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Dedicated to the memory of Professor Nicholas Alexandrou

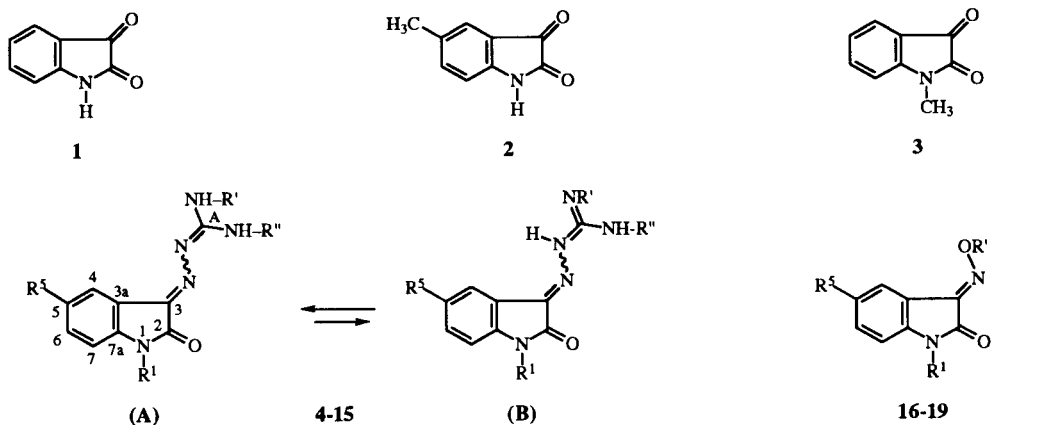
The synthesis of some novel (substituted) guanylhydrazones of isatin, 5-methylisatin and 1-methylisatin is described. Moreover, detailed nmr-spectroscopic studies (^1H -nmr, ^{13}C -nmr) with these compounds and previously known congeners are presented.

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The well-known guanylhydrazones [1] (alkylidene-aminoguanidines, amidohydrazones, diaminomethylenehydrazones, *Chem. Abstr.*: 2-ylidenehydrazinocarboximidamides) represent a class of substances showing a wide variety of biological activities [2]. Moreover, they have also an established role in the construction of polyfunctional nitrogen heterocycles [3]. Thus, for instance, we quite recently reported the transformation of aromatic aldehyde guanylhydrazones into 3-acylamino-5-aryl-1,4-diacyl-4,5-dihydro-1,2,4-triazoles, a class of hitherto not amenable compounds [4]. Whereas the biological and

chemical aspects of guanylhydrazones have been intensively studied, relatively little attention had been addressed to the determination of their stereochemistry - usually these compounds can exist as (*E*)- or (*Z*)-isomers. In this regard, investigations with *e.g.* the biological active guanylhydrazones Guanabenz [5-8], testosterone guanylhydrazone [9,10] and 2-amino-5-chlorobenzophenone guanylhydrazone [2,11] have to be mentioned. Moreover, a detailed nmr study dealing with guanylhydrazones derived from aromatic aldehydes was published recently [8]. The first guanylhydrazone with both isomers

Scheme 1



No.	R ¹	R ⁵	R' *	R'' *
4	H	H	H	H
5	H	H	Me	H
6	H	H	Ph	H
7	H	H	COMe	COMe
8	H	Me	H	H
9	H	Me	Me	H
10	H	Me	Ph	H
11	H	Me	COMe	COMe
12	Me	H	H	H
13	Me	H	Me	H
14	Me	H	Ph	H
15	Me	H	COMe	COMe

No.	R ¹	R ⁵	R'
16	H	H	H
17	H	Me	H
18	Me	H	H
19	Me	H	Me

* May be interchanged.

isolated was (*N*-methyl)isatin β -guanylhydrazone [12] (published in 1948), configurational assignment with the latter pair of compounds was carried out on basis of reactivity considerations (ring closure reactions [12,13]). However, the reported assignments seem to be problematic when compared with those made with related isatin derivatives (such as semicarbazones and thiosemicarbazones [14,15]) on basis of spectroscopic investigations, and thus call for a reinvestigation. Especially the latter class of compounds is also of considerable biological interest due to antiviral [16] and antibacterial [17] activity observed with many representatives thereof. In this regard, it should be mentioned that also for (*E*)-isatin guanylhydrazone antiviral activity has been reported [18].

In the light of these findings we here present nmr spectroscopic investigations with (substituted) guanylhydrazones derived from isatin (1), 5-methylisatin (2) and 1-methylisatin (3) (structures 4-15 in Scheme 1), particularly in order to elucidate the stereochemistry of the central C³=N- double bond and to provide sufficient ¹H-nmr and ¹³C-nmr data material for structural determinations with related compounds. Additionally, the nmr methods used for configurational assignments with guanylhydrazones 4-15 were also applied to the structurally related (substituted) isatin oximes 16-19 (Scheme 1).

Synthesis.

