2-Chloro-3*H*-indol-3-one and its Reactions with Nucleophiles

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The title compound reacts with *N*- and *S*-nucleophiles to form 3-substituted indol-2-ones, but with *C*-nucleophiles to afford either these or the corresponding 2-substituted indol-3-ones. This dichotomy of behavior is documented and rationalized.

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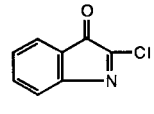
Introduction.

2-Chloro-3*H*-indol-3-one (**1**) was first obtained in 1879 by heating isatin and phosphorus pentachloride in benzene [1]. Since then, considerable interest has been shown in this interesting compound. Grimshaw and Begley claimed to have prepared substituted 2-chloro-3*H*-indol-3-ones by refluxing substituted isatins and phosphorus pentachloride in benzene [2]. However, the readily hydrolyzable compounds were neither purified nor characterized. An early paper [3] stated that, besides the 2-chloro-3*H*-indol-3-one (**1**) formed from isatin and phosphorus pentachloride in hot benzene, the same starting materials reacted slowly at room temperature to give 3,3-dichloroindol-2-one (**2**), and more recently, Bacalogu and Bader [4] also reported the preparation of both **1** and **2** from this reaction. The structures **1** and **2** have not been firmly based. No published analytical nor spectral data support the structure of 3,3-dichloroindol-2-one (**2**). The extensive literature for 2-chloro-3*H*-indol-3-one (**1**) includes only one satisfactory microanalysis [5]. Many investigators have pointed out that chloro compound **1** resists purification by conventional techniques, and is hydrolyzed [6] or decomposed [2] completely on standing overnight.

Block 1



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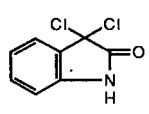

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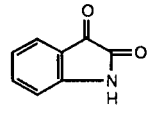

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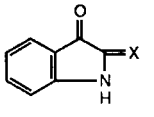

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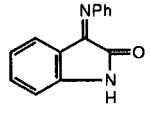

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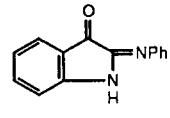

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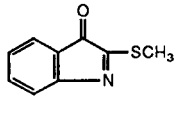

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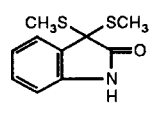

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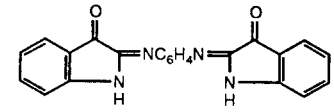

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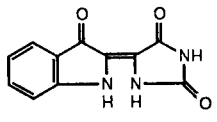
Chloroisatin (**1**) reacts readily with many nucleophiles, but apparently gives products both of structures (**3**) and of (**4**) depending on the nucleophile. Nitrogen and sulfur nucleophiles, such as amines [7], hydrazines [6], and thiols [8], yield 3-substituted indol-2-one or **8**, and these structures appear to be firmly based, as they are distinct from the authentic 2-isomers **4** which have been prepared by indirect methods [2,6]. For instance, previous workers [7], who attempted to prepare 2-anilino-3*H*-indol-3-one (**6**) from 2-chloroisatin and aniline, isolated only the isatin-3-anil **5** using an equimolar ratio, and the 2,3-dianil using an excess of aniline; authentic isatin-2-anil **6** was prepared either by the ring closure of an acyclic precursor [6] or by controlled hydrolysis of the dianil [2]. The reaction of 2-chloroisatin (**1**) with thiols was studied by Baker and Duke [5], who reported that one equivalent of methanethiol did not give the expected 2-methylthioindoleninone (**7**), and that reaction of **1** with methanethiol in the presence of water yielded 3,3-di(methylthio)indolin-2-one (**8**). We consider that the evidence for these 3-substituted indolin-2-one structures is sound since it should be easy to distinguish between the different isomers. Indeed, they are supported by their ^{1}H nmr spectra, *eg.* different NH signals in alkylthio substituted indolinone structures **3** and **4** [5], and proven by indirect syntheses *via* ring closure of appropriate precursors [2,6]. Bacaloglu [8] claimed that the reaction of 2-chloroisatin with 1,4- or 1,3-diaminobenzene afforded the corresponding bis-(3-oxo-2-indylidene) derivatives **9**. This appears to be the only example in the literature in which a 2-substituted indol-3-one has been claimed to be the product of a reaction of 2-chloroisatin and a nitrogen nucleophile, but the conclusion is based only on ir and analytical data, no ^{1}H nor ^{13}C nmr nor X-ray data were reported.

In contrast to the aforementioned heteroatom nucleophiles, compounds formed by the condensation of 2-chloroisatin with carbon nucleophiles (*eg.* active methylene compounds) have been formulated in the literature as 2-in-

dolylidene derivatives **4** (partial indigo structures). Hill and his coworkers [9] described the condensation of 2-chloroisatin (**1**) with hydantoins in acetic acid to produce indoxylidene dyes, *cf.* **10**; a similar reaction of chloroisatin with thioindol-3-one was also recently reported to give **11** [10]. Recently, Bergman reported the preparation of the natural compound indirubin (**12**) from the condensation of 2-chloroindol-3-one and 2-indolinone in dry toluene [11]; however, no detailed characterization was given. No previous report has claimed that a 2-oxo-3-indolylidene derivative was produced from the condensation of 2-chloroisatin and a carbon nucleophile.



