Cyclization of Cyanoethylated Ketones as a Route to 6-Substituted Indole Derivatives

Jan Bergman[a]* and Birgitta Stensland[a†]

KI, Unit of Organic Chemistry, Department of Biosciences at Novum, SE 141 57 Huddinge, Sweden
*E-mail:jan.bergman@ki.se
†Retired

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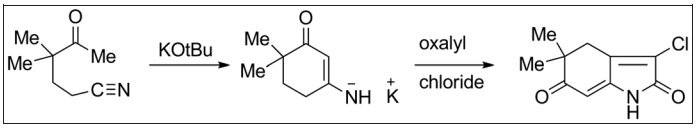

δ-Cyanoketones are quickly cyclized with KOtBu to 3-aminocyclohex-2-enone derivatives, which in turn will give substituted indoles when treated with oxalyl chloride. Thus, 3-amino-6,6-dimethylcyclohex-2-enone gave 3-chloro-6,6-dimethyl-2,5,6,7-tetrahydroindole-2,5-dione, whose structure was corroborated by X-ray crystallography, whereas the corresponding molecule without the blocking gem-dimethyl groups, 3-aminocyclohex-2-enone, gave *via* hydrogen shifts 6-chloro-3-hydroxyoxindole.

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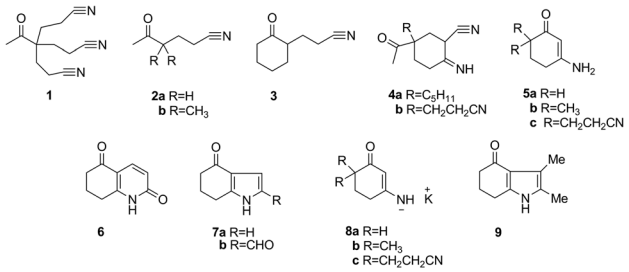
INTRODUCTION

Cyanoethylation is a simple and synthetically useful operation [1,2]. Thus, acetone and acrylonitrile plus a suitable basic catalyst will readily give the tris-cyanoethylated product **1** because the reaction steps two and three proceed faster than the first step. On an industrial scale, however, the 1:1 product 5-ketohexanenitrile **2a** can readily be prepared, and the substance is also commercially available. α,α-Dialkylketones are regioselectively cyanoethylated at the carbon atom bearing the alkyl groups. Thus, for instance, methylisopropylketone readily regioselectively will give compound **2b** [3]. Enamine derivatives of ketones can also be used to obtain 1:1 products. In this fashion, for example, **3** is readily available by cyanoethylation of the morpholino enamine derivative of cyclohexanone [2].

In spite of their ready availability at a low cost, very few secondary transformations on **1** and **2** and related molecules have been reported. In 1972, Cason *et al*. reported incorrectly that base-induced condensation of 3,3-biscyanoethylated octane-2-one will give rise to **4a** [4], that is, a Thorpe cyclization, which in principle should be evident from work reported by Colonge [5] and by Pfleiderer [6]. In fact, condensations leading to 3-aminocyclohex-2-enones **5** will invariably occur. Cason *et al*. also incorrectly contended that **1** should be its cyclized isomer **4b**.

In fact (as NMR data now clearly demonstrate), the originally (1942) assigned structure is indeed correct [7]. Thus, condensation of **2b** under basic conditions likewise readily yields the condensation product **5b** and not a Thorpe product. The trinitrile **1** similarly yields **5c** [8]. Molecule **5a** is a commonly used starting material for synthesis of various nitrogen heterocycles (e.g., **6** [9–11], **7a** [11], and **7b** [12,13]).

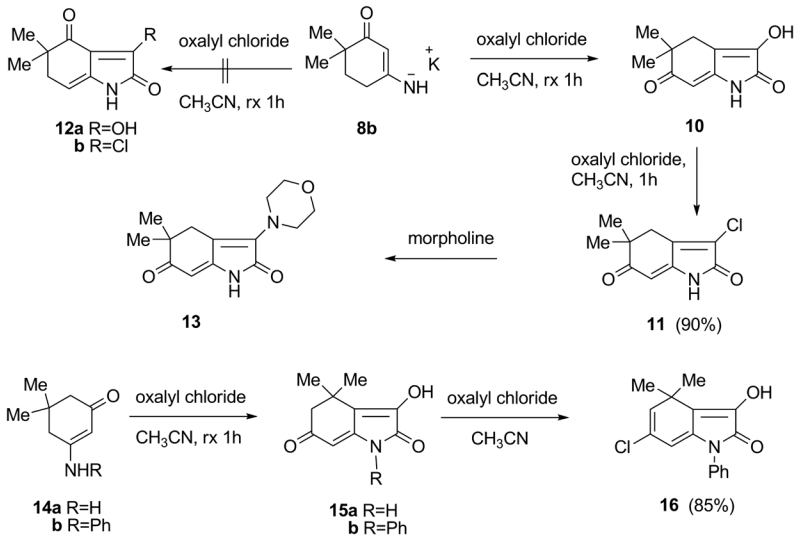


RESULTS AND DISCUSSION

It has now been found that the monocyanoethylated ketones **2a** and **2b** under the influence of potassium *tert*-butoxide in hot THF (for **2b**) or dioxane (for **2a**) quickly (5–10 min) will give the potassium salts **8a** and **8b**, respectively, as readily isolable solids in high yields. The *gem*-dimethyl derivative **8b** is rather insensitive and can even be recrystallized from water. Acidic hydrolysis of **8b** gave the known molecule 3-hydroxy-6,6-dimethylcyclohex-2-enone [14,15]. Alkylation of **8a** with 3-chloro-2-butanone followed by heating gave the expected and already known indole derivative **9** [16,17], whereas treatment of **8b** with oxalyl chloride gave an unexpected indole derivative, **11**, as outlined in Scheme 1. The yield was high (90%).

The chlorine atom in **11** could readily be displaced by nucleophiles, such as morpholine, which gave **13** (Scheme 1). The known amino derivatives of dimedone, **14a** and **14b**, when treated similarly gave the chlorine-free products **15a** and **15b**. Under forcing conditions, **15b** could be converted to the mono chloro derivative **16**. Obviously, the sterically demanding *gem*-dimethyl group in 4-position is preventing any transformation of the hydroxyl group in the 3-position.

Scheme 1



The conventionally expected regioisomeric products from **8b**, **12a**, or **12b** were not formed at all that might be explained in terms of a severely deactivated enaminone system in the initial product **17a** that will therefore react as the enol **17b** (Scheme 2).

3-Hydroxycyclohex-2-enone similarly gave an unstable intermediate that readily eliminated CO and CO_2 yielding the known molecule **18** [18,19] rather than any cyclized product. That the product of the reaction between **8b** and oxalyl chloride could not be **12b** was clearly indicated by the fact that the coupling constant between the CH_2 group and the olefinic proton is very low ($J = 0.1$ Hz) in the ^{1}H NMR spectrum of **11**. The correct structure was finally corroborated by an X-ray analysis (Fig. 1). The crystal structure of **11** crystallizes in the monoclinic space group $P2_1/n$ with four molecules in the unit-cell. The unit-cell axes are as follows: $a = 5.716(1)$, $b = 29.947(2)$, and $c = 5.934(1)$ Å, $\beta = 102.93(1)$.

