Mass Spectral Fragmentation and Rearrangement of Isatin Derivatives

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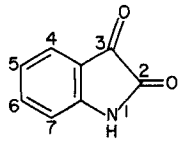
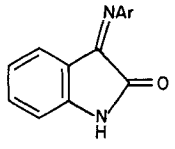
Mass spectral fragmentation pathways were formulated for 1-alkylisatins, 1-alkyl-3-arylimino-2-indolinones and 3-arylimino-2-indolinones bearing no substituent at the 1-position. Deuterium-labelled and ^{13}C-labelled compounds were utilized in this study. An interesting rearrangement of the 1-alkyl compounds, in which the 1-alkyl substituent is incorporated into a fulvene ion, was established.

INTRODUCTION

Isatin (1H-indole-2,3-dione) and its derivatives have been the subject of several instrumentation studies. Of particular interest have been the 3-arylimino-2-indolinones (3-(arylimino)-1,3-dihydro-2H-indol-2-ones), which have been the subject of infrared,[1] ultraviolet[2,3] and visible[3] spectroscopic studies, as well as polarographic[2,4,5] studies. The 3-arylimino-2-indolinones have also been the subject of a mass

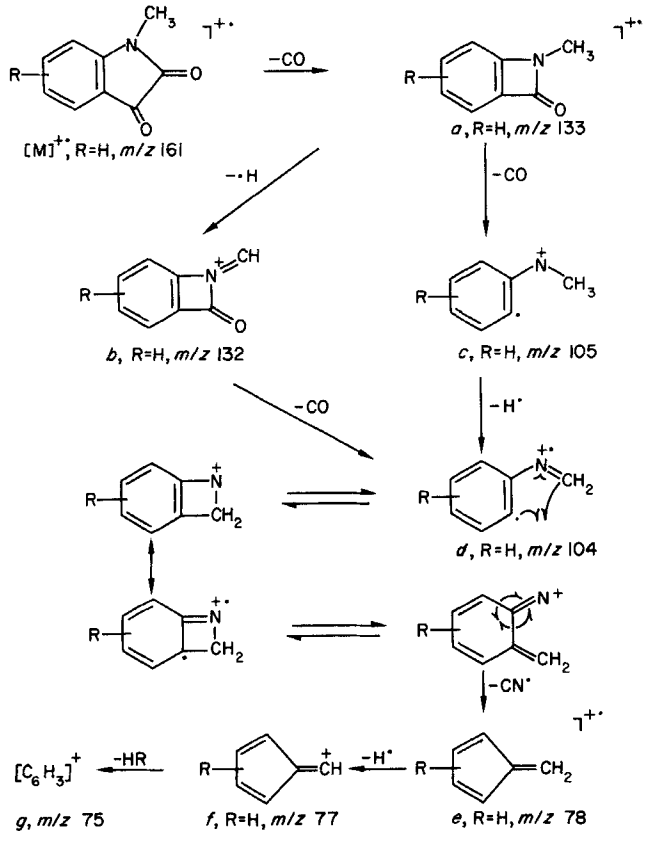

Isatin


3-Arylimino-2-indolinones

spectral investigation by Ballantine, Fenwick and Popp,[6] in which it was determined that interesting rearrangements occurred during fragmentation. This report was preceded with one by Ballantine, Fenwick and Alam[7] in which the mass spectra of isatin, 1-methylisatin and other simple derivatives of isatin were examined. It was the purpose of this study to further define the fragmentation pathways and rearrangements of 1-alkylisatins and 3-arylimino-2-indolinones.

RESULTS AND DISCUSSION

Scheme 1 depicts the fragmentation pathway for substituted 1-alkylisatins, wherein specific ions are indicated for the parent compound **2**, 1-methylisatin. Ion *a*, which results from loss of CO from the parent ion, leads to ion *d* via loss of a hydrogen radical and CO, or vice versa, proceeding through ions *b* or *c*, respectively. Ions *a*–*d* are the same as shown by Ballantine, Fenwick and Alam in their fragmentation scheme for **2**. However, Scheme 1 shows that in the subsequent loss of cyanide radical from ion *d* to form fulvene radical ion *e*, the carbon lost is *not* the methyl carbon.



Scheme 1

Instead, a *benzene ring carbon is lost* with the cyanide radical.