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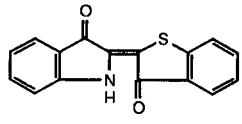

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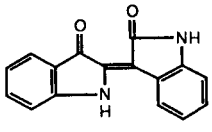

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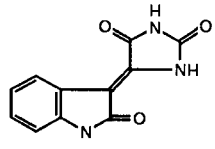

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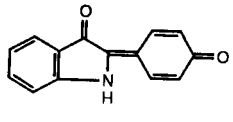
We have now repeated some of this work. (i) Freshly prepared 2-chloroisatin (**1**) reacts with hydantoin in acetic acid and acetic anhydride to give violet red **10**, mp 307-309°. The reaction of hydantoin with isatin produced the brown 2-oxo-3-indolylidene **13**, mp 312-314°. These two products show quite different ir spectra; the former is much more soluble in organic solvents and its ^1H and ^{13}C nmr spectra could be obtained in deuterated dimethyl sulfoxide, the latter has very limited solubility and its nmr spectra could not be taken. Both compounds analyse for $C_{11}H_7N_3O_3$.

(ii) Reaction of 2-chloroisatin with 2-indolinone in dry toluene by Bergman's procedure [11] gave the unsymmetrical isomer **12**, showing sixteen carbon signals in its ^{13}C nmr spectrum and two different NH peaks (δ 11.10 and 8.90 ppm) in the ^1H nmr spectrum; the symmetrical structure would have shown only eight carbon signals and one NH.



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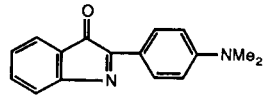

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Condensation of 2-chloroisatin with a variety of phenols and naphthanols was reported to give indoxylylidene derivatives, and 2-substituted indol-3-one **14** structures were proposed [12,13]. However, the authors did not mention nor apparently consider the corresponding 3-isomers, *cf* **3**. The possibility that structures of type **3** are formed is not easy to rule out based on their spectral and analytical data: thus, a 1H singlet at around δ 13 ppm, typical of an amide NH, was usually observed [13]. Recently, 2-(4-dimethylaminophenyl)indolenin-3-one (**15**) was also prepared by the condensation of 2-chloroisatin (**1**) with *N,N*-dimethylaniline [14]. Structure **15** was supported by ^1H and ^{13}C nmr spectroscopy and by reactions with nucleophiles.

As mentioned above, the structure of chloroisatin is still in question due to its instability and since it is extremely difficult to purify and to characterize. Both 3-substituted indol-2-ones **3** and 2-substituted indol-3-ones **4** have been claimed as products of reactions between chloroisatin and nucleophiles. However, it has never been reported that both **3** and **4** were formed in one reaction. Furthermore, no one has claimed that the formation of a 3-substituted indol-2-one **3** or of a 2-substituted indol-3-one **4** depended on the reaction conditions.

Very recently, we ourselves described condensation reactions of chloroisatin with 1,4-diacetylpiperazine-2,5-dione, 1-acetyl-3-arylmethylidenepiperazine-2,5-dione, indan-1,3-dione, anthrone and other active methylene compounds during our research on indigo-type dyes [15,16]. We first believed that these compounds were 3-oxo-2-indolidenes, but surprisingly, these products were shown instead to be 2-oxo-3-indolylidenes **16** and **19** by an X-ray crystal structure determination of **16**, by ^1H and ^{13}C nmr spectra, and by comparisons with anthentic specimens. This demonstrated for the first time that 2-oxo-3-indolylidene derivatives could be formed from the condensation of 2-chloroisatin and carbon nucleophiles.

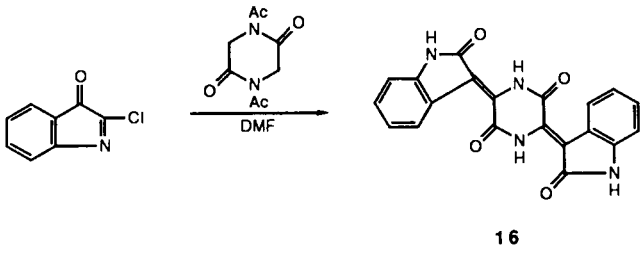
In this paper, we now present conclusive chemical and physical evidence (in particular, details of the X-ray result) that many condensations of chloroisatin with carbon nucleophiles yield 2-oxo-3-indolylidene, *cf.* **3** and not 3-oxo-2-indolylidene, *cf.* **4** isomers. We also describe new and direct chemical and physical evidence to reconfirm the structure of 2-chloroisatin. We have further attempted to ascertain if the formation of different isomers **3** and **4** depends upon the reaction conditions utilized by carrying out the condensation under different conditions and by repeating some of the early works in this field.