The cyclization of the enaminone **8b** in 4-position (and not in 2-position) relative the carbonyl function as outlined in Scheme 1 seems to be without precedents, and the closest example is due to Sha *et al*. [20] who found that the silylated derivative **19** could be brominated by *N*-bromosuccinimide in the presence of azo-bisisobutyronitrile to give the product **20**,which subsequently could be cyclized to **21** [18]. Another intriguing example has been provided by Langer *et al*. [21] who treated doubly silylated dimedone, **22** with oxalyl chloride and obtained the benzofuranone derivative **23**, obviously a cousin to **15a**.

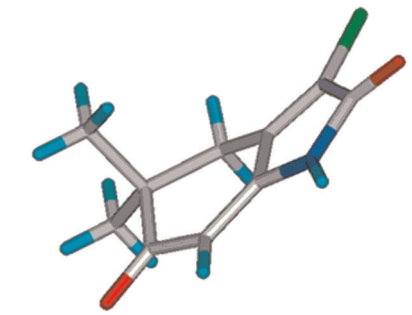
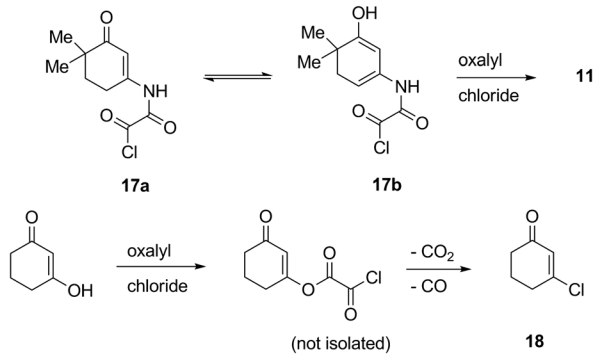
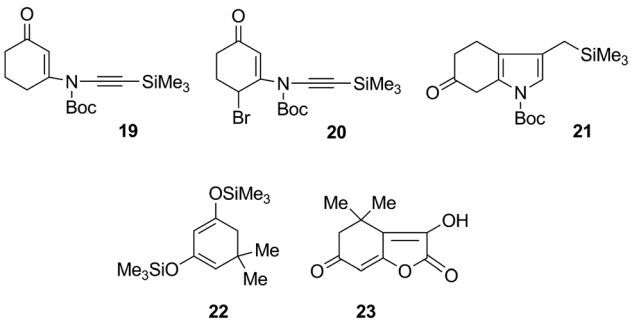


Figure 1. The crystal structure of **11**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scheme 2



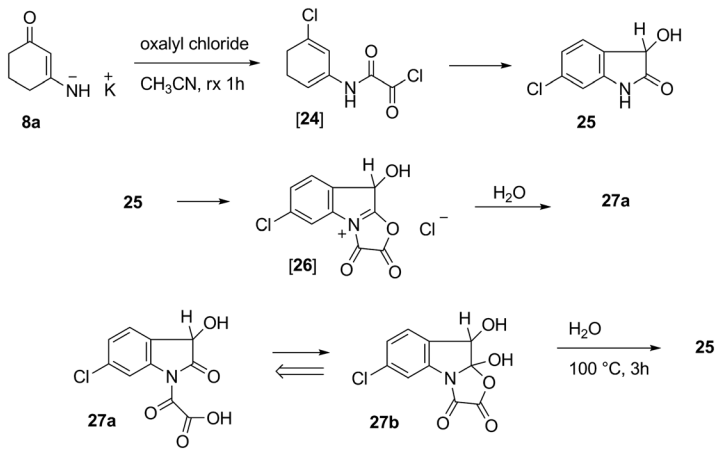


Reaction of **8a**, or equally well the corresponding acid, 3-aminocyclohex-2-enone, with oxalyl chloride gave a product with a chlorine atom in the 6-membered and not in the 5-membered ring as indicated in Scheme 3. The proposed intermediate **24** contains chlorine in the 6-membered ring as distinct from the corresponding intermediate, **17b**, discussed in Scheme 2, where the *gem*-dimethyl group is preventing a chlorination process. In similarity with the previous case, the intermediate **24** will cyclize to the 4-position rather than to the 2-position, thus yielding, after transposition of hydrogen atoms, the 6-chlorinated indole derivative **25**, which under the conditions will react with a second molecule of oxalyl chloride to give **27a**.

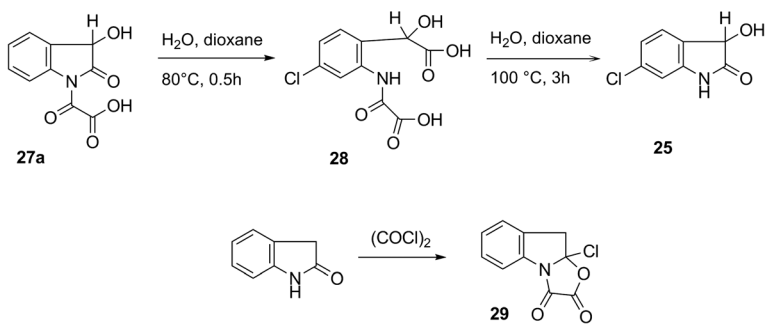
The final product **27** existed exclusively as the chain tautomer **27a**, rather than the ring tautomer **27b** that could be transformed to a pyridinium salt, which differed very little from **27a** when it comes to the signals in the ^{13}C NMR spectrum. As expected, signal differences were only clearly observable in the side chain. In connection with the discussion of the intermediate **26** and the final product **27a**, the isolation of **29**, from treatment of oxindole with oxalyl chloride, by Magnus is of considerable interest [22]. The side chain in **27a** could be removed by hot water yielding 6-chloro-3-hydroxyoxindole **25**, a reaction that starts with a ring opening to **28**, which subsequently will lose the side chain followed by a recyclization to **25**. Compound **27a** featured an aliphatic signal at 71.1 ppm, whereas the ring-opened molecule **28** had a CH function that resonated at 40.8 ppm. The final recyclization yielded 6-chloro-3-hydroxyoxindole that as a cyclic molecule featured a aliphatic CH signal at 67.8 ppm. The structure of **25** was proven by an independent synthetic reduction of 6-chloroisatin with hypophosphorous acid. This reductive agent previously had been used on one single occasion, namely reduction of 5,7-diiodoisatin to 5,7-diiodo-3-hydroxyoxindole a long time ago [23] (Scheme 4).