Table 1 displays the major fragment ions of isatin and the 1-alkylisatins which led to the mechanistic interpretation in Scheme 1. Initially, in an examination of the spectrum of 1-methylisatin, it seemed improbable that the carbon lost with the cyanide radical could be the methyl carbon, since that would involve the unprecedented loss of three hydrogen atoms from the same carbon atom. The next compound examined was the trideuteromethyl compound **3**. Ion *e* for **3** was two mass units higher than for **2**. It seemed unlikely that two deuterium atoms were being transferred from the trideuteromethyl group to the benzene ring. More

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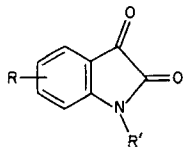
Table 1. Relative abundances of the major fragment ions of isatin and 1-alkylisatins



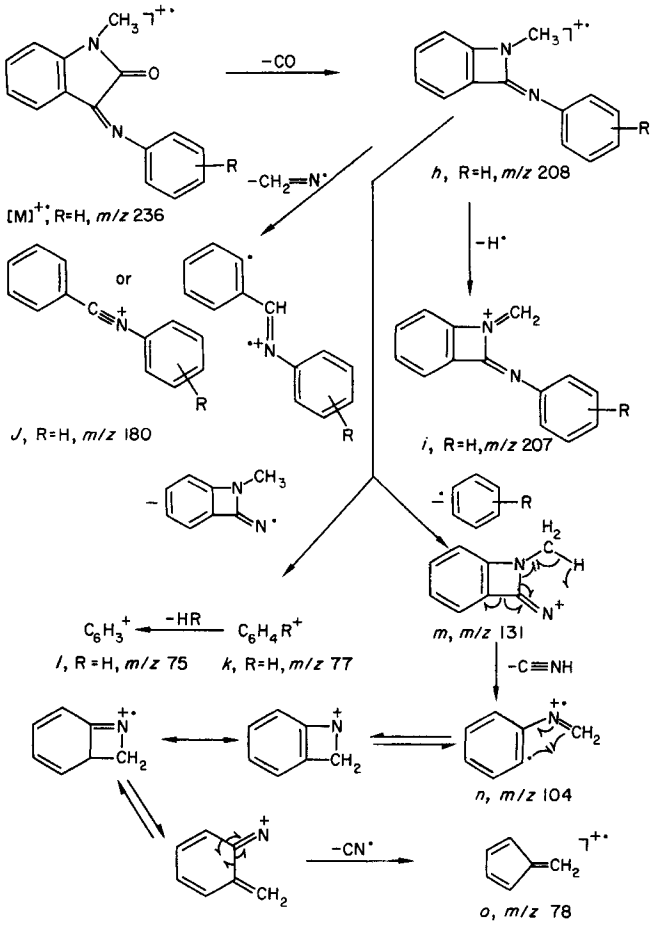
Compound	R	R'	[M]$^{+\cdot}$	Mass fragment, m/z (relative abundance) a	b	c	d	e	f	g
1	H	H	147	119	118	91	90	78	77	75
			(63)	(100)	(2)	(17)	(8)	(0)	(0)	(3)
2	H	CH_3	161	133	132	105	104	78	77	75
			(100)	(52)	(15)	(92)	(98)	(61)	(34)	(8)
3	H	CD_3	164	136	134	108	106	80	78	75
			(77)	(36)	(9)	(70)	(100)	(62)	(20)	(7)
4	H	CH_2CH_3	175	147	146	119	118	92	91	89
			(100)	(13)	(17)	(64)	(64)	(14)	(17)	(4)
5	H	CD_2CD_3	180	152	150	124	122	96	94	92
			(100)	(11)	(4)	(63)	(28)	(9)	(4)	(4)
6	H	$^{13}CH_3$	162	134	133	106	105	79	78	76
			(90)	(37)	(12)	(56)	(100)	(27)	(17)	(8)
7	5-Br	CH_3	239	211	210	183	182	156	155	75
			(77)	(71)	(6)	(84)	(100)	(28)	(16)	(38)
8	5-CH_3	CH_3	175	147	146	119	118	92	91	75
			(80)	(44)	(11)	(66)	(100)	(25)	(38)	(3)
9	7-CH_3	CH_3	175	147	146	119	118	92	91	75
			(100)	(35)	(6)	(70)	(69)	(18)	(36)	(3)
10	5-NO_2	CH_3	206	178	177	150	149	123	122	75
			(100)	(76)	(4)	(69)	(35)	(<2)	(<1)	(17)

likely was the possibility that a CD_2 unit from the trideuteromethyl group was an integral part of ion *e*.

