6H_4, *J* 6.6 Hz), 7.29 d.d (2H, C_6H_4OH, *J* 8.8 Hz), 7.30 t (1H, C_6H_4, *J* 7.1 Hz), 9.36 s (1H, NH), 12.72 s (1H, OH). Found, %: C 67.39; H 5.85; N 15.74. $C_{15}H_{13}N_3O_2$. Calculated, %: C 67.41; H 4.86; N 15.73.

5-Bromo-3-[2-(4-hydroxyphenyl)hydrazinylidene]-1-methyl-1,3-dihydro-2*H*-indol-2-one (1c). Yield 66%, bright orange crystals, mp 205–208°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.24 s (3H, CH_3), 6.79 d (1H, C_6H_4OH, *J* 8.1 Hz), 7.05 d (1H, C_6H_4OH, *J* 8.3 Hz), 7.35 d (1H, C_6H_4Br, *J* 11.4 Hz), 7.44 d (1H, C_6H_4Br, *J* 9.8 Hz), 7.66 s (1H, C_6H_4Br), 9.41 s (1H, NH), 12.72 s (1H, OH). Found, %: C 52.01; H 3.48; Br 23.12; N 12.16. $C_{15}H_{12}BrN_3O_2$. Calculated, %: C 52.02; H 3.47; Br 23.12; N 12.14.

3-[2-(4-Hydroxyphenyl)hydrazinylidene]-1-methyl-5-nitro-1,3-dihydro-2*H*-indol-2-one (1d). Yield 82%, orange crystals, mp 242–244°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.26 s (3H, CH_3), 6.80 d (1H, C_6H_4OH, *J* 8.4 Hz), 7.20 d (1H, $C_6H_4NO_2$, *J* 8.5 Hz), 7.33 d (1H, C_6H_4OH, *J* 8.4 Hz), 8.10 d (1H, $C_6H_4NO_2$, *J* 8.5 Hz), 8.15 s (1H, $C_6H_4NO_2$), 9.41 s (1H, NH), 12.64 s (1H, OH). Found, %: C 57.70; H 3.83; N 17.96. $C_{15}H_{12}N_4O_4$. Calculated, %: C 57.69; H 3.85; N 17.95.

3-[(4-Oxocyclohexa-2,5-dien-1-ylidene)hydrazinylidene]-1,3-dihydro-2*H*-indol-2-ones 2a–2d. To a solution of 5.8 mmol of hydrazone **1a–1d** in a sufficient amount of 1,2-dichloroethane was added 5 g of anhydrous sodium sulfate, 10 g of lead dioxide, and 1.5 g of lead tetraacetate. The mixture was stirred for 30 min, filtered, and the filtrate was evaporated till dryness, the residue was crystallized from benzene and dried.

3-[(4-Oxocyclohexa-2,5-dien-1-ylidene)hydrazinylidene]-1,3-dihydro-2*H*-indol-2-one (2a). Yield 60%, brown crystals, mp 120–123°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.53 d (1H, C_6H_4O, *J* 10, 2 Hz), 6.93 d (1H, C_6H_4O, *J* 10, 2 Hz), 6.93 d (1H, C_6H_4, *J* 7.8, 1.5 Hz), 7.05 t (1H, C_6H_4, *J* 7.8, 1.5 Hz), 7.41 t (1H, C_6H_4, *J* 7.8, 1.5 Hz), 7.44 d (1H, C_6H_4, *J* 7.8, 1.5 Hz), 7.49 d (1H, C_6H_4O, *J* 10, 2 Hz), 7.59 d (1H, C_6H_4O, *J* 10, 2 Hz). Found, %: C 66.94; H 4.60; N 16.70. $C_{14}H_9N_3O_2$. Calculated, %: C 66.93; H 3.58; N 16.73.

1-Methyl-3-[(4-oxocyclohexa-2,5-dien-1-ylidene)-hydrazinylidene]-1,3-dihydro-2*H*-indol-2-one (2b). Yield 91%, brown crystals, mp 170–172°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.22 s (3H, CH_3), 6.51 d.d (1H, C_6H_4O, *J* 10, 2.1 Hz), 6.67 d.d (1H, C_6H_4O, *J* 10, 2.1 Hz), 6.88 d (1H, C_6H_4, *J* 7.8 Hz), 7.05 t (1H, C_6H_4, *J* 7.8 Hz), 7.47 t (1H, C_6H_4, *J* 7.4 Hz), 7.48 d.d (1H, C_6H_4O, *J* 10.4, 2.5 Hz), 7.56 d (1H, C_6H_4, *J* 7.4 Hz), 7.57 d.d (1H, C_6H_4O, *J* 10.4, 2.5 Hz). Found, %: C 67.92; H 4.15; N 15.84. $C_{15}H_{11}N_3O_2$. Calculated, %: 67.92; H 4.15; N 15.85.

5-Bromo-1-methyl-3-[(4-oxocyclohexa-2,5-dien-1-ylidene)hydrazinylidene]-1,3-dihydro-2*H*-indol-2-one (2c). Yield 77%, dark brown crystals, mp 127–130°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.29 s (3H, CH_3), 6.53–6.56 d.d (1H, C_6H_4O, *J* 10.2, 2.4 Hz), 6.69–6.72 d.d (1H, C_6H_4O, *J* 9.4, 1.8 Hz), 7.49–7.52 d.d (1H, C_6H_4O, *J* 10.2, 1.8 Hz), 7.57–7.63 m (d.d + d,

2H). Found, %: C 52.38; H 2.93; Br 23.23; N 12.21. $C_{15}H_{10}BrN_3O_2$. Calculated, %: C 52.33; H 2.90; Br 23.25; N 12.20.