The hitherto unknown guanylhydrazone 8 was prepared by treatment of 5-methylisatin (2) with aminoguanidine. The *N*-methylguanylhydrazones 5, 9 and 13 were obtained upon reaction of the parent guanylhydrazones 4, 8 and 12, respectively, with 1-amino-3-methylguanidine hydroiodide. Similarly, employing 1-amino-3-phenylguanidine nitrate as the reactant led to *N*-phenyl congeners 6, 10 and 14. Finally, reaction of 4, 8, or 12 with excessive acetic anhydride at 100° smoothly afforded the *N,N'*-diacetyl compounds 7, 11 and 15.

NMR-Spectroscopic Investigations.

The ¹H-nmr data of compounds 4-19 are given in the Experimental, their ¹³C-nmr data and those of parent isatins 1-3 are collected in Table 1.

Guanylhydrazones can exist in two tautomeric forms (forms A and B in Scheme 1), considering the number and relative intensities of NH₍₂₎ signals in the ¹H-nmr spectra of compounds 4-15 gives a hint that the latter are present rather in the diaminomethylene form (form A) in deuteriodimethyl sulfoxide solution. Unambiguous assignments for all proton and carbon resonances were achieved on basis of NOE-difference experiments, fully

Table 1
¹³C-Chemical Shifts (δ , ppm) of Compounds 1-19 (in Deuteriodimethyl Sulfoxide Solution)

No.	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	R ¹ [b]	R ⁵ [c]	R'	R''	C _A
1	159.3	184.3	117.7	124.6	122.7	138.3	112.2	150.7	-	-	-	-	-
2	159.4	184.5	117.7	124.7	132.0	138.7	112.0	148.5	-	20.0	-	-	-
3	158.1	183.3	117.3	124.1	123.1	138.1	110.5	151.3	25.9	-	-	-	-
4 (<i>E</i>)	166.8	134.6	118.9	125.5	120.8	128.1	109.0	140.7	-	-	-	-	164.1
4 (<i>Z</i>)	158.9	132.2	124.3	118.5	120.6	127.1	109.0	139.6	-	-	-	-	164.8
5 (<i>E</i>)	166.7	[a]	118.9	125.3	120.8	128.0	108.9	140.6	-	-	27.7 (Me) [d]	-	163.5
6 (<i>E</i>)	166.2	138.1	118.2	125.3	121.1	129.3	109.3	141.6	-	-	Ph: 138.5 (1), 121.5 (2,6), 128.7 (3,5), 123.3 (4)	-	160.8
7 (<i>E</i>)	165.3	148.0	117.1	128.3	122.0	132.6	110.2	143.9	-	-	170.4 (C=O), 24.7 (Me)	168.6 (C=O), 24.2 (Me)	149.0
8 (<i>E</i>)	166.8	134.8	118.9	126.1	129.4	128.4	108.6	138.5	-	20.9	-	-	164.1
9 (<i>E</i>)	166.9	[a]	119.0	126.0	129.4	128.3	108.7	138.4	-	20.9	27.7 (Me)	-	163.6
10 (<i>E</i>)	166.4	[a]	118.2	126.1	129.7	129.6	109.0	139.3	-	20.7	Ph: 138.7 (1), 121.7 (2,6), 128.6 (3,5), 123.2 (4)	-	160.7
11 (<i>E</i>)	165.3	148.3	117.1	128.8	130.7	132.8	109.9	141.6	-	20.6	170.5 (C=O), 24.1 (Me)	168.5 (C=O), 24.8 (Me)	148.9
12 (<i>E</i>)	165.1	133.8	118.0	125.2	121.3	128.0	107.5	141.9	25.5	-	-	-	164.1
12 (<i>Z</i>)	156.9	130.8	123.4	118.0	120.9	126.8	107.4	140.7	25.2	-	-	-	164.8
13 (<i>E</i>)	165.2	[a]	118.0	124.9	121.4	127.9	107.5	141.7	25.5	-	27.7 (Me)	-	163.6
13 (<i>Z</i>)	157.1	[a]	123.6	118.0	120.9	126.5	107.5	140.4	25.2	-	27.8 (Me)	-	164.5
14 (<i>E</i>)	164.7	137.1	117.3	124.9	121.5	129.2	107.9	142.7	25.6	-	Ph: 138.4 (1), 121.6 (2,6), 128.8 (3,5), 123.4 (4)	-	160.9
15 (<i>E</i>)	163.7	147.2	116.3	127.9	122.4	132.4	108.8	144.9	25.8	-	169.8 (C=O), 24.4 (Me)	169.8 (C=O), 24.4 (Me)	148.9
16 (<i>E</i>)	164.5	144.2	116.0	127.1	122.0	132.0	110.2	142.6	-	-	-	-	-
17 (<i>E</i>)	164.6	144.3	116.0	127.5	130.8	132.2	110.0	140.3	-	20.5	-	-	-
18 (<i>E</i>)	163.9	143.2	115.6	125.5	122.2	130.6	108.4	142.7	25.6	-	-	-	-
19 (<i>E</i>)	162.1	143.3	114.7	127.0	122.6	132.8	109.1	144.3	25.8	-	64.3 (Me) [e]	-	-

[a] Not unambiguously identified. [b] ¹J(N1-CH₃) = 139 Hz. [c] ¹J(C5-CH₃) = 126 Hz. [d] ¹J = 137.8 Hz. [e] ¹J = 145.5 Hz.