The above contention was further supported by compounds **4** and **5**. Ion *e* for compound **4** was 14 mass units greater than for **2**, while ion *e* for **5** was 18 mass units higher than for **2**. These results were consistent with the incorporation of the 1-alkyl substituents ($CHCH_3$ and $CDCD_3$, respectively) into the benzo portion of the molecule prior to the loss of cyanide radical.

Proof that the carbon lost with the cyanide radical in the fragmentation of **2** was a ring carbon came from an examination of the mass spectrum of 1-(methyl-^{13}C)-1H-indole-2,3-dione (**6**). Ion *e* appeared at *m/z* 79, a single mass unit greater than for **2**. Thus, the fulvene radical ion *e* is the postulated structure arising after loss of cyanide radical in the fragmentation pathway of compounds **2–10**.

Ion *f* results from the fulvene ion radical *e* by loss of a hydrogen radical. However, an alternate ion with the same mass as ion *f*, arising from ion *d*, can also contribute to its intensity. A phenyl ion can result from ion *d* by hydrogen transfer from the methylene carbon to the ring, followed by loss of HCN. This alternate pathway was supported by the appearance of the phenyl ion at *m/z* 77 (relative abundance of 20%) for compound **6**. The intensities of fulvene radical ions *e* and ions *f* (whose intensities are increased by a contribution from phenyl ions) for compounds **2–10** indicate that the loss of a ring carbon as cyanide radical predominates over the loss of the methyl carbon as HCN. Loss of hydrogen plus substituent (HR) from fulvene ion *e* (or the corresponding phenyl ion) was also noted. The latter loss was more abundant



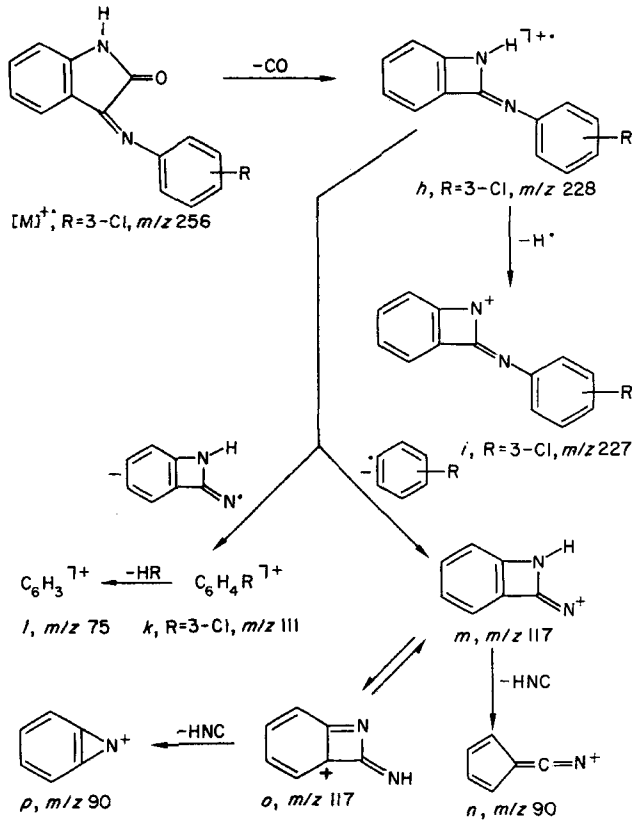
Scheme 2

with compounds bearing substituents with the best leaving ability, i.e. the bromo compound **7**[8] and the nitro compound **10**.

Ion *h* in Scheme 2, which results from the loss of CO from the parent 1-alkyl-3-arylimino-2-indolinones, is a pivotal intermediate, much the same as ion *a* (also resulting from the loss of CO from parent) is a pivotal intermediate in Scheme 1. All of the ions emanating from ion *h* (ions *i*–*o*) are supported by the chloro compound **12** and the corresponding trideutero compound **13** (Table 2). For instance, ion *i* for **13** is two mass units higher than for **12**, which is consistent with its production from *h*. In a fragmentation pathway reminiscent of Scheme 1, fulvene radical ion *o* arises from ion *h* via ions *m* and *n* in a process which involves the subsequent losses of aryl radical, HNC and cyanide radical, respectively. Incorporation of two deuterium atoms into ion *o* for the *N*-trideuteromethyl compound **13** is consistent with this scheme.