Reduction of 6-chloroisatin with sodium borohydride in ethanol or acetic acid failed, and dimeric products were obtained. Actually, hypophosphorous acid proved to be a useful reductive agent as several isatin derivatives could conveniently be reduced to 3-hydroxyoxindoles. In connections with NMR studies of, for example, 5-fluoro-3-hydroxyoxindole, it was observed that in a solution of dimethylsulfoxide (DMSO), oxidative coupling to 3,3′-dihydroxy-5,5′-difluoro-3,3′-bioxindole was complete within 24 h at room temperature.

Scheme 3



Scheme 4



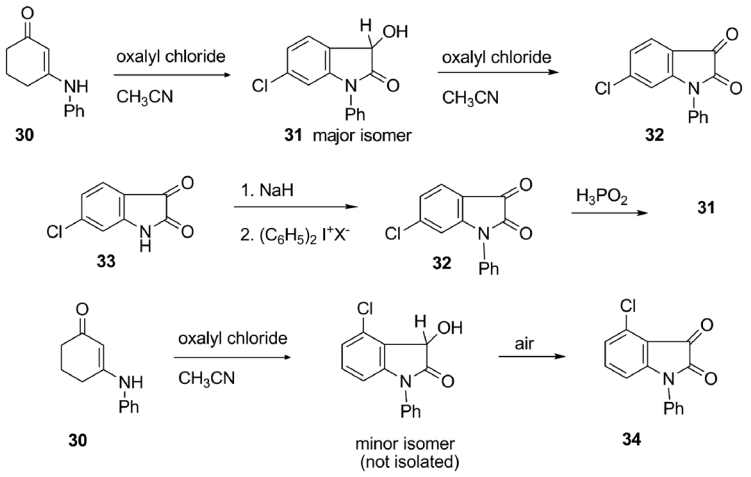
The phenylamino derivative **30**, readily prepared from 1,3-cyclohexanedione and aniline, 130°C/5 min, similarly could by cyclized to **31**, whose structure was proven by phenylation of the anion of 6-chloroisatin **33** with diphenyliodonium triflate as outlined in Scheme 5. This new procedure appears to be general, and isatin itself could be similarly transformed to *N*-phenylisatin. 4-Chloroisatin similarly could be phenylated to **34**, a molecule that also could be isolated in small amounts from the mother liquor of **31** after several days. Obviously, a "conventional" cyclization of **30** induced by oxalyl chloride had to a minor extent occurred, and subsequent aerial oxidation led to **34**. Ready aerial oxidation of N-substituted (e.g., *N*-phenyl-3-hydroxy-oxindole) 3-hydroxyoxindoles is a well-known process [24]. The two substituted isatins, **33** and **36**, needed for the phenylation studies were synthesized from the oxime **35** obtained *via* the classical Sandmeyer procedure [25]. Separation of the mixture of **33** and **36** was very easy, following literature procedures [25,26] outlined in Scheme 6.

Acidification of the mother liquor with hydrochloric acid after isolation of the 4-isomer, **36**, gave, due to cyclization of **37**, the 6-isomer in pure form. The relative ratio of the isomers was 2:1 with the 4-chloroisomer predominating, which is in agreement with results reported by Senear [27] but in disagreement with the relative yields reported by Sadler, who reported the ratio 33/35 with the 6-isomer slightly predominating [25,26]. The facile synthesis of **33** and **36** is in sharp contrast to a report by Kraynack *et al.* [28]. These workers prepared **33** and **36** in a lengthy and time-consuming way. The ring phenylated molecule **38** could be similarly cyclized to **39** with oxalyl chloride as outlined in Scheme 7.

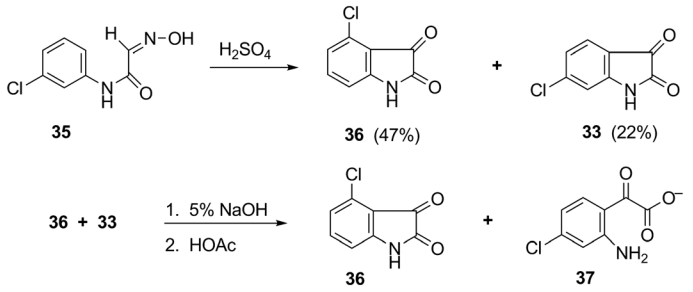
The 3-hydroxycyclohex-2-enone derivatives **25**, **27**, and **31** could easily be ring-opened with piperidine or morpholine. During that process also, oxidation took place and the product, as illustrated in Scheme 8, was identical with the product obtained by ring opening of the corresponding isatin derivative. Isatin itself **41** undergoes a similar ring opening to **42** [29].

As expected, because of hindered rotation around the amide bond, the CH_2 groups in the piperidine ring featured five signals in the ^{13}C NMR spectra. From the transformation **10** → **11**, it is clear that hydroxyl groups in position 3 of the indole rings can be converted to the corresponding chloro derivatives, and in order, to study the generality of