^1H -coupled ^{13}C -nmr spectra, HMQC [19], 1D-TOCSY [20], 1D-HETCOR [21] and long-range INEPT spectra with selective DANTE excitation [22]. As an example, compounds (*E*)-12 and (*Z*)-12 may serve. With (*E*)-12, irradiation of the NCH_3 -resonance in an NOE difference experiment enhanced the doublet signal of H-7 (δ 6.92 ppm, which in the "normal" ^1H -nmr spectrum is overlapped by the triplet-signal of H-5). Irradiation of the other doublet-signal (δ 8.42 ppm, which must be that due to H-4) permits to identify the signal of the spatially close, adjacent proton H-5 (δ 6.95 ppm), the remaining triplet-signal now can be assigned to H-6 (δ 7.19 ppm). Assignments of the signals of the carbon atoms directly bounded to the above protons (C-4, C-5, C-6, C-7) were performed on basis of an HMQC experiment. The remaining quarternary carbon atoms were unambiguously identified *via* long-range INEPT experiments with selective DANTE excitation (optimized for couplings of 5-8 Hz). Thus, for instance, excitation of the NCH_3 -resonance enhanced the signals of C-2 and C-7a, positioning the selective pulse on the H-4 line resulting in an enhancement of the signals due to C-6, C-3 and C-7a (Figure 1). Excitation of H-5/H-7 assigned the C-3a signal (Figure 1). Finally, the remaining resonance (δ 164.1 ppm) being not affected by any of the above long-range heteronuclear correlation experiments could be attributed to the guanidine carbon atom (C_A).

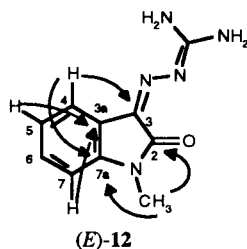


Figure 1. Assignment of Quarternary C-Atoms in (*E*)-12 *via* Long-Range INEPT Experiments with Selective Excitation of NCH_3 , H-4, H-5 and H-7.

(*E*)-Configuration of (*E*)-12 unequivocally follows from NOE-difference experiments (significant enhancement of the H-4 signal upon irradiation of the NH_2 line - which is not possible in the (*Z*)-configuration). Independently, the stereochemistry at the $\text{C}^3=\text{N}$ double bond could be deduced by comparison of the ^{13}C -chemical shifts of both isomers of 12 (Table 1) considering γ -effects: carbon atoms being in γ -position (α to $\text{C}=\text{N}$) to a *syn* located hydrazono N-2 atom suffer an upfield shift compared to the γ -C-atoms in the *anti*-position due to steric compression [23]. Thus, the signal of C-3a in (*E*)-12 (*syn*-position to the guanylhydrazono moiety regarding the $\text{C}^3=\text{N}$ bond) is characterized by a 5.4 ppm

upfield shift compared to that of C-3a in (*Z*)-12. Inversely, the *syn*-position of C-2 and the $\text{C}^3=\text{N}=\text{N}=\text{N}$ substructure in (*Z*)-12 is reflected by a 8.2 ppm upfield shift of the C-2 resonance compared to the corresponding line in (*E*)-12 (Table 1). These findings are in good accordance with the ^{13}C -nmr data found with (*E*)/(*Z*)-pairs of related isatin (thio)semicarbazones [15,24]. However, it should be emphasized that this approach (configurational assignment of compounds with a $\text{C}=\text{N}$ bond *via* γ -effects) requires both isomers at hand or at least the availability of ^{13}C -nmr data of closely related species with defined stereochemistry.

Deduction of stereochemistry and assignment of resonances with the other isatin derivatives included in this study were carried out similarly as described for compounds 12. As an example, an HMQC experiment with (*E*)-14, which established direct (one-bond) proton-carbon chemical shift concordance in the aromatic region, is depicted in Figure 2.