Structure of Indolylidene Derivatives of Piperazine-2,5-diones.

1,4-Diacetylpiperazine-2,5-dione reacted with 2-chloroisatin (**1**), (prepared by the reaction of isatin with phosphorus pentachloride in benzene and used immediately after preparation), at 25° in dimethylformamide, with tri-

ethylamine as a base, to give 3,6-di(2-oxo-3-indolylidene)-piperazine-2,5-dione (**16**) as previously described [15]; similarly, reaction of (**1**) with 1-acetyl-3-arylmethylidene-piperazine-2,5-diones **18** afforded 3-arylmethylidene-6-(2-oxo-3-indolylidene)piperazine-2,5-diones **19**.

Scheme 1



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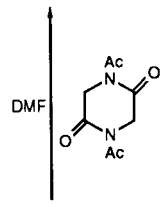

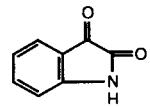

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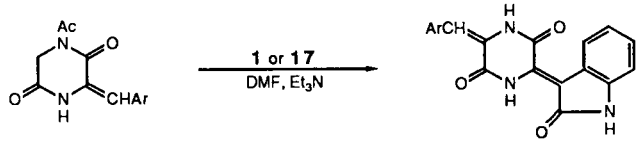

18 **19**

Ar = C_6H_5- (a) p-$CH_3OC_6H_4$- (b) p-$O_2NC_6H_4$- (c) m-ClC_6H_4- (d) 4-C_5H_4N (e)

The evidence for the 2-oxo-3-indolylidene structures **16** and **19** instead of the corresponding 3-oxo-2-indolylidenes comes from the following facts:

(1) The X-ray structure determination of **16** is shown in Figure 1. Compound **16** crystallizes with two molecules of dimethylformamide in the lattice. The piperazine ring is located on a center of symmetry and is required to be planar. There is an internal hydrogen bond from N(1) of the piperazine ring to O(2) of the indole ring which presumably stabilizes that conformation. The indole ring is planar and is at an angle of only 2.6° to the piperazine ring.

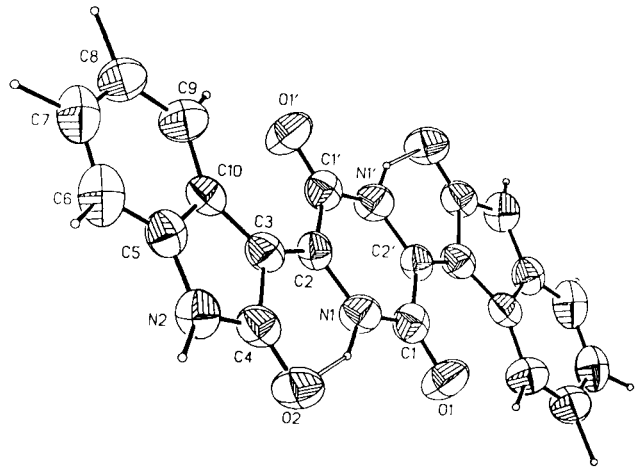

Figure 1. A view of the 3,6-di(2-oxo-3-indolylidene)piperazine-2,5-dione molecule (**16**), showing the atomic numbering used in the X-ray study. The ellipsoids are 50% probability. The piperazine ring sits on a center of symmetry which relates the primed and unprimed atoms.

The C(2)-C(3) distance of 1.357(8) Å is very close to the expected value for a pure double bond which suggests only a slight interaction between the central piperazine ring and the two indole groups. The C(3)-C(4) distance is shorter than that observed in isatin **17** which is expected since the nonbonded repulsions have decreased. In fact, C(3)-C(4) is close to the 1.48 Å expected for a single bond between two sp^2 hybridized carbon atoms. The remaining distances and angles are close to the expected values. The relevant crystal data are listed in Tables 1 to 3.

(2) Reaction of these piperazinediones **18** with isatin (**17**) gives the same products **19** as shown by comparing their melting points and spectra with those obtained by the reaction with 2-chloroisatin (see Table 4). For example, 3,6-di(2-oxo-3-indolylidene)piperazine-2,5-dione was formed in almost quantitative yield by the reaction of isatin and 1,4-diacetylpiperazine-2,5-dione in dimethylformamide. It is well known [6] that the 3-oxo group in isatin is more reactive than the 2-oxo and thus a 2-oxo-3-indolylidene should be produced.