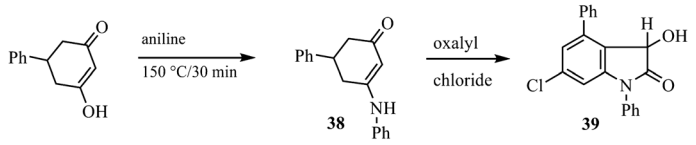
Scheme 5



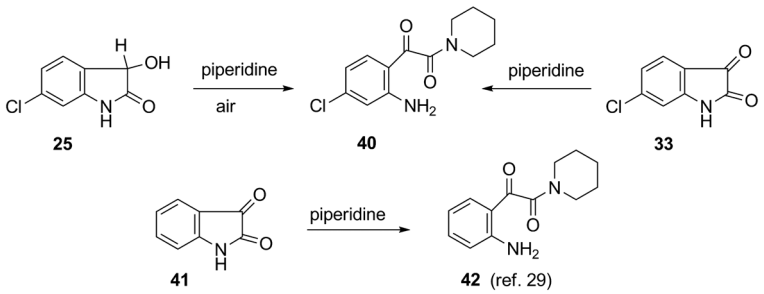
Scheme 6



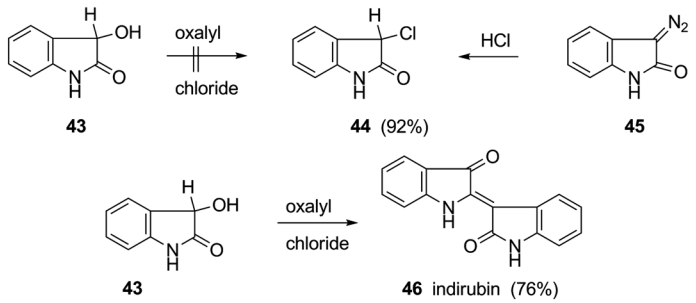
Scheme 7



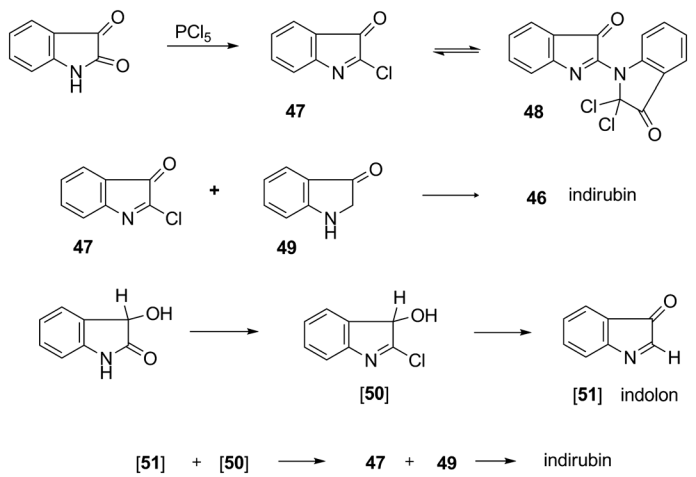
Scheme 8



Scheme 9



Scheme 10



this reaction, 3-hydroxyindole **43** itself was treated with oxalyl chloride in acetonitrile and the expected product, the known molecule 3-chlorooxindole **44**, was not formed (Scheme 9). However, **44** could readily be prepared from the diazo compound **45**. 3,6-Dichlorooxindole could be similarly prepared.

After 3 h, the violet-red reaction solution from **43** and oxalyl chloride deposited indirubin **46** in a respectable yield (76%). In Scheme 10, a speculative rationalization is offered, which involves the classical intermediate indolon **51** as the crucial intermediate. Traditionally, indirubin **46** has been prepared in excellent yields by reacting indoxyl **49** (or *N*-acetylindoxyl) with a product obtained by treating isatin with PCl_5 in hot benzene. This orange-red product was a long time considered to be **47** but is in fact largely its dimer **48** [30]. However, they are interrelated *via* an equilibrium. As indicated in Scheme 10, formation of indirubin from 3-hydroxyoxindole and oxalyl chloride seems to involve similar types of transformations.

Finally, it should be added that indirubin **46** and some of its derivatives have attracted considerable attention among biochemists ever since it was reported that indirubin **46** and several of its derivatives selectively inhibit cyclin-dependent kinases [31–34].

CONCLUSIONS

A novel but limited synthetic method to substituted indole derivatives has been developed. As spin-offs, a simple (and fast) method to the valuable synthon 3-aminocyclohex-2-enone has been found, and perhaps most importantly, a one-step method to indirubin has been realized.

EXPERIMENTAL

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 instrument at 300.1 MHz for ^{1}H and 75.5 for ^{13}C, respectively, using the residual (DMSO-d_6) resonances as reference, unless otherwise stated. The IR spectra were performed on an Avatar 300 FT-IR spectrometer (Thermo Nicolet). The elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. All chemicals originated from commercial sources and were used as received, except THF, which was distilled from sodium and benzophenone. 5-Ketohexanenitrile **2a** was purchased from TCI Europe, Belgium.

α,α,α-Triscyanoethylacetone (1). This molecule was prepared as described in the literature [3]. Yield: 92%, mp 166–167°C; IR 2957, 2250 (C≡N), 1695 (C=O), 1474, 1361, 1171 cm^1; ^{1}H NMR δ: 1.87 (t, CH_2), 2.17 (s, CH_3), 2.32 (t, CH_2); ^{13}C NMR δ: 11.4 (t, CH_2), 25.6 (q, CH_3), 27.3 (t, CH_2), 52.2 (s), 120.2 (s, C≡N), 211.1 (s, C=O).

4,4-Dimethyl-5-ketohexanenitrile (2b). Methyl isopropyl ketone was cyanoethylated following a literature procedure [3]. Yield: 88%, bp 132–134°C/18 mm; ^{1}H NMR δ: 1.08 (s, 6H, $2CH_3$), 1.80 (t, 2H, CH_2), 2.11 (s, 3H, $COCH_3$), 2.35 (t, 2H, CH_2); ^{13}C NMR δ:12.1 (t), 23.3 (t), 25.0 (q), 33.7 (q), 46.4 (s), 120.6 (s), 212.0 (s).

3-Amino-6,6-dimethylcyclohex-2-enone, potassium salt (8b). The ketonitrile **2b** (13.9 g, 0.1 mol) was added dropwise to a stirred solution of potassium *t*-butoxide (11.2, 0.1 mol) in THF (80 mL) under argon. The reaction mixture was heated at reflux for 15 min and then allowed to cool. After 2 h, the solid formed was collected and dried, 15.9 g (93%) of **8b** mp >260 dec. This potassium salt is not sensitive to water and can in fact be recrystallized from this medium. Actually, evaporation of the THF mother liquor followed by recrystallization from water gave an additional quantity (1.0 g) of **8b**. ^{1}H NMR δ: 0.93 (s, 6H, 2 CH_3), 1.61 (q, 2H, CH_2), 2.25 (q, 2H, CH_2), 4.70 (s, 1H, CH), 4.91 (s, 1H, NH); ^{13}C NMR δ: 25.3 (q), 25.9 (t), 35.6 (t), 37.9 (s), 95.5 (d), 167.2 (s), 197.1 (s).

3-Amino-6,6-dimethylcyclohex-2-enone (5b). The potassium salt **8b** (1.77 g, 10 mmol) was stirred in water (10 mL) containing acetic acid (1.0 mL) for 0.5 h, whereupon the mixture was extracted with ether (2 × 50 mL). The extract was dried and evaporated. Crystallization from benzene gave the title compound, 1.11 g (80%) mp 208–210°C; IR 3343, 3138, 2956, 2919, 1649 (w), 1530, 1469, 1440, 1388, 1211, 1162, 824 cm^{-1}; ^{1}H NMR δ: 0.95 (s, 6H, 2 CH_3), 1.64 (q, 2H, CH_2), 2.27 (q, 2H, CH_2), 4.80 (s, 1H, CH), 6.62 (2H, NH_2); ^{13}C NMR δ: 25.0 (t), 25.1 (q), 35.3 (t), 38.3 (s), 95.5 (d), 165.5 (s), 199.3 (s). *Anal*. Calcd for $C_8H_{13}NO$: C 69.03; H 9.41; N 10.06. Found: C 68.90; H 9.62; N 10.12.

3-Hydroxy-6,6-dimethylcyclohex-2-enone. The potassium salt **8b** (2 mmol) was added to ethanol (5 mL) containing hydrochloric acid (0.5 mL). After a period of reflux (20 min), the solution was evaporated and the residue extracted with ether. After a drying period over $MgSO_4$, the solvent was evaporated, and the residue, 1.5 mmol, (75%) was identified as the title compound. The ^{13}C data were identical with those reported by Maini *et al*. [14]

3-Amino-6,6-bis-cyanoethylcyclohexene-2-one (5c). The trisnitrile **1** (10.85 g, 0.05 mol) was dissolved in DMF (90 mL) plus THF (80 mL), and potassium *t*-butoxide (5.6 g) was added to the stirred solution under argon at 55°C. After 1 h at this temperature, the reaction mixture was concentrated and poured into water and acidified with acetic acid. The solid formed was collected after 4 h, 9.05 (83%) mp 215–217°C (lit. [5] mp 215–217°C); ^{1}H NMR δ: 1.73 (m, 6H), 2.37 (m, 6H), 4.87 (s, 1H), 6.76 + 6.99 (2s, 2NH); ^{13}C NMR δ: 11.5 (t), 23.8 (t), 29.9 (t), 31.2 (t), 43.5 (s), 96.5 (d), 121.0 (s), 166.2 (s), 195.4 (s).