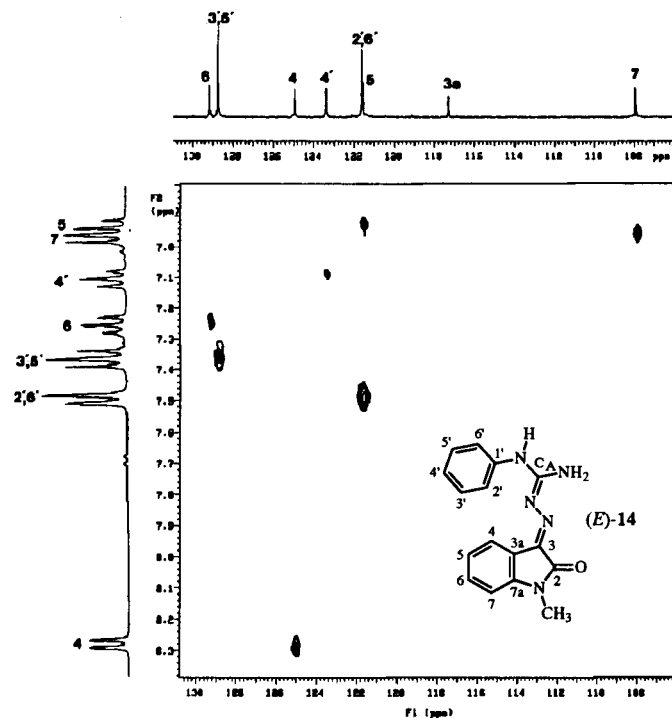


Figure 2. HMQC Spectrum of (*E*)-14 (Aromatic Region).

Most isatin derivatives investigated were found to be (*E*)-isomers, occasionally accompanied by small amounts (<10%) of the corresponding (*Z*)-form. (*E*)-Configuration of congeners 5, 9 and the main isomer of 13 also followed from additional NOE difference experiments (positive NOEs between NHMe and H-4), the same applies for *N*-phenyl derivatives 6, 10 and 14 (detected spatial closeness of H-4 and Ph H-2,6) [25]. Figure 3 shows the evidence of (*E*)-configuration in (*E*)-14 considering an NOE

on Ph H-2,6 upon irradiation of H-4; additionally this experiment unequivocally identifies the H-5 signal (through-space connection H-4 → H-5).

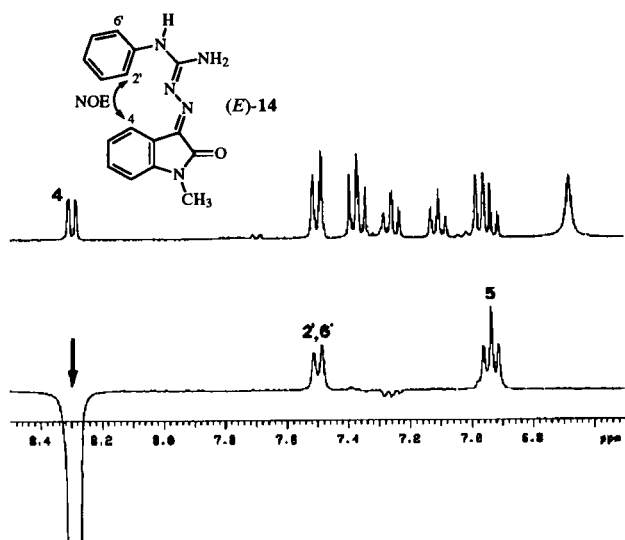


Figure 3. a) ^1H -nmr Spectrum of (*E*)-14 (6.5-8.5 ppm). b) NOE-Difference Spectrum of (*E*)-14 Resulting from irradiation of the H-4 Resonance.

In a similar manner, simple NOE-difference experiments also enabled us to determine the stereochemistry of isatin oximes **16-19**, which were obtained as single isomers. The appearance of a significant NOE to H-4 when the OH-transition (**16-18**) or the OMe line (**19**) was irradiated, proved these compounds to exist in the (*E*)-configuration.

Comparing the ^{13}C -nmr spectra summarized in Table 1 shows a high consistency of the data set. The drastic downfield shift of the C-3 resonance in acetyl derivatives (*E*)-7, (*E*)-11 and (*E*)-15 appears to be worthy of note. It should also be mentioned that in some cases (for instance structures **5**, **9** and **13**) the C-3 signal (which is always characterized by a low intensity) could not be observed (or was unambiguously identified). Additionally, with the latter compounds some ^{13}C resonances are relatively broad providing some hint for a possible dynamic behaviour.

EXPERIMENTAL

Melting points were detected on a Boetius hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 5000 or on a Varian MAT 311A instrument (both EI, 70 eV). The nmr spectra were recorded on a Varian UnityPlus 300 spectrometer (299.95 MHz for ^1H , 75.43 MHz for ^{13}C) from deuteriodimethyl sulfoxide solutions at 28°. The center of the solvent signal was used as an internal standard which was related to tetramethylsilane with δ 2.49 ppm (^1H) and δ 39.5 ppm (^{13}C). The ^{13}C -nmr spectra were recorded with digital resolutions of 0.55 Hz/data point, ^1H -nmr spectra have a digital resolution of

0.25 Hz/data point. Isatin (**1**) and 1-methylisatin (**3**) are commercially available.

2-(1,2-Dihydro-2-oxo-3*H*-indol-3-ylidene)hydrazinecarboximidamide (**4**).

Compound (*E*)-**4** was prepared according to ref [12] (procedure given for the synthesis of "syn"- β -isatin guanylhydrazone). Following the procedure described for the preparation of the "anti"-isomer [12] resulted in a 5:1 mixture of (*E*)-**4** and (*Z*)-**4** [26].