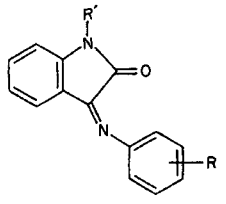
Ion *k*, the counterpart of ion *m* which results when the charge remains with the aryl portion of the molecule, suffers a loss of hydrogen plus substituent (HR) to produce ion *l*. Compounds having substituents with the best leaving ability, i.e. halogen[8] (compounds **12**–**14**) displayed ion *l* with high relative abundance. The converse was true also, as ion *l* appeared at low relative abundance with compounds **11**, **15** and **16**.

Fragmentation pathways for compounds **17**–**20** of Table 2 are depicted in Scheme 3, with specific ions



Scheme 3

Table 2. Relative abundances of the major fragment ions of 3-arylimino-2-indolinones



Compound	R	R′	[M]+·	Mass fragment, m/z (relative abundance)							
				h	*i*	*j*	*k*	*l*	*m*	*n*	*o*
11	H	CH_3	236	208	207	180	77	75	131	104	78
			(82)	(45)	(100)	(25)	(88)	(8)	(53)	(21)	(11)
12	3-Cl	CH_3	270	242	241	214	111	75	131	104	78
			(78)	(48)	(83)	(20)	(64)	(94)	(100)	(26)	(14)
13	3-Cl	CD_3	273	245	243	215	111	75	134	106	80
			(100)	(41)	(43)	(8)	(20)	(30)	(31)	(7)	(4)
14	2-F	CH_3	254	226	225	198	95	75	131	104	78
			(100)	(41)	(90)	(40)	(49)	(78)	(99)	(27)	(17)
15	3-CH_3	CH_3	250	222	221	194	91	75	131	104	78
			(83)	(45)	(100)	(19)	(69)	(7)	(59)	(15)	(10)
16	2-OCH_3	CH_3	266	238	237	210	107	75	131	104	78
			(100)	(13)	(35)	(2)	(2)	(4)	(30)	(10)	(6)
17	3-Cl	H	256	228	227	—	111	75	117	90	—
			(56)	(100)	(12)		(36)	(69)	(7)	(18)	
18	2-OCH_3	H	252[a]	224	223	—	107	75	117	90	—
			(73)	(43)	(7)		(2)	(3)	(39)	(8)	
19	3-OCH_3	H	252	224	223	—	107	75	117	90	—
			(65)	(100)	(16)		(9)	(9)	(5)	(12)	
20	2-Cl,5-CH_3	H	270[b]	242	241	—	125	89[c]	117	90	—
			(15)	(58)	(15)		(9)	(24)	(8)	(11)	

[a] Base peak *m/z* 195.
[b] Base peak *m/z* 235 = $[M-Cl]^+$.
[c] *m/z* 75 (3).

indicated for compound **17**. Again, the loss of CO from the parent yields the central intermediate ion *h*. Loss of hydrogen radical produces ion *i*, while losses of aryl radical and HNC from ion *h* results in the postulated fulvene ion *n*. This pathway is in agreement with that devised by Ballantine, Fenwick and Popp[6] in their scheme for the fragmentation of similar 3-arylimino-2-indolinones. Alternatively, the fragment ion at *m/z* 90 could be postulated as the benzoazirine ion *p*, resulting from hydrogen transfer (ion *o*) followed by loss of HNC.

It is interesting to note that the fragmentation schemes show fulvene ion formation from isatin derivatives in two mechanistically distinct processes. In Schemes 1 and 2 fulvene ion formation occurs with incorporation of the 1-alkyl substituent, while in Scheme 3 the proposed fulvene ion results from compounds bearing no 1-alkyl substituent. In Scheme 3 ion *h* undergoes *N*-aryl scission (as in Scheme 2), to produce the two even-electron fragment ions *m* and *k*. It is felt that *most* of the *m/z* 75 fragment (ion *l*) results from ion *k* through the loss of HR, *rather* than from the benzo portion of the molecule as suggested by Ballantine, Fenwick and Popp.[6] In fact, the data generated by these authors also supports the generation of *m/z* 75 from ion *k*. Of the thirteen compounds which they studied, only three showed a significant *m/z* 75 fragment, and those were the ones containing a halogen substituent on the phenyl ring.[8] Thus, the compounds bearing substituents with an affinity for leaving are those which produce a significant *m/z* 75 fragment. Compounds **17–20** also support the production of ion *l* from ion *k*. Chloro compounds **17** and **20** both produce significant abundances of ions *l*, whereas methoxy compounds **18** and **19** do not. Compound **20**, upon loss of HR (HCl), produces ion *l* of *m/z* 89, because of the methyl substituent. A much smaller abundance of *m/z* 75 is also produced with **20**, presumably from the benzo portion of the molecule.