3-Aminocyclohexene-2-one, potassium salt (8a). The same procedure as for **8b** was used except that protection with nitrogen (or preferably argon) was necessary. Yield 75%; ^{13}C NMR δ: 22.6 (t), 34.0 (t), 35.6 (t), 96.5 (d), 176.2 (s), 183.2 (s).

3-Aminocyclohexene-2-one (5a). The potassium salt **8a** (1 mmol) was treated with water containing acetic acid as described for the *gem*-dimethyl derivative. Yield 65%, mp 133–134°C (lit. [35] mp 133–134°C). The NMR data were in agreement with data reported in the literature [35].

3-Chloro-5,5-dimethyl-2,4,5,6-tetrahydro-2,6-dioxoindole (11). Oxalyl chloride (5.0 mL) in acetonitrile (20 mL) was added dropwise to a stirred solution of 6,6-dimethyl-3-aminocyclohexene-2-one (2.78 g, 0.02 mol) in acetonitrile (70 mL). This operation resulted in the formation of a precipitate of an acid chloride, which quickly went in solution during the following period (4 h) of reflux. After filtration, the solution was evaporated and treated with methyl acetate, 3.80 g (90%); mp 207–208°C. IR 3219, 2968 (w), 2928 (w), 1732, 1694, 1642, 1630, 1139, 1123, 1053, 870 cm^{-1};

^{1}H NMR δ: 1.11 (s, 6H, 2 CH_3), 2.82 (s, 2H, CH_2, J = 0.1), 5.61 (s, 1H, CH, J = 0.1), 11.0 (s, 1H, NH); ^{13}C NMR δ: 26.0 (q), 34.4 (s). 42.6 (t), 104.9 (d), 123.8 (s), 140.0 (s), 149.2 (s), 165.0 (s), 201.5 (s); *Anal*. Calcd for $C_{10}H_{10}ClNO_2$: C 56.91; H 4.73; N 6.03. Found: C 56.88; H 4.79; N 5.99.

3-Chloro-5,5-bis-cyanoethyl-2,4,5,6-tetrahydro-2,6-dioxoindole. The procedure given for **11** was followed starting with **5c**. Yield: 77%, mp 210°C, dec. ^{1}H NMR except for a CH-singlet at 5.61 ppm, a complex pattern of multiplets; ^{13}C NMR δ: 11.7 (t) 29.4 (t), 31.1 (t), 47.9 (s), 105.5 (d), 120.3 (s), 124.7 (s), 138.8 (s), 149.5 (s), 164.9 (s), 198.3 (s). *Anal*. Calcd for $C_{14}H_{12}ClN_3O_2$: C 58.25; H 4.17; N 4.84. Found: C 57.99; H 4.25; N 4.73.

3-Hydroxy-4,4-dimethyl-2,4,5,6-tetrahydro-2,6-dioxoindole (15a). The same procedure as for **11** was used, starting with compound **14a**, a known molecule [36]. Yield 82%, mp 190°C, dec. IR 3350, 1706, 1615, 1480, 1449, 1326, 1180, 1068, 923, 868 cm^{-1}; ^{1}H NMR δ: 1.28 (s, 6H, 2CH_3), 2.44 (s, 2H, CH_2), 3.90 (br s, 1H, OH), 5.54 (s, 1H, CH), 10.4 (s, 1H, NH); ^{13}C NMR δ: 27.7 (q), 32.5 (s), 52.1 (t), 104.2 (d), 118.3 (s), 144.3 (s), 152.6 (s), 166.7 (s), 196.5 (s). *Anal*. Calcd for $C_{10}H_{11}NO_3$: C 62.16; H 5.74; N 7.25. Found: C 61.85; H 5.90; N 7.11.

3-Morpholino-5,5-dimethyl-2,4,5,6-tetrahydro-2,6-dioxoindole (13). 3-Chloro-5,5-dimethyl-2,4,5,6-tetrahydro-2,6-dioxoindole **11** (212 mg, 1 mmol) was heated at reflux for 10 min in dioxane (5 mL) containing morpholine (200 mg). After completed reaction, the mixture was poured into water, and the yellowish solid was collected and dried, 220 mg (83%) mp 187–188°C. ^{1}H NMR δ: 1.15 (s, 6H, 2CH_3), 2.68 (s, 2H, CH_2), 3.52 (s, 4H, 2CH_3), 3.64 (s, 4H, 2CH_2O), 5.25 (s, 1H, CH), 10.4 (s, 1H, NH); ^{13}C NMR δ: 26.0 (q), 35.7 (t), 41.9 (s), 48.1 (t), 66.1 (t), 100.1 (d), 109.8 (s), 138.3 (s), 152.5 (s), 167.5 (s), 201.2 (s). *Anal*. Calcd for $C_{14}H_{18}N_2O_3$; C 63.10; H 6.92; N 10.68. Found: C 63.22; H. 6.99; N 10.72.

2,3-Dimethyl-4-oxo-4,5,6,7-tetrahydroindole (9). The potassium salt **8a** (1.49 g, 10 mmol) and 3-bromo-2-butanone (1.51 g, 10 mmol) were heated at reflux temperature in dioxane for 1 h. After filtration and evaporation, the residue was crystallized from toluene, 1.29 g (79%); mp 226–227°C (lit. [16] mp 226–227°C); ^{13}C NMR δ: 9.8 (q), 9.9 (q), 22.2 (t), 23.7 (t), 38.3 (t), 111.5 (s), 117.9 (s), 123.7 (s), 141.5 (s), 193.3 (s).

5-Methyl-3-aminocyclohex-2-enone. 5-Methyl-3-hydroxycyclohex-2-enone (2.52 g, 20 mmol) was dissolved in concentrated aqueous ammonia (8 mL). After 24 h at room temperature, the solvent was evaporated to yield a white solid, 2.40 g (100%) mp 146–148°C (lit. [37] mp 146–148°C); ^{13}C NMR δ: 20.7 (q), 28.7 (d), 36.0 (t), 49.0 (t), 96.8 (d), 167.5 (s), 194.9 (s).