Compound (*E*)-**4** had ^1H -nmr (deuteriodimethyl sulfoxide): δ 10.25 (s, 1H, indole N1-H), 8.37 (dd [27], 1H, indole H-4), 7.11 (dt [27], 1H, indole H-6), 6.88 (dt [27], 1H, indole H-5), 6.79 (dd, 1H, indole H-7), 6.65 (s, 4H, NH_2); ms: m/z (%) 203 (M^+ , 63), 175 (49), 132 (27), 104 (45), 103 (23), 77 (21), 76 (23), 58 (22), 44 (82), 43 (100).

Compound (*Z*)-**4** had ^1H -nmr (deuteriodimethyl sulfoxide): δ 10.25 (s, 1H, indole N1-H), 7.58 (dd, 1H, indole H-4), 7.09 (dt, 1H, indole H-6), 6.88 (dt, 1H, indole H-5), 6.75 (dd, 1H, indole H-7), 6.65 (s, 4H, NH_2).

(*E*)-2-(1,2-Dihydro-2-oxo-3*H*-indol-3-ylidene)-*N*-methylhydrazinecarboximidamide (**5**).

To a hot solution of isatin (**1**) (1.47 g, 10 mmoles) in 25 ml of methanol, 2.16 g (10 mmoles) of 1-amino-3-methylguanidine hydroiodide [28] was added and the resulting mixture was heated to reflux for 1 hour. The deep red reaction mixture was then concentrated *in vacuo* and treated with excessive cold 2*N* potassium hydroxide solution. The precipitated base was filtered off and recrystallized from dimethyl formamide-water to afford 1.89 g (87%) of **5** as orange crystals, mp 247-248°; ^1H -nmr (deuteriodimethyl sulfoxide): δ 10.22 (s, 1H, indole N1-H), 8.30 (dd, 1H, indole H-4), 7.11 (dt, 1H, indole H-6), 6.90 (dt, 1H, indole H-5), 6.79 (dd, 1H, indole H-7), 7.20-6.20 (br, 3H, NH, NH_2), 2.88 (s, 3H, NMe); ms: m/z (%) 217 (M^+ , 71), 189 (31), 161 (32), 133 (32), 132 (31), 118 (31), 104 (58), 72 (42), 58 (52), 57 (100), 43 (72).

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_5\text{O}\cdot 0.3\text{H}_2\text{O}$ [29]: C, 53.95; H, 5.25; N, 31.46. Found: C, 54.33; H, 5.00; N, 31.16.

(*E*)-2-(1,2-Dihydro-2-oxo-3*H*-indol-3-ylidene)-*N*-phenylhydrazinecarboximidamide (**6**).

To a hot mixture of 1-amino-3-phenylguanidine nitrate [30] (2.13 g, 10 mmoles) and sodium ethylate (681 mg, 10 mmoles) in 25 ml of dry ethanol 1.47 g (10 mmoles) of isatin (**1**) were added and the mixture was then heated to reflux for 1 hour. After cooling, 80 ml of water were added, the precipitated material was filtered off, washed with water and recrystallized from dimethyl formamide-water to afford 2.26 g (81%) of orange crystals, mp 234-235°; ^1H -nmr (deuteriodimethyl sulfoxide): δ 10.36 (s, 1H, indole N1-H), 9.15 (s, 1H, NH), 8.27 (dd, 1H, indole H-4), 7.51 (m, 2H, Ph H-2,6), 7.36 (m, 2H, Ph H-3,5), 7.17 (dt, 1H, indole H-6), 7.09 (m, 1H, Ph H-4), 6.87 (dt, 1H, indole H-5), 6.81 (dd, 1H, indole H-7), 6.64 (s, 2H, NH_2); ms: m/z (%) 279 (M^+ , 24), 251 (100), 133 (31), 119 (63), 104 (44), 93 (32), 77 (63), 65 (52), 51 (41), 44 (32), 43 (33).

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}\cdot 0.2\text{H}_2\text{O}$ [29]: C, 63.68; H, 4.77; N, 24.76. Found: C, 63.63; H, 4.75; N, 24.54.

(*E*)-*N,N'*-Diacetyl-2-(1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)hydrazinecarboximidamide (**7**).

The guanylhydrazone (*E*)-**4** (1.02 g, 5 mmoles) was heated with 11 ml of acetic anhydride for 10 minutes at 100°. After

cooling, the dark yellow precipitate was collected by filtration and washed with diethyl ether. Recrystallization from a large volume of ethanol afforded 1.38 g (96%) of yellow crystals, mp 225-228° dec (lit [12] mp 220-221°); ¹H-nmr (deuteriodimethyl sulfoxide): δ 11.20-10.40 (br, 2H, NH), 10.70 (s, 1H, indole N1-H), 8.41 (dd, 1H, indole H-4), 7.33 (dt, 1H, indole H-6), 6.99 (dt, 1H, indole H-5), 6.86 (dd, 1H, indole H-7), 2.15 (s, 6H, COMe); ms: m/z (%) 287 (M⁺, 22), 245 (31), 217 (38), 175 (54), 161 (22), 132 (25), 44 (23), 43 (100).