(3) As mentioned briefly in our previous paper [15], the indolylidenes **16** and **19** produced by reaction of acetylpiperazine-2,5-dione with either 2-chloroisatin or with isatin itself, not only show identical spectra (^1H, ^{13}C nmr, ir and uv/vis), but these spectra strongly favor the 2-oxo-3-indolylidene structures. In the ir spectra, the amide bands were observed at around 1680-1620 cm^{-1}; if the structure were 3-oxo-2-indolylidene, an absorption above 1700 cm^{-1},

Table I

Crystal data for 3,6-di(2-oxo-3-indolylidene)piperazine-2,5-dione (**16**)

Formula $C_{30}H_{18}N_4O_4 \cdot 2C_3H_7NO$ ($C_{36}H_{36}N_6O_6$)	
Formula weight 518.53	
Space group $P2_1/n$	No. of molecules 2
a (Å) 12.483(2)	
b (Å) 5.869(1)	
c (Å) 17.328(3)	
β (°) 96.19(1)	
Volume (cubic Ang) 1262.1(4)	F(000) 544
Density Calcd. g/cm^{-3} 1.364	
Crystal size (mm) 0.07 × 0.10 × 0.24	μ (cm^{-1}) 8.40
Radiation CuKα-Ni filter	Scan mode Θ-2Θ
Scan Speed (deg/min) 1.8-29.3	Scan Range ±1.0°
Orientation matrix (No. relfections, range)	17, 8.3-27.3°
Number of check reflections and frequency	2, 98
Variation in check reflections 7%	
Number of data collected and unique	2004, 1661
Number of data observed and r merge	1074, 0.011
F(obs)/σF(obs) ≥ 2	Range of hkl 0-13, 0-6, ±18
Weighting scheme $\sigma(F_o)^{-2}$	
Number of Parameters and GOF 172, 1.89	
R(unweighted) and R(weighted) 0.099, 0.044	
Min, Max in final difference fourier −0.33, +0.33	
max shift/esd in last LS cycle 0.01	

Table II

Atomic Coordinates (× 10^4) and Isotropic Thermal Parameters (Å × 10^3)

	X	Y	Z	U
N(1)	1041(3)	4595(9)	4943(3)	52(2)*
C(1)	628(5)	6508(11)	4560(4)	50(3)*
O(1)	1197(3)	7679(8)	4197(3)	72(2)*
C(2)	533(4)	3047(10)	5400(3)	42(2)*
C(3)	1117(4)	1297(11)	5741(3)	47(3)*
C(4)	2277(4)	1023(11)	5604(4)	53(3)*
O(2)	2820(3)	2254(8)	5216(3)	66(2)*
N(2)	2659(4)	−886(9)	5999(3)	54(2)*
C(5)	1844(4)	−1861(10)	6391(3)	52(3)*
C(6)	1945(5)	−3774(12)	6862(3)	65(3)*
C(7)	1025(5)	−4490(12)	7196(4)	69(3)*
C(8)	72(5)	−3240(11)	7071(4)	67(3)*
C(9)	−5(5)	−1331(12)	6593(3)	61(3)*
C(10)	885(4)	−609(11)	6252(3)	49(3)*
C(1S)	3932(6)	−2154(12)	4081(4)	96(4)*
N(1S)	4125(4)	−4355(12)	3789(3)	68(2)*
C(2S)	3251(5)	−5421(13)	3331(4)	99(4)*
C(3S)	5076(5)	−5310(12)	3915(4)	74(3)*
O(1S)	5294(3)	−7250(8)	3692(3)	91(2)-

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

characteristic of the 3-carbonyl group should be found. The 3-oxo group in some 2-substituted indol-3-ones prepared by indirect methods absorbed at 1720-1730 cm^{-1} [6], absent in our compounds. The ^{1}H nmr also supported the 2-oxo-3-indolylidene structures **16** and **19**: 2-oxo-3-indolylidenes **3** show the NH signal at low field, characteristic of secondary amides, whereas for 3-oxo-2-indolylidenes **4** the NH absorb at higher field (4-5 ppm), characteristic of a secondary amine [5]. In no case were such high field signals observed for our indolylidene derivatives, all three NH resonances in 3-(2-oxo-3-indolylidene)-6-arylmethylidenepiperazine-2,5-diones **19** appear at low field (8.80-11.5 ppm), in agreement with the assigned amide structures. Their ^{13}C nmr spectra are also consistent with structure **19**, with amide C=O signals. Finally, the uv/vis absorption maximum is at much shorter wavelengths than that expected for 3-oxo-2-indolylidenes **4** which possess a partial indigo structure and should show deeper color according to the principle of merostabilization [17-18].

Reconfirmation of the Structure of 2-Chloroindol-3-one.

The condensation of 2-chloroindol-3-one with carbon nucleophiles thus can in some cases produce 2-oxo-3-indolylidene derivatives, just like heteroatom nucleophiles. Any one of the following explanations could rationalize why the reaction of chloroisatin with many nucleophiles, including some active methylene compounds, produced 3-substituted indol-2-one:

(1) The effective species reacting is isatin, the product of unstable and easily hydrolyzed 2-chloroisatin.

(2) The structure of 2-chloroisatin is incorrect and the 3-isomers derive not from (**1**) but from another intermediate, for instance, 3,3-dichloroindol-2-one [3,4].