Synthesis of compound 27a. Oxalyl chloride (6.34 g, 50 mmol) was added dropwise to a stirred solution of 3-aminocyclohex-2-enone (2.22 g, 20 mmol) or an equivalent suspension of the potassium salt **8a** in acetonitrile (80 mL) at 50°C. A period of reflux (2.5 h) finalized the conversion to the product that was isolated after filtration (hot), evaporation, and titruation with methyl acetate, and dried, 5.75 g(93%) mp ≈ 200°C dec.; IR 3300–3000 (br), 1744, 1725, 1671, 1616, 1485, 1172, 921, 817 cm^{-1}; ^{1}H NMR δ: 6.08 (s, 1H, 3-H), 6.91 (d, 1H, 7-H, J_1 = 1.98), 6.99 (dd, 1H, 5-H, J_1 = 1.98, J_2 = 7.93), 7.33 (d, 1H, 4-H, J_2 = 7.93), 10.9 (s, 1H, OH); ^{13}C NMR δ: 70.9 (d), 110.3 (d), 121.7 (d), 122.8 (s), 126.8 (d), 133.6 (s), 144.6 (s), 158.1 (s), 158.2 (s), 172.4 (s); *Anal*. Calcd for $C_{10}H_6ClNO_5$: C 47.21; H 2.36; N 5.52. Found: C 46.98; H 2.44; N 5.47.

Pyridinium salt of 27a. Compound **27a** (256 mg, 1 mmol) and pyridine (79 mg, 1 mmol) were dissolved in acetonitrile (10 mL) at 70°C. The solid formed on cooling was collected 225 mg (62%) mp >260°C; ^{13}C NMR δ: 70.5 (d), 110.2 (d), 121.7 (d), 123.2 (s), 124.8 (d), 126.7 (d), 134.5 (s), 138.9 (d), 144.6 (s), 147.5 (d), 159.4 (s), 160.2 (s), 172.7 (s).

Hydrolysis of 27a. Preparation of 28. Compound **27a** (256 mg, 1 mmol) was heated for 0.5 h at 80°C in dioxan (5 mL) and water (3 mL). After filtration, the filtrate was concentrated, and the crystals formed were collected, 160 mg (54%), mp 160°C dec.; ^{1}H NMR δ: 4.50 (s, 1H), 5.7 (br s, OH), 6.78–6.86 (m, 3H), 10.4 (s, 1H). No clear assignments of the OH groups in the carboxyl functions could be made. ^{13}C NMR δ: 40.8 (d), 108.6 (d), 111.5 (s), 120.4 (d), 123.9 (d), 129.6 (s), 131.0 (s), 144.5 (s), 162.6 (s), 178.2 (s). *Anal*. Calcd for $C_{10}H_8ClNO_6$: C 43.87; H 2.92; N 5.13. Found: C 43.55; H 3.06; N 4.97.

6-Chloro-3-hydroxyoxindole (25). A mixture of 6-chloroisatin (1.86 g) dioxane (6 mL), water (4 mL), and H_3PO_2 (50%, in water, 6 mL) was heated under nitrogen at reflux temperature for 1 h. The solution obtained was allowed to cool and the whitish solid collected after 24 h, 1.49 g (79%) mp 190–195°C. IR 3300–3100, 1708, 1616, 1181, 1069, 920 cm^{-1}; ^{13}C NMR δ: 68.8 (d), 109.7 (d), 121.4 (d), 126.2 (d), 128.3 (s), 133.4 (s), 143.8 (s), 177.9 (s); *Anal*. Calcd for $C_8H_6ClNO_2$: C, 52.40; H 3.27; N 7.63. Found; 52.17; H 3.40; N 7.49.

Hydrolysis (3h) of compound 27a. Compound **10** (2.22 g, 10 mmol) was heated at reflux temperature in water (30 mL) and dioxane (30 mL) for 3 h, whereupon the mixture was filtered and the solid formed on cooling (after concentration) was collected 1.05 g (56%). The spectral data showed its identity with 6-chloro-3-hydroxyoxindole **25**.

2-Amino-4-chloroglyoxylylpiperidide (40) from 6-chloroisatin. A mixture of 6-chloroisatin (1.86 g), water (8 mL), dioxane (8 mL), and piperidine (0.6 g) was heated at reflux temperature for 5 min. After concentration, additional water was added, and the light yellow solid formed was collected, 2.36 g (80%), mp 132–133°C. IR: 3418, 3295, 2939, 2855, 1601, 15540, 1473, 1431, 1240, 1209, 969, 920, 851 cm^{-1}; ^{1}H NMR δ: 1.41 (m, 2H), 1.60 (dd, 4H), 3.18 (dd, 2H), 3.54 (dd, 2H), 6.60 (dd, 1H, J_1 = 1.83, J_2 = 8.71), 6.91 (d, 1H, J_1 = 1.83), 7.30 (d, 1H, J_2 = 8.71), 7.52 (br s, 2H, NH_2); ^{13}C NMR δ: 23.7 (t), 25.0 (t), 25.7 (t), 41.1 (t), 46.3 (t), 111.7 (s), 115.1 (d), 115.8 (d), 134.7 (d), 140.4 (s), 153.0 (s), 164.5 (s), 193.2 (s); *Anal*. Calcd for $C_{13}H_{15}ClN_2O_2$: C 58.70; H 5.74; N 10.53. Found: C 58.63; H 5.81; N 10.40.

2-Amino-4-chloroglyoxylylpiperidide from 27a. Compound **27a** (256 mg, 1 mmol) and piperidine (0.25 mL) were heated at reflux in dioxane (5 mL) for 0.5 h, whereupon the reaction mixture was concentrated and treated with water. The light yellow solid formed was collected, washed with water, and dried, yield 85%. This sample was identical with a sample from the previous preparation.

3-Hydroxyoxindole. Isatin (14.7 g, 0.1 mol) was reduced with sodium dithionate following a literature procedure [38]. Yield: 73%, mp 167–168°C (lit. [39] mp 167–168°C); ^{1}H NMR δ: 4.85 (d, 1H, 3-H, J = 6.6), 6.20 (d, 1H, OH, J = 6.6), 6.80 (d, 1H, 7-H), 6.95 (dd, 1H, 5-H), 7.18 (dd, 1H, 6-H), 7.29 (d, 1H, 4-H), 10.2 (s, 1H, NH); ^{13}C NMR δ: 69.2 (d), 109.5 (d), 121.6 (d), 124.8 (d), 128.9 (d), 129.3 (s), 142.1 (s), 178.0 (s).

5-Fluoro-3-hydroxyoxindole. 5-Fluoroisatin (8.25 g, 50 mmol) was added in portions to a stirred solution of hypophosphorous acid (aq., 25%, 70 mL) at 65°C. After 0.5 h at this temperature, the mixture was allowed to cool and the whitish solid collected 6.8 g (81%) mp 200–201°C; IR 3300–3100, 1697, 1631, 1484, 1463, 1263, 1192, 1137, 1106, 1054, 946, 878, 819 cm^{-1}; ^{1}H

NMR δ: 4.85 (s, 1H, 3H), 6.2 (br s, 1H, OH), 6.71 (m, 1H), 7.01 (m, 1H), 7.12 (m, 1H); ^{13}C NMR δ: 69.4 (d, 3C, J_{CF} = 1.6 Hz), 110.2 (d, 7-C, J_{CF} = 7.7 Hz), 112.4 (d, 6-C, J_{CF} = 24.7 Hz), 115.1 (d, 4-C, J_{CF} = 23.5 Hz), 131.1 (d, 3a-C, J_{CF} = 7.7 Hz), 138.2 (d, 7a-C, J_{CF} = 2.2 Hz), 157.9 (d, 5-C, J_{CF} = 237.7 Hz), 177.9 (s, C=O). *Anal*. Calcd for $C_8H_6FNO_2$: C 57.50; H 3.59; N 8.39. Found: C 57.23; H 3.65; N 8.30.