(*E*)-2-(1,2-Dihydro-5-methyl-2-oxo-3*H*-indol-3-ylidene)hydrazinecarboximidamide (**8**).

Aminoguanidine hydrogencarbonate (2.04 g, 15 mmoles) was dissolved in 15 ml of 1*N* hydrochloric acid. After the evolution of carbon dioxide had ceased, 2.42 g (15 mmoles) of 5-methylisatin (**2**) [31] were added to the clear, cold solution. Then the reaction mixture was heated to 100° for 20 minutes. After cooling, an excess of aqueous ammonia was added, the yellow precipitate was filtered off and dissolved in hot dimethyl formamide (~ 9 ml). Gradual addition of water afforded a yellow precipitate, which was filtered off and washed with water. After drying over phosphorous pentoxide, 2.89 g (89%) of **8** were obtained, mp 252-253°; ¹H-nmr (deuteriodimethyl sulfoxide): δ 10.13 (s, 1H, indole N1-H), 8.21 (d, 1H, indole H-4), 6.92 (dd, 1H, indole H-6), 6.67 (d, 1H, indole H-7), 6.61 (s, 4H, NH₂), 2.24 (s, 3H, indole 5-Me); ms: m/z (%) 218 (14), 217 (M⁺, 94), 188 (100), 175 (20), 146 (52), 131 (22), 118 (42), 117 (22), 91 (21), 89 (23), 77 (23), 58 (27), 51 (21), 44 (45), 43 (93).

Anal. Calcd. for C₁₀H₁₁N₅O•0.1H₂O [29]: C, 54.84; H, 5.15; N, 31.97. Found: C, 55.07; H, 5.35; N, 31.97.

(*E*)-5,*N*-Dimethyl-2-(1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)hydrazinecarboximidamide (**9**).

Compound **9** was prepared from 5-methylisatin (**2**) [31] (1.61 g, 10 mmoles) and 1-amino-3-methylguanidine hydroiodide [28] (2.16 g, 10 mmoles) according to the procedure given for the synthesis of product **5**. Recrystallization from dimethyl formamide-water afforded 1.60 g (69%) of orange-red crystals, mp 247-248°; ¹H-nmr (deuteriodimethyl sulfoxide): δ 10.13 (s, 1H, indole N1-H), 8.15 (d, 1H, indole H-4), 7.10 (br, 1H, NH), 6.92 (dd, 1H, indole H-6), 6.68 (d, 1H, indole H-7), 7.00-6.40 (br, 2H, NH₂), 2.88 (d, J = 4.8 Hz, 3H, NMe), 2.24 (s, 3H, indole 5-Me); ms: m/z (%) 231 (M⁺, 56), 203 (26), 146 (31), 118 (23), 72 (27), 58 (34), 57 (83), 43 (100).

Anal. Calcd. for C₁₁H₁₃N₅O•0.2H₂O [29]: C, 56.26; H, 5.75; N, 29.82. Found: C, 56.59; H, 6.04; N, 29.72.

(*E*)-2-(1,2-Dihydro-5-methyl-2-oxo-3*H*-indol-3-ylidene)-*N*-phenylhydrazinecarboximidamide (**10**).

Compound **10** was prepared from 1-amino-3-phenylguanidine nitrate [30] (2.13 g, 10 mmoles) and 5-methylisatin (**2**) [31] (1.61 g, 10 mmoles) as described for the preparation of product **6**. Recrystallization from dimethyl formamide-water afforded 2.79 g (95%) of orange crystals, mp 262-263°; ¹H-nmr (deuteriodimethyl sulfoxide): δ 10.26 (s, 1H, indole N1-H), 9.10 (s, 1H, NH), 8.13 (d, 1H, indole H-4), 7.55 (m, 2H, Ph H-2,6), 7.37 (m, 2H, Ph H-3,5), 7.10 (m, 1H, Ph H-4), 6.98 (dd, 1H, indole H-6), 6.70 (d, 1H, indole H-7), 6.59 (s, 2H, NH₂), 2.18 (s, 3H, indole 5-Me); ms: m/z (%) 293 (M⁺, 25), 266 (20), 265 (100), 146 (24), 119 (49), 118 (22), 92 (22), 91 (21), 77 (53), 65 (46), 51 (30), 43 (25).

Anal. Calcd. for C₁₆H₁₅N₅O•0.1H₂O [29]: C, 65.12; H, 5.19; N, 23.73. Found: C, 65.03; H, 5.21; N, 23.61.

(*E*)-*N,N'*-Diacetyl-2-(1,2-dihydro-5-methyl-2-oxo-3*H*-indol-3-ylidene)hydrazinecarboximidamide (**11**).