(3) The greater reactivity of 3-oxo group in 2-chloroisatin led to the formation of a compound of type **20**, and the reaction was accompanied or followed by hydrolysis of the imidoyl chloride function in **20**.

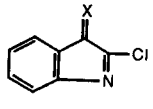

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Table III

Bond Lengths (Å) and Angles (°)

N(1)-C(1)	1.377(8)	N(1)-C(2)	1.401(8)
C(1)-O(1)	1.211(8)	C(1)-C(2)(i)	1.481(8)
C(2)-C(3)	1.357(8)	C(3)-C(4)	1.501(8)
C(3)-C(10)	1.476(8)	C(4)-O(2)	1.237(8)
C(4)-N(2)	1.371(8)	N(2)-C(5)	1.406(7)
C(5)-C(6)	1.386(9)	C(5)-C(10)	1.403(8)
C(6)-C(7)	1.405(10)	C(7)-C(8)	1.394(9)
C(8)-C(9)	1.390(9)	C(9)-C(10)	1.380(8)
C(1S)-N(1S)	1.418(9)	N(1S)-C(2S)	1.423(8)
N(1S)-C(3S)	1.309(8)	C(3S)-O(1S)	1.242(8)
C(1)-N(1)-C(2)	129.3(5)	N(1)-C(1)-O(1)	120.2(6)
N(1)-C(1)-C(2)(i)	116.0(5)	O(1)-C(1)-C(2)(i)	123.7(6)
N(1)-C(2)-C(3)	118.8(5)	N(1)-C(2)-C(1)(i)	114.7(5)
C(3)-C(2)-C(1)(i)	126.6(6)	C(2)-C(3)-C(4)	119.7(5)
C(2)-C(3)-C(10)	134.7(5)	C(4)-C(3)-C(10)	105.6(5)
C(3)-C(4)-O(2)	128.1(6)	C(3)-C(4)-N(2)	107.4(5)
O(2)-C(4)-N(2)	124.5(5)	C(4)-N(2)-C(5)	110.1(5)
N(2)-C(5)-C(6)	126.2(5)	N(2)-C(5)-C(10)	110.6(5)
C(6)-C(5)-C(10)	123.2(5)	C(5)-C(6)-C(7)	117.3(6)
C(6)-C(7)-C(8)	120.0(6)	C(7)-C(8)-C(9)	121.3(6)
C(8)-C(9)-C(10)	119.7(6)	C(3)-C(10)-C(5)	106.3(5)
C(3)-C(10)-C(9)	135.2(5)	C(5)-C(10)-C(9)	118.5(6)
C(1S)-N(1S)-C(2S)	116.7(5)	C(1S)-N(1S)-C(3S)	121.1(6)
C(2S)-N(1S)-C(3C)	122.1(6)	N(1S)-C(3S)-O(1S)	124.4(6)

Symmetry code (i) −x, 1-y, 1-z.

Both Baeyer [1] and Moriconi [6] reported that indigo was formed when chloroisatin was treated with zinc dust. This fact strongly supported its formulation as 2-chloroindol-3-one. We have now found that indigo is also produced in good yield by the reaction of chloroisatin with thiophenol or substituted thiophenols. Thus, refluxing freshly prepared chloroisatin and thiophenol, or para- and meta-substituted thiophenols, in dry benzene afforded indigo (**21**) (Table 5). The structure of indigo was confirmed by comparison of its melting point and ir and visible spectra with authentic indigo (Aldrich). However, similar attempts to convert chloroisatin into indigo by reacting with thiophenols in dimethylformamide gave complicated mixtures containing less than 20% of indigo, isatin, and unidentified compounds. Furthermore, when the reaction was conducted in wet benzene, or by using stored chloroisatin (*e.g.* several days after the preparation), still less or even no indigo could be isolated (particularly from aged chloroisatin). Evidently, indigo was produced from 2-chloroindol-3-one *via* a 2-arylthioindoleninone intermediate; 2,2-diarylthioindolinones are reported to give, when exposed to sunlight, indigo [5]. As 2-chloroindol-3-one is necessary for the formation of indigo, and as it is extremely easily hydrolyzed by water and decomposes completely on standing in air [2,6], this explains the lack of the formation of indigo in dimethylformamide and in wet benzene or by utilizing stored chloroisatin. The presence of water in dimethyl-

Scheme 2

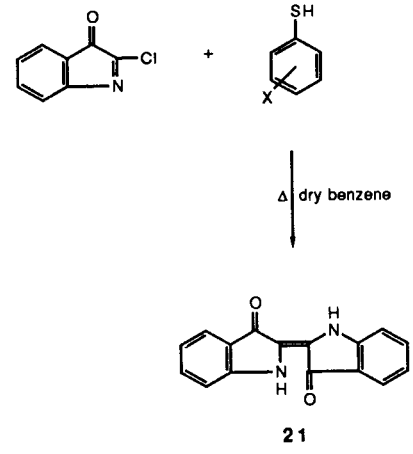

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Table IV

Preparation of Indolylidene Derivatives from Isatin [a] and Partial Spectral Data