5-Fluoro-3-hydroxy-2-oxo-3-biindole. 5-Fluoro-3-hydroxyoxindole (1.67 g, 10 mmol) was dissolved in DMSO (10 mL) and the solution kept at 40°C for 24 h and then poured into water to yield a grayish solid, 1.55 g (94%) mp >260°C; IR 3317, 3208, 1697, 1684, 1628, 1482, 1463, 1345, 1261, 1197, 1147, 1122, 869, 828 cm^{-1}; ^{1}H NMR δ: 5.8 (br s, 1H, OH), 6.60 (m, 1H), 6.78 (m, 1H), 7.07 (m, 1H), 10.4 (s, NH); ^{13}C NMR δ: 77.6 (d, 3-C, J_{CF} = 1.6 Hz), 110.4 (d, 6-C, J_{CF} = 7.8 Hz), 113.0 (d, 6-C, J_{CF} = 25.2 Hz), 116.3 (d, 4-C, J_{CF} = 23.1 Hz), 128.5 (d, 3a-C, J_{CF} = 7.7 Hz), 138.7 (d, 7a-C, J_{CF} = 1.9 Hz), 157.5 (d, 5-C, J_{CF} = 240.0 Hz), 176.0 (s, C=O). *Anal.* Calcd for $C_{16}H_{10}F_2N_2O_4$; C 58.08; H 3.08; N 8.47. Found: C 57.97; H 3.16; N 8.42.

3-Phenylaminocyclohex-2-enone (30). A mixture of 3-hydroxycyclohex-2-enone (11.2 g, 0.1 mol) and aniline (10.5 g, 0.11 mol) was heated under nitrogen for 10 min at 140°C. The solid formed was treated with 2-propanol, and the beige title compound was collected 14.6 g (78 %) mp 178–179°C (lit. [36] mp 176–177°C); ^{1}H NMR δ: 1.87 (m, 2H, CH_2), 2.18 (m, 2H, CH_2), 2.51 (m, 2H, CH_2), 5.37 (s, 1H, CH), 7.1–7.4 (m, 5H, arom CH), 8.9 (s, 1H, NH); ^{13}C NMR δ: 21.5 (t), 28.5 (t), 36.4 (t), 97.9 (d), 122.9 (d), 124.3 (d), 129.1 (d), 139.1 (s), 162.0 (s), 195.8 (s).

5,5-Dimethyl-3-phenylaminocyclohex-2-enone (14b). The procedure described earlier was used, starting with dimedone (0.1 mol). Yield: 85%, lit. [36,40]. The NMR spectra were in agreement with data given by Edmondson *et al*. [41].

3-Chlorooxindole (42). 3-Diazooxindole **43**, (1.59 g, 10 mmol) [42,43] was added in portions to conc. hydrochloric acid (10 mL) diluted with water (5 mL) at 30°C. Vigorous evolution of N_2 ensued, and the product separated was collected after 0.5 h, yield 1.55 g (92%), mp 163–164°C (lit. [44] mp 163°C). IR 3148, 3086, 1730, 1681, 1619, 1468, 1206, 1188, 740, 6.81 cm^{-1}; ^{1}H NMR δ: 5.57, (s, 1H, 3-H), 6.85 (d, 1H), 7.01 (dd, 1H), 7.27 (dd, 1H), 7.35 (d, 1H), 10.8 (s, 1H, NH). ^{13}C NMR δ: 52.2 (d), 110.2 (d), 122.3 (d), 125.6 (d), 126.5 (s), 130.3 (d), 142.4 (s), 173.2 (s).

3,6-Dichlorooxindole. 6-Chloro-3-diazo-oxindole (3.90 g, 20 mmol) was added in portions under stirring to conc. HCl (20 mL) kept at 60–65°C. When the evolution of nitrogen had ceased (0.5 h), the mixture was allowed to cool and the light-beige product collected, 3.81 g (91%), mp 157–158°C (lit. [45] mp 157–158°C). ^{1}H NMR δ: 5.53 (s, 1H, 3-H), 6.88 (d, 7-H, J_1 = 2.0), 7.04 (dd, 1H, 5-H, J_1 = 2.0, J_2 = 8.1), 7.34 (d, 1H, 4-H, J_2 = 8.1), 10.9 (s, NH). ^{13}C NMR δ: 51.6 (d), 110.5 (d), 122.2 (d), 125.5 (s), 127.2 (d), 134.7 (s), 144.0 (s), 173.3 (s).

6-Chloro-4,4-dimethyl-N-phenyl-3-hydroxy-2,4-dihydro-2-oxoindole (16). The procedure given for (**11**) was used starting with **15b**. The light-beige product crystallized directly from the reaction medium. Yield 85%, mp 215–216°C. IR: 3210, 1675, 1637, 1619, 1403, 1321, 1159, 952, 855 cm^{-1}. ^{1}H NMR δ: 1.40 (s, 6H, 2CH_3), 5.38 (d, 1H, J = 1.20) 5.80 (d, 1H, J = 1.20), 7.32–7.53 (m, 5H), 10.7 (br s, 1H, OH). ^{13}C NMR δ: 25.8 (q), 37.1 (s), 102.1 (d), 119.1 (s), 124.3 (s), 127.0 (d), 127.7 (d), 129.4 (d), 131.6 (d), 133.6 (s), 138.2 (s), 142.9 (s), 163.6 (s). *Anal*. Calcd for $C_{16}H_{14}ClNO_2$; C 60.35; H 4.92; N 4.88. Found: C 60.12; H 5.10; N 4.75.

3-Chlorocyclohex-2-enone (18). Oxalyl chloride (6.5 mL) was added in portions to 3-hydroxycyclohex-2-enone (4.48 g, 40 mmol) in acetonitrile (40 mL) at 20°C. The solid part of the starting material quickly went into solution under vigorous evolution of hydrogen chloride. After 2 h, the solvent was evaporated, leaving the product as viscous oil, 4.90 g (92%). The NMR data were identical with those in the literature [19].

6-Chloro-4-methyl-3-hydroxyoxindole. The procedure given for 6-chloro-3-hydroxy-oxindole was followed. Yield 45%, mp 112–115°C. ^{1}H NMR δ: 2.26 (s, 3H, CH_3), 4.82 (s, 1H, 3-H), 5.51 (br s, 1H, OH), 6.60 (d, 1H, J = 1.25), 6.78 (d, 1H, J = 1.25), 10.3 (s, 1H, NH). ^{13}C NMR δ: 17.1 (q), 68.4 (d), 107. (d), 122.5 (d), 124.3 (s), 133.0 (s), 137.7 (s), 143.7 (s), 177.8 (s). *Anal*. Calcd for $C_9H_8ClNO_2$; C 54.60; H 4.05; N 7.08. Found: C 54.43; H 4.11; N 6.96.