Compound **11** was prepared from guanylhydrazone (*E*)-**8** (1.09 g, 5 mmoles) and acetic anhydride as described for the preparation of product **7**. Recrystallization from a large volume of ethanol afforded 0.81 g (54%) of yellow crystals, mp 239-240°; ¹H-nmr (deuteriodimethyl sulfoxide): δ 10.90 (s, 1H, NH), 10.56 (s, 1H, indole N1-H), 10.35 (s, 1H, NH), 8.28 (d, 1H, indole H-4), 7.13 (dd, 1H, indole H-6), 6.73 (d, 1H, indole H-7), 2.24 (s, 3H, indole 5-Me), 2.18 (s, 3H, COMe), 2.16 (s, 3H, COMe); ms: m/z (%) 301 (M⁺, 21), 259 (22), 231 (48), 189 (57), 146 (31), 44 (20), 43 (100), 40 (23).

Anal. Calcd. for C₁₄H₁₅N₅O₃•0.9H₂O [29]: C, 52.96; H, 5.33; N, 22.06. Found: C, 53.25; H, 5.25; N, 22.00.

2-(1,2-Dihydro-1-methyl-2-oxo-3*H*-indol-3-ylidene)hydrazinecarboximidamide (**12**).

Compound (*E*)-**12** was prepared according to the procedure given for the synthesis of "*syn*"-*N*-methylisatin β-guanylhydrazone [12]. Following the procedure given for the preparation of the corresponding "*anti*"-isomer [12] led to a 2:1 mixture of (*E*)-**12** and (*Z*)-**12** [26].

Compound (*E*)-**12** had ¹H-nmr (deuteriodimethyl sulfoxide): δ 8.42 (dd, 1H, indole H-4), 7.19 (dt, 1H, indole H-6), 6.95 (dt, 1H, indole H-5), 6.92 (dd, 1H, indole H-7), 6.67 (s, 4H, NH₂), 3.16 (s, 3H, indole NMe); ms: m/z (%) 217 (M⁺, 100), 189 (68), 175 (41), 147 (20), 146 (54), 118 (29), 117 (30), 91 (30), 90 (20), 44 (20), 43 (52).

Compound (*Z*)-**12** had ¹H-nmr (deuteriodimethyl sulfoxide): δ 7.61 (dd, 1H, indole H-4), 7.16 (dt, 1H, indole H-6), 6.93 (dt, 1H, indole H-5), 6.88 (dd, 1H, indole H-7), 6.75 (s, 4H, NH₂), 3.12 (s, 3H, indole NMe).

1,*N*-Dimethyl-2-(1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)hydrazinecarboximidamide (**13**).

Compound **13** was prepared from 1-methylisatin (**3**) (1.61 g, 10 mmoles) and 2.16 g (10 mmoles) of 1-amino-3-methylguanidine hydroiodide [28] according to the procedure given for the preparation of product **5**. The crude reaction product consisted of an isomeric mixture (*E*:*Z* ~ 3:1), subsequent recrystallization from dimethyl formamide-water afforded 1.90 g (82%) of (*E*)-**13** (containing 10% of the (*Z*)-isomer) as orange-red crystals, mp 217-218°.

Compound (*E*)-**13** had ¹H-nmr (deuteriodimethyl sulfoxide): δ 8.34 (dd, 1H, indole H-4), 7.20 (dt, 1H, indole H-6), 6.97 (dt, 1H, indole H-5), 6.92 (dd, 1H, indole H-7), 7.60-6.40 (br, 3H, NH, NH₂), 3.17 (s, 3H, indole NMe), 2.89 (s, 3H, NMe); ms: m/z (%) 231 (M⁺, 15), 58 (25), 57 (70), 43 (100), 42 (15).

Anal. Calcd. for C₁₁H₁₃N₅O•0.2H₂O [29]: C, 56.26; H, 5.77; N, 29.82. Found: C, 56.27; H, 5.94; N, 29.44.

Compound (*Z*)-**13** had ¹H-nmr (deuteriodimethyl sulfoxide): δ 7.66 (dd, 1H, indole H-4), 7.14 (dt, 1H, indole H-6), 6.93 (dt, 1H, indole H-5), 6.86 (dd, 1H, indole H-7), 7.60-6.40 (br, 3H, NH, NH₂), 3.13 (s, 3H, indole NMe), 2.86 (s, 3H, NMe).

(*E*)-2-(1,2-Dihydro-1-methyl-2-oxo-3*H*-indol-3-ylidene)-*N*-phenylhydrazinecarboximidamide (**14**).

Compound **14** was prepared from 1-amino-3-phenylguanidine nitrate [30] (2.13 g, 10 mmoles) and 1-methylisatin (**3**) (1.61 g, 10 mmoles) as described for the preparation of product **6**. Recrystallization from dimethyl formamide-water afforded 1.79 g (61%) of yellow crystals, mp 190-191°; ¹H-nmr (deuteriodimethyl

sulfoxide): δ 9.17 (s, 1H, NH), 8.29 (dd, 1H, indole H-4), 7.50 (m, 2H, Ph H-2,6), 7.37 (m, 2H, Ph H-3,5), 7.26 (dt, 1H, indole H-6), 7.10 (m, 1H, Ph H-4), 6.97 (dd, 1H, indole H-7), 6.94 (dt, 1H, indole H-5), 6.68 (s, 2H, NH₂), 3.17 (s, 3H, indole NMe); ms: m/z (%) 293 (M⁺, 36), 265 (76), 175 (36), 147 (42), 146 (30), 119 (92), 118 (37), 104 (33), 93 (38), 91 (33), 77 (100), 65 (55), 51 (47), 43 (32).