No.	Ar	Yield (%)	mp (°C)	lit [15] mp (°C)	ν C=O in ir bromoform		δ NH in nmr (dimethyl sulfoxide-d_6)		
5	—	~100	>300	>300	1680	1660		—	
19a	C_6H_5	39	304-307	306-308	1690	1660	8.85	10.85	11.40
19b	*p*-$CH_3OC_6H_4$	42	266-268	263-365	1665	1625	8.85	11.45	12.70
19c	*p*-$O_2NC_6H_4$		>300	>300	1675	1665	8.95	11.30	11.62
19d	*m*-ClC_6H_4	45	285-288	290-292	1680	1655	8.85	11.15	12.75
19e	4-C_5H_4N	48	>300	>320	1695	1650	10.30	12.20	

[a] These compounds were also prepared from the reactions of 2-chloroindol-3-one, and their detailed spectra data were discussed previously [15].

Table V

Preparation of Indigo from the Reaction of 2-Chloroindol-3-one [a] with Thiolphenols

Entry	thiolphenol	solvent	heating/time	yield (%)
1	C_6H_5SH	dry benzene	reflux/4 hours	70
2	*p*-$CH_3C_6H_4SH$	dry benzene	reflux/4 hours	65
3	*p*-ClC_6H_4SH	dry benzene	reflux/5 hours	59
4	*m*-$CH_3C_6H_4SH$	dry benzene	reflux/5 hours	48
5	*o*-$CH_3C_6H_4SH$	dry benzene	reflux/6 hours	30
6	C_6H_5SH	dimethylformamide	100°/4 hours	~15
7	*p*-$CH_3C_6H_4SH$	dimethylformamide	100°/4 hours	<20
8	*o*-$CH_3C_6H_4SH$	dimethylformamide	100°/5 hours	trace
9	C_6H_5SH	wet benzene	reflux/4 hours	<30
10	*p*-$CH_3C_6H_4SH$	wet benzene	reflux/4 hours	<30
11 [b]	C_6H_4SH	dry benzene	reflux/4 hours	none
12 [b]	*p*-$CH_3C_6H_4SH$	dry benzene	reflux/4 hours	none

[a] Freshly prepared 2-chloroindol-3-one was used except for Entry 11 and 12. [b] The stored 2-chloroindol-3-one (one week after preparation) was used.

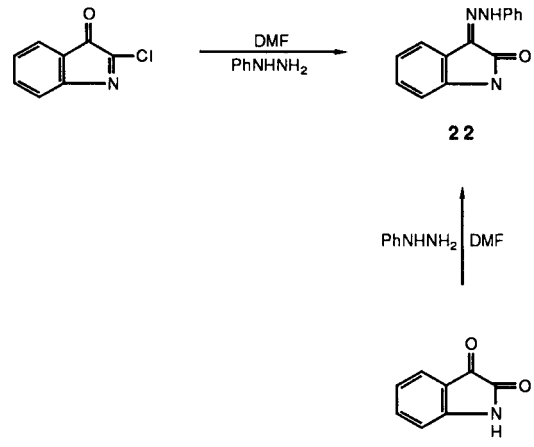
formamide and in wet benzene led to the hydrolysis of 2-chloroindol-3-one, and long storage led to its decomposition. Other previous workers isolated only traces of indigo from the reaction of chloroisatin with thiophenol [5], evidently not using the critical optimum reaction conditions (*i.e.* dry, freshly distilled benzene and freshly prepared chloroisatin).

Piperazine-2,5-dione did not condense with 2-chloroisatin at all in dry toluene, and the starting material was recovered; presumably the base or acid catalysis is necessary for the condensation of piperazine-2,5-dione. When 2-chloroisatin was heated with piperazine-2,5-dione in acetic acid and acetic anhydride, a complicated mixture was formed, and it was too difficult to characterize.

Based on these observations, 2-chloroindol-3-one is the correct structure of chloroisatin, and explanation (2) above could be ruled out. The structure of the products from the reaction of 2-chloroindol-3-one strongly depends on the nucleophile and on the reaction conditions. It appears that reactions carried out under rigorously water-free conditions produce 2-substituted indol-3-ones, otherwise 3-substituted indol-2-ones are the major products. This probably provides a partial explanation for the formation of different isomers. It appears that the explanation (1) is most reasonable, although (3) might also be possible.

As 2-chloroisatin is very unstable and is easily hydrolyzed in solvents containing water, the reactive form in such reaction conditions is isatin itself, and it should give the same products in reactions with nucleophile as those produced from the similar reactions with isatin. Indeed, reactions of either 2-chloroisatin or isatin with 1,4-diacetylpiperazine-2,5-dione gave the same products. Similar behaviour was observed with phenylhydrazine as the nucleophile: treatment of 2-chloroisation with phenylhydrazine in dimethylformamide led only to the isatin 3-phenylhydrazone (**22**), and the same product **22** was isolated from the reaction of isatin with phenylhydrazine in dimethylformamide.