In summary, this study has dealt with the mass spectral fragmentation pathways of isatin derivatives, and represents an extension and clarification of results obtained by earlier workers who laid the groundwork for study in this area. An interesting finding was that 1-alkylisatins and 1-alkyl-3-arylimino-2-indolinones undergo fragmentation and rearrangement to fulvene ions which have incorporated the 1-alkyl substituents.

EXPERIMENTAL

All mass spectra were recorded using a Finnigan Model 4023 (70 eV, electron impact) mass spectrometer. Samples were introduced by direct probe insertion. General procedures for the preparation of the 1-alkylisatins and the 3-arylimino-2-indolinones are illustrated with the specific preparations below. The physical constants for these compounds are recorded in Tables 3 and 4. For the preparation of the isotopically labelled compounds, iodomethane-d_3 was purchased from Aldrich Chemical Company and iodoethane-d_5 and iodomethane-^{13}C were purchased from Stohler Isotope Chemicals. Isotopic purities of all labelled compounds were determined to be greater than 95%. Isotopic purity was established by finding the ratio of the parent ion ($[M]^{+\cdot}$) to the sum of $[M]^{+\cdot}$ and $[M-1]^{+\cdot}$ and multiplying by 100%.

1-Methyl-d_3-1*H*-indole-2,3-dione (3). To a solution of 20.0 g (0.136 mol) of isatin in 100 cm^3 of dimethylformamide was added, in portions with icebath cooling, 4.13 g (0.172 mol) of sodium hydride. After 15 minutes of stirring, a solution of 25.0 g (0.172 mol) of iodomethane-d_3 in 25 cm^3 of dimethylformamide was added to the dark solution over a period of 15 min. After stirring overnight, the mixture was diluted with water (200 ml). The fine orange needles which formed

Table 3. Physical constants for the 1-alkylisatins[a]

Compound	Yield (%)	m.p. (°C)	Formula	Calc. (%) C	H	N	Found (%) C	H	N
3	63	131.5–132.5	$C_9H_4D_3NO_2$	65.84	4.30[b]	8.53	65.59	4.24	8.54
4	40[c]	91–92[d]	$C_{10}H_9NO_2$	68.56	5.18	8.00	68.50	5.20	7.93
5	40[c]	91–93	$C_{10}H_4D_5NO_2$	66.64	5.03[e]	7.77	66.55	5.07	7.81
6	28	131–132	$^{13}CC_8H_7NO_2$	66.66[f]	4.35	8.64	66.60	4.42	8.66
7	48[g]	170–172[h]	$C_9H_6BrNO_2$	45.03	2.52	5.84	45.30	2.63	5.89
8	48[g]	150–152[i]	$C_{10}H_9NO_2$	68.56	5.18	8.00	68.50	5.21	7.98
9	57[j]	173.5–175.5[k]	$C_{10}H_9NO_2$	68.56	5.18	8.00	68.50	5.36	7.98
10	86[g,l]	202–204[m]	$C_9H_6N_2O_4$	52.43	2.93	13.59	52.60	3.22	13.49

[a] Those compounds studied but not included in this table were commercially available.
[b] H_4+D_3 calc. as H_7.
[c] Recryst. from toluene–hexane.
[d] Lit. m.p. 95 °C; R. Stolle, R. Bergdoll, M. Luther, A. Auerhahn and W. Wacker, *J. Prakt. Chem.* **128**, 1 (1930).
[e] H_4+D_5 calc. as H_9.
[f] $^{13}C+C_8$ calc. as C_9.
[g] Recryst. from ethanol–water.
[h] Lit. m.p. 172–173 °C; G. Heller, *Chem. Ber.* **53B**, 1545 (1920).
[i] Lit. m.p. 148 °C; Hegel, *Ann. Chem.* **232**, 217 (1886).
[j] Recryst. from ethanol.
[k] Lit. m.p. 171–172 °C; G. Heller, R. Fuchs, P. Jacobsohn, M. Raschig and E. Schutze, *Chem. Ber.* **59B**, 704 (1926).
[l] Unrecryst. yield.
[m] Lit. m.p. 203 °C; W. Borsche, H. Weussmann and A. Fritzsche, *Chem. Ber.* **57B**, 1149 (1924).