1-Methyl-5-nitro-3-[(4-oxocyclohexa-2,5-dien-1-ylidene)hydrazinylidene]-1,3-dihydro-2*H*-indol-2-one (2d). Yield 65%, dark brown crystals, mp 152–155°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.36 s (3H, CH_3), 6.55 d.d (1H, C_6H_4O, *J* 9.5 Hz), 7.05 d.d (1H, C_6H_4O, *J* 8.7 Hz), 7.32 d (1H, $C_6H_3NO_2$), 7.60 d.d (1H, C_6H_4O, *J* 9.5 Hz), 8.40–8.56 m (d.d + d, 2H). Found, %: C 58.03; H 3.20; N 18.10. $C_{15}H_{10}N_4O_4$. Calculated, %: C 58.06; H 3.23; N 18.06.

Addition of hydrogen chloride to reagents 3b–3d *(general procedure)*. To a solution of 3 mmol of azine **2b–2d** in a sufficient amount of 1,2-dichlo-roethane was added 2 mL of 32% hydrochloric acid, the mixture was strongly shaken for 3 min and was stirred at room temperature for 1 h. Afterwards it was diluted with 100 mL of water, the organic layer was separated, the water layer was several times extracted with 1,2-dichloroethane. The dichloroethane extracts were combined, dried with anhydrous sodium sulfate, the solvent was distilled off, the residue was purified by column chromatography.

3-[2-(4-Hydroxy-3-chlorophenyl)hydrazinylidene]-1-methyl-1,3-dihydro-2*H*-indol-2-one (3b). Yield 64%, orange crystals, mp 215–216°C (from benzene). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.25 s (3H, CH_3), 6.98 d (1H, C_6H_3, *J* 8.8 Hz), 7.10 d (1H, C_6H_4, *J* 6.8 Hz), 7.10 t (1H, C_6H_4, *J* 6.8 Hz), 7.25 d.d (1H, C_6H_3, *J* 8.8, 2.7 Hz), 7.31 t (1H, C_6H_4, *J* 7.3 Hz), 7.50 d (1H, C_6H_3, *J* 2.7 Hz), 7.58 d (1H, C_6H_4, *J* 7.3 Hz), 9.97 s (1H, NH), 12.6 s (1H, OH). Found, %: C 59.73; H 4.00; Cl 11.75; N 13.94. $C_{15}H_{12}ClN_3O_2$. Calculated, %: C 59.70; H 3.98; Cl 11.77; N 13.93.

5-Bromo-3-[2-(4-hydroxy-3-chlorophenyl)hydrazineylidene]-1-methyl-1,3-dihydro-2*H*-indol-2-one (3c). Yield 88%, dark orange crystals, mp 185–187°C (from benzene). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.22 s (3H, CH_3), 6.97 d (1H, C_6H_3Br, *J* 8.3 Hz), 7.05 d (1H, C_6H_3ClOH, *J* 7.3 Hz), 7.28 d (1H, C_6H_3ClOH, *J* 7.6 Hz), 7.43 d (1H, C_6H_3Br, *J* 9.2 Hz), 7.58 s (1H, C_6H_3ClOH), 7.69 s (1H, C_6H_3Br), 10.08 s (1H, NH), 12.53 s (1H, OH). Found, %: C 52.21; H 3.20; Br 23.16; N 12.15. $C_{15}H_{11}BrN_3O_2$. Calculated, %: C 52.17; H 3.18; Br 23.18; N 12.17.

3-[2-(4-Hydroxy-3-chlorophenyl)hydrazinylidene]-1-methyl-5-nitro-1,3-dihydro-2*H*-indol-2-one (3d). Yield 62%, dark crystals, mp 214–218°C (from benzene). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.26 s (3H, CH_3), 6.96 d (1H, C_6H_3ClOH, *J* 8.7 Hz), 7.22 d (1H, C_6H_3ClOH, *J* 8.5 Hz), 7.29 d (1H, $C_6H_3NO_2$, *J* 8.5 Hz), 12.52 s (1H, OH), 7.54 s (1H, C_6H_3ClOH), 8.13 d (1H, $C_6H_3NO_2$, *J* 8.1 Hz), 8.20 s (1H, $C_6H_3NO_2$), 10.09 s (1H, NH). Found, %: C 51.98; H 3.18; Cl 10.21; N 16.15. $C_{15}H_{11}ClN_4O_4$. Calculated, %: C 51.95; H 3.17; Cl 10.24; N 16.16.

Independent synthesis of 3-[2-(4-hydroxy-3-chlorophenyl)hydrazinylidene]-1-methyl-1,3-dihydro-2*H*-indol-2-one (3b). To a solution of 8 g (0.05 mol) of 4-amino-2-chlorophenol in a mixture of 50 mL of water and 15 mL of 32% hydrochloric acid cooled to 0°C while continuous stirring at the temperature below 5°C was added a solution of 4 g (0.055 mol) of sodium nitrite in 15 mL of water, and the mixture was stirred for 40 min. Further reaction was performed as described for the synthesis of 4-hydroxyphenyl-substituted isatins. Yield 63%, mp 215–216°C. The melting of a sample mixed with the product obtained from azine **2b** did not show a melting point depression.

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