Scheme 3



2-Chloroindol-3-one (**1**) decomposed readily on standing by absorbing moisture in the air to form isatin. This has also been demonstrated by an X-ray determination: 2-chloroisatin (**1**) was prepared as described before and the crystals were obtained in very dilute benzene; however, the X-ray result shows clearly that the structure of the crystals is isatin, which indicates that the 2-chloroisatin had been

converted completely into the isatin. The structure of isatin had been determined earlier [19] but was not very accurate. A redetermination of the structure of isatin will be reported elsewhere [20].

An attempt to obtain the ^{13}C nmr spectrum of 2-chloroindol-3-one in dimethyl sulfoxide-d_6 gave ^{13}C nmr spectrum of isatin identical with that of an authentic spectrum, probably due to the unavoidable presence of water in dimethyl sulfoxide-d_6. An attempt to obtain the spectrum by heating isatin with phosphorus pentachloride in benzene-d_6 failed because of limited solubility.

Conclusion.

2-Chloroindol-3-one (**1**) is the correct structure of the chloroisatin produced from isatin and phosphorus pentachloride, although it is unstable and easily hydrolyzed. The evidenced supporting structure **1** is chemical, as described in this paper. 2-Chloroindol-3-one condenses readily with a variety of *N*- and *S*-nucleophiles to yield 2-oxo-3-indolylidenes. However with active methylene compounds, it yields either 3-oxo-2-indolylidenes or 2-oxo-3-indolylidenes depending on the reaction conditions.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Capillary Melting Point Apparatus without correction. The ^1H and ^{13}C nmr spectra were obtained on a JEOL JNM FX100 spectrometer. The ir spectra were recorded on a Perkin-Elmer 330 spectrometer. 1,4-Diacetylpiperazine-2,5-dione and 1-acetyl-3-arylidenepiperazine-2,5-dione were prepared as previously described [15].

2-Chloroindol-3-one (**1**).

Isatin (7.35 g, 0.05 mole) was refluxed with phosphorus pentachloride (11 g) in fresh distilled, dry benzene (refluxing with sodium and benzophenone) for 4 hours. After cooling to room temperature, the resulting purple solid was collected by filtration, and washed twice with dry benzene, mp 176-178° (lit [1] mp 180°). For the reaction described in this paper, it was used immediately after preparation, without storage.

3,6-Di(2-oxo-e3-indolylidene)piperazine-2,5-dione (**16**).

Method A.

Compound **16** was prepared by the reaction of 1,4-diacetylpiperazine-2,5-dione with 2-chloroisatin as previously described [15].

Method B.

A mixture of 1,4-diacetylpiperazine-2,5-dione (0.99 g, 5 mmoles), isatin (1.47 g, 10 mmoles) and triethylamine (1.1 g, 11 mmoles) in dimethylformamide was stirred at 40° for 5 hours. The purple precipitate was separated by filtration and washed with ethanol to give **16**, mp >300°; ir (bromoform): 3200 (NH), 1680 (C=O), 1665 (C=O), 1615 (C=C); uv/vis (ethanol): λ max (ε) 480 (17300), 420 (22900).

Anal. Calcd. for $C_{20}H_{12}N_4O_4$: C, 64.51; H, 3.22; N, 15.05. Found: C, 64.67; H, 3.13; N, 15.27.

3-(2-Oxo-3-indolylidene)-6-arylmethylidenepiperazine-2,5-dione (**19**).

Method A.

Preparation was made from the condensation of 1-acetyl-3-arylmethylidenepiperazine-2,5-dione and 2-chloroindol-3-one as previously reported [15].

Method B.

The appropriate 1-acetyl-3-arylmethylidenepiperazine-2,5-dione (10 mmoles), isatin (10 mmoles) and triethylamine (11 mmoles) were heated and stirred in dimethylformamide at 50° for 10 hours. The reaction mixture was poured into water; after cooling, the resulting solid was filtered off and washed with ethanol to give the desired products **19a-19e**.

A typical example of the spectral data of **19**: **19b** ir (bromoform): ν 3200 (NH), 1665, 1625, 1600 (C=C) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 12.70 (NH), 11.45 (NH), 8.85 (NH), 6.95-8.00 (m, ArH), 3.95 (s, 3H, OCH_3) ppm; ^{13}C nmr: δ 170.5, 157.4, 156.1, 140.8, 136.1, 134.5, 131.2, 128.6, 126.8, 125.1, 123.3, 121.6, 121.3, 121.0, 120.4, 116.9, 88.9, 55.1 (OCH_3); uv/vis (ethanol): λ max (ε) 398 (18500) nm.

Reaction of 2-Chloroindol-3-one with Thiolphenols, Formation of Indigo.