Table 4. Physical constants for the 3-arylimino-2-indolinones

Compound	Yield (%)	m.p. (°C)	Formula	Calc. (%) C	Calc. (%) H	Calc. (%) N	Found (%) C	Found (%) H	Found (%) N
11	75[a]	147–148	$C_{15}H_{12}N_2O$	76.25	5.12	11.86	76.43	5.07	11.87
12	88[b]	157–158.5	$C_{15}H_{11}ClN_2O$	66.54	4.10	10.35	66.50	4.26	10.41
13	99[b]	155–157	$C_{15}H_8D_3ClN_2O$	65.81	4.05[c]	10.24	65.89	3.95	10.07
14	45[b]	119–122	$C_{15}H_{11}FN_2O$	70.85	4.36	11.02	71.06	4.46	10.91
15	75[b]	131–132.5	$C_{16}H_{14}N_2O$	76.78	5.64	11.19	76.90	5.79	11.01
16	97[d,e]	106–112	$C_{16}H_{14}N_2O_2$	72.16	5.30	10.52	72.20	5.48	10.46
17	90[f]	229–231	$C_{14}H_9ClN_2O$	65.50	3.53	10.92	65.29	3.47	10.81
18	61[f]	182–184	$C_{15}H_{12}N_2O_2$	71.41	4.80	11.11	71.30	5.07	10.97
19	22[g]	181–184	$C_{15}H_{12}N_2O_2$	71.41	4.80	11.11	70.80	5.21	10.86
20	52[b]	149–151	$C_{15}H_{11}ClN_2O$	66.54	4.10	10.35	66.80	4.19	10.44

[a] Recryst. from toluene–hexane.
[b] Cryst. by addn of hexane to toluene reaction medium.
[c] H_8+D_3 calc. as H_{11}.
[d] Unrecryst. yield.
[e] Recryst. from ether–hexane.
[f] Cryst. directly from ethanol reaction medium.
[g] Recryst. from ethanol.

were collected and air-dried to yield 14.0 g (85.3 mmol), 63% of **3**, m.p. 131–132.5 °C; IR (potassium bromide) 1720 (C=O) cm^{-1}; NMR (deuteriochloroform) δ 7.80–7.55 (m, 2, protons at the 4- and 6-positions), 7.40–6.87 (m, 2, protons at the 5- and 7-positions).

3-[(3-Chlorophenyl)imino]-1,3-dihydro-1-methyl-2*H*-indol-2-one (12). A solution of 10.0 g (62.9 mmol) of 1-methylisatin and 10.0 g (78.4 mmol) of 3-chloroaniline in 125 cm^3 of toluene was heated at reflux for 24 hours with Dean–Stark separation of water. (In the preparation of the *ortho*-substituted compounds **14** and **16**, a catalytic amount of *p*-toluenesulfonic acid was used.) The hot solution was diluted with 50 cm^3 of hexane and crystallization commenced. After standing overnight the rust-colored prisms were collected and air-dried to yield 14.7 g (88%) of **12**, m.p. 157–158.5 °C; IR (potassium bromide) 1730 (C=O) cm^{-1}; NMR (dimethyl sulfoxide-d_6) δ 7.72–6.75 (m, 7, aromatic), 6.44 (d, $J = 8$ Hz, 1, H at 7-position), 3.20 (s, 3, CH_3).

3-[(-3-Chlorophenyl) imino]-1,3-dihydro-2*H*-indol-2-one (17). A solution of 14.7 g (0.100 mol) of isatin and 12.8 g (0.100 mol) of 3-chloroaniline in 150 cm^3 of absolute ethanol was heated at reflux for 30 min and then allowed to stand overnight. (In the preparation of compound **20**, toluene was employed as the reaction solvent and a catalytic amount of *p*-toluenesulfonic acid was used. Reaction time was 20 h.) The resulting orange prisms were collected and air-dried to yield 23.1 g (90%) of **17**, m.p. 229–231 °C; IR (potassium bromide) 1740 (C=O) cm^{-1}; NMR (deuteriochloroform) δ 10.57 (broad s, 1, NH), 7.54–6.47 (m, 8, aromatic).

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