Anal. Calcd. for C₁₆H₁₅N₅O•0.2H₂O [29]: C, 64.72; H, 5.23; N, 23.59. Found: C, 64.63; H, 5.35; N, 23.65.

N,N'-Diacetyl-2-(1,2-dihydro-1-methyl-2-oxo-3*H*-indol-3-ylidene)hydrazinecarboximidamide (15).

Compound (E)-15 was prepared from guanylhyazone (E)-12 (1.09 g, 5 mmoles) and acetic anhydride as described for the preparation of product 7. Recrystallization from a large amount of ethanol afforded 1.08 g (72%) of yellow crystals, mp 229–230° (lit [12] mp 237° dec); ¹H-nmr (deuteriodimethyl sulfoxide): δ 10.66 (s, br, 2H, NH), 8.44 (dd, 1H, indole H-4), 7.42 (dt, 1H, indole H-6), 7.06 (dt, 1H, indole H-5), 7.04 (dd, 1H, indole H-7), 3.17 (s, 3H, indole NMe), 2.14 (s, 6H, COMe); ms: m/z (%) 301 (M⁺, 21), 231 (28), 175 (20), 146 (30), 43 (100).

Anal. Calcd. for C₁₄H₁₅N₅O₃•0.8H₂O [29]: C, 53.26; H, 5.30; N, 22.18. Found: C, 53.46; H, 5.41; N, 22.12.

(E)-1*H*-Indole-2,3-dione 3-Oxime (16).

Compound 16 (preparation according to ref [32]) had ¹H-nmr (deuteriodimethyl sulfoxide): δ 13.25 (s, 1H, OH), 10.65 (s, 1H, indole N1-H), 7.93 (dd, 1H, indole H-4), 7.31 (dt, 1H, indole H-6), 6.98 (dt, 1H, indole H-5), 6.86 (dd, 1H, indole H-7); ms: m/z (%) 162 (M⁺, 100), 145 (43), 117 (39), 90 (32), 63 (27), 52 (25), 51 (29), 50 (33).

(E)-5-Methyl-1*H*-indole-2,3-dione 3-Oxime (17).

Compound 17 (preparation according to ref [33]) had ¹H-nmr (deuteriodimethyl sulfoxide): δ 13.23 (s, 1H, OH), 10.58 (s, 1H, indole N1-H), 7.76 (d, 1H, indole H-4), 7.11 (dd, 1H, indole H-6), 6.75 (d, 1H, indole H-7), 2.23 (s, 3H, indole 5-Me); ms: m/z (%) 176 (M⁺, 100), 159 (33), 131 (56), 104 (21), 77 (28), 52 (20), 51 (23).

(E)-1-Methyl-1*H*-indole-2,3-dione 3-Oxime (18).

Compound 18 (preparation according to ref [32]) had ¹H-nmr (deuteriodimethyl sulfoxide): δ 12.50–8.50 (br, 1H, OH), 8.05 (dd, 1H, indole H-4), 7.34 (dt, 1H, indole H-6), 7.03 (dt, 1H, indole H-5), 6.99 (dd, 1H, indole H-7), 3.15 (s, 3H, indole NMe); ms: m/z (%) 176 (M⁺, 100), 159 (45), 131 (25).

(E)-1,*O*-Dimethyl-1*H*-indole-2,3-dione 3-Oxime (19).

Compound 19 (preparation according to ref [34]) had ¹H-nmr (deuteriodimethyl sulfoxide): δ 7.81 (dd, 1H, indole H-4), 7.43 (dt, 1H, indole H-6), 7.04 (dt, 1H, indole H-5), 7.02 (dd, 1H, indole H-7), 4.18 (s, 3H, OMe), 3.12 (s, 3H, indole NMe); ms: m/z (%) 190 (M⁺, 100), 159 (43), 132 (31), 131 (40), 104 (21), 77 (27).

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[26] The *E:Z* ratio varied somewhat with time and concentration. Thus, in deuteriodimethyl sulfoxide solution a slow equilibration process is probable.

[27] Typical ¹H,¹H coupling constants of the isatin moiety: ³J(H₄,H₅) = 7.5 Hz; ⁴J(H₄,H₆) = 1.3 Hz; ³J(H₅,H₆) = 7.7 Hz; ⁴J(H₅,H₇) = 1.1 Hz; ³J(H₆,H₇) = 7.7 Hz. The signal of H-7 is somewhat broader than those of the other isatin-H signals, thus ⁴J(H₅,H₇) emerges only upon an appropriate resolution enhancement.

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