A mixture of 10 mmoles of freshly prepared 2-chloroindol-3-one and 10 mmoles of thiophenol was refluxed in dry benzene for 4 hours. After cooling to room temperature, the dark blue indigo was filtered off and washed with benzene and ethanol, mp >300°; ir (bromoform): ν 3260, 1620, 1600, 1580, 1450, 1050 cm^{-1}.

Anal. Calcd. for $C_{16}H_{10}N_2O_2$: C, 73.28; H, 3.82; N, 10.69. Found: C, 73.06; H, 3.99, N, 10.34.

Heating 2-chloroindol-3-one and thiophenol in dimethylformamide gave the mixture of indigo, isatin and some unidentified products.

5-(3-Oxo-2-indolylidene)hydantoin (**10**) [9].

The reaction mixture of 2-chloroisatin (3.30 g) and hydantoin (2 g) in acetic acid (30 ml) and acetic anhydride (2 ml) was heated at 160° for 8 hours. After cooling to 25°, it was poured into water, the resulting precipitate was collected and washed with ethanol, then recrystallized from ethanol-dimethylformamide, mp 307-309° (lit [9] mp >300°); ^1H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 11.84 (s, 1H, NH), 10.91 (s, 1H, NH), 10.46 (s, 1H, NH), 8.50 (d, 1H, ArH), 7.93 (m, 1H, ArH), 6.95-7.30 (m, 2H, ArH) ppm; ^{13}C nmr: δ 169.6 (CO), 164.9 (CONH), 154.1 (CONH), 141.4, 134.2, 129.7, 126.9, 125.3, 121.6, 120.3, 109.9 ppm; ir (nujol): ν 3430, 3320, 3150, 1715, 1600 cm^{-1}.

Anal. Calcd. for $C_{11}H_7N_3O_3$: C, 57.64; H, 3.57; N, 18.34. Found: C, 57.89; H, 3.36; N, 18.21.

5-(2-Oxo-3-indolylidene)hydantoin (**11**) [9].

The reaction mixture of isatin (7.4 g), hydantoin (5 g), and fused sodium acetate (10 g) was heated in acetic acid (50 ml) and acetic anhydride (2 ml) at 50° for 4 hours and then poured into water. The solid was filtered off, washed with water and ethanol, and dried at 100°, mp 312-314° (lit [9] mp >300°); not soluble in nmr solvents; ir (nujol): ν 3250, 3150, 1755, 1685, 1620, 1290 cm^{-1}.

Anal. Calcd. for $C_{11}H_7N_3O_3$: C, 57.64; H, 3.57; N, 18.34. Found: C, 57.92; H, 3.47; N, 18.70.

3-Oxo-2-(2-oxo-3-indolylidene)indole (**12**) [11].

2-Chloroisatin (4.95 g) and 2-indolinone (4.00 g) were refluxed in dry toluene (100 ml) for 2 hours, the resulting violet red solid was collected, washed with toluene and ethanol, and recrystallized from dimethylformamide mp > 330° (lit [11] mp > 340°); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 11.10 (d, 1H, NH), 8.90 (d, 1H, NH), 6.95-7.90 (m, 8H, ArH); ^{13}C nmr: δ 170.6 (CO), 151.9 (CONH), 140.6, 138.0, 136.4, 131.9, 128.7, 124.2, 123.8, 121.1, 120.7, 118.8, 112.8, 111.5, 109.1, 106.5.

Anal. Calcd. for $C_{16}H_{10}N_2O_2$: C, 73.21; H, 3.82; N, 10.69. Found: C, 72.82; H, 3.90; N, 10.73.

Reaction of 2-Chloroindol-3-one with Phenylhydrazine.

A reaction mixture of 2-chloroindol-3-one (10 mmoles) or isatin (10 mmoles) and phenylhydrazine (10 mmoles) was stirred at 25° for 4 hours. Then the whole was poured into water, the precipitate was collected by filtration and washed with water, recrystallized from ethanol to give an orange solid **24**, yield 62%; mp 205-207°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 13.05 (s, 1H, CONH), 11.25 (s, s NNH), 7.75-7.00 (m, 9H, ArH); ^{13}C nmr: δ 163.3 (CONH), 142.5, 139.9, 129.4, 128.3, 127.8, 122.7, 121.8, 121.2, 118.6, 114.0, 110.5.

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.89; H, 4.64; N, 17.72. Found: C, 70.61; H, 4.80; N, 17.57.

Crystal Structure Study of **16**.

A red-brown crystal of **16** was sealed in a thin-walled X-ray capillary. The pertinent crystallographic data are presented in Table 1. The data were measured on a Nicolet P3F diffractometer. All calculations were carried out using the SHELXTL system on a DG-Model 30 Eclipse. The final positional parameters are given in Table 2, with the distances and angles in Table 3. Tables of the anisotropic thermal parameters, hydrogen arom parameters, and observed and calculated structure amplitudes are available as supplementary material.

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