6-Chloro-4-methylisatin. A solution of 6-chloro-4-metyl-3-hydroxyoxindole (1 mmol) in DMSO (8 mL) was prepared. After 3 days, the solution was poured into water, and the yellow solid formed (0.8 mmol) was collected, mp 230°C dec. ^{1}H NMR δ: 2.40 (s, 3H, CH_3), 6.70 (d, 1H, J = 1.25), 6.93 (d, 1H, J = 1.25), 11.1 (s, 1H, NH). ^{13}C NMR δ: 17.2 (q), 109.6 (d), 124.3 (d), 141.5 (s), 141.7 (s), 145.5 (s), 151.9 (s), 159.2 (s), 183.5 (s). *Anal*. Calcd for $C_9H_6ClNO_2$; C 55.04; H, 3.06; N 7.16. Found: C 54.86; H 3.17; N 7.00.

6-Chloro-N-phenyl-3-hydroxyoxindole (31). 3-Phenylaminocyclohex-2-enone **30** (1.87 g, 10 mmol) was dissolved in acetonitrile (40 mL), and oxalyl chloride (3.17 g, 25 mmol) in acetonitrile (20 mL) was added dropwise during 15 min. After a period (10 min) of reflux, the solution was evaporated and the residue dissolved in warm 2-propanol. The crystals formed on cooling were collected, 1.42 g (57%), mp 199–200°C. ^{1}H NMR δ: 5.13 (s, 1H, 3-H), 6.63 (d, 1H, 7-H, J_1 = 1.98), 7.14 (dd, 1H, 5-H, J_1 = 1.98, J_2 = 7.93), 7.56 (1H, 4-H, J_1 = 7.93), 7.40–7.60 (m, 5H), 6.5 (br s, 1H, OH). IR 3343, 1715, 1614, 1587, 1502, 1480, 1422, 1372, 1179, 1115, 1064, 926, 864 cm^{-1}. ^{13}C NMR δ: 68.5 (d), 108.8 (d), 122.5 (d), 126.5 (d), 126.6 (d), 127.5 (s), 128.3 (d), 129.8 (d), 133.4 (s), 133.8 (s), 144.9 (s), 175.5 (s). *Anal*. Calcd for $C_{14}H_{10}ClNO_2$; C 64.96; H 3.87; N 5.42. Found: C 64.84; H 3.98; N 5.24.

6-Chloro-N-phenylisatin (32). 6-Chloro-*N*-phenyl-3-hydroxyoxindole **31** (263 mg, 1 mmol) was dissolved in acetonitrile (10 mL), and thionyl chloride (195 mg, 1.5 mmol) was added at 25°C. After approx. 5 min, the solution became turbid. Heating at reflux temperature for 15 min completed the oxidation, and the orange product was collected after cooling and a storage period of 2 h, 220 mg (84%), mp 230°C dec. IR 3075 (w), 1736, 1603, 1596, 1497, 1427, 1365, 1263, 1155, 1069, 938, 877 cm^{-1}. ^{13}C NMR δ: 6.78 (d, 1H, 7-H, J_1 = 1.5), 7.23 (dd, 1H, 5-H, J_1 = 1.5, J_2 = 8.1), 7.68 (d, 1H, 4-H, J_2 = 8.1), 7.5–7.6 (m, 5H). ^{13}C NMR δ: 110.8 (d), 116.6 (s), 123.6 (d), 126.3 (d), 126.6 (d), 128.8 (d), 129.9 (d), 133.0 (s), 142.2 (s), 152.3 (s), 157.6 (s), 181.4 (s). *Anal*. Calcd for $C_{14}H_8ClNO_2$; C 65.36; H 3.13; N 5.47. Found: C 65.13; H 3.28; N 5.42.

4-Chloro-N-phenylisatin (34). The 2-propanol mother liquor from the preparation of **31** was allowed to be in a beaker, in free contact with the air, for several days. Pale orange crystals of the title compound slowly separated, 0.65 (26%), mp 190–191°C. IR 3030 (w), 1731, 1590, 1584, 1351, 1255, 1168, 931 877 cm^{-1}. ^{1}H NMR δ: 6.78 (dd, 1H, 7-H, J_1 = 0.7, J_2 = 7.9), 7.12 (dd, 1H, 5-H, J_1 = 0.7, J_2 = 7.9), 7.58 (dd, 1H, 6-H, J_1 = J_2 = 7.9), 7.3–7.7 (m, 5H). ^{13}C NMR δ: 109.5 (d), 114.7 (s), 124.5 (d), 126.8 (d), 128.7 (d), 129.8 (d), 131.2 (s), 133.1 (s),

138.5 (d), 152.6 (s), 156.8 (s), 179.3 (s). *Anal*. Calcd for $C_{14}H_8ClNO_2$; C 65.36; H 3.13; N 5.47. Found: C 65.08; H 3.26; N 5.39.

N-Phenylisatin. Isatin (1.47 g, 10 mmol) was dissolved in dry DMF (25 mL), whereupon under stirring and N_2-protection, sodium hydride (0.30 g, 80% in oil) was added at 25°C. After completed addition, diphenyliodonium triflate [46] (4.26 g, 10 mmol) was added and the mixture stirred at 40°C for 1 h when water was added to the mixture, which was extracted with ether. This extract in turn was treated with a solution (5%) of sodium hydroxide in water. The water phase was separated and acidified with hydrochloric acid, and the orange-red solid formed was collected 1.95 g (82%), mp 138–139°C (lit. [24,47] mp 138°C; mp 137–139°C). IR 1735, 1608, 1454, 1361, 1299, 1180, 929 cm^{-1}. ^1H NMR δ: 6.82 (d, 1H, 7-H, $J_1 = 8.0$), 7.19 (dd, 1H, 7-H, $J_1 = J_2 = 8.0$), 7.48–7.67 (m, 8H). ^{13}C NMR δ: 110.8 (d), 117.7 (s), 123.7 (d), 124.7 (d), 126.5 (d), 128.5 (d), 129.7 (d), 133.4 (s), 138.1 (d), 151.3 (s), 157.5 (s), 182.8 (s).

Phenylation of 6-chloroisatin. The procedure described earlier was used. Yield: 80% of (**32**). This product was identical with a sample from oxidation of 6-chloro-3-hydroxy-*N*-phenyl-oxindole described earlier.

Phenylation of 4-chloroisatin. The procedure described earlier was used. Yield: 75% of **34**. This product was identical with a sample from oxidation of 4-chloro-3-hydroxy-*N*-phenyl-oxindole described earlier.

5-Phenyl-3-phenylaminocyclohex-2-enone (38). The procedure described for **30** was used. Yield: 93%, mp 210°C dec. ^1H NMR δ: 2.30–2.35 (m, 5H), 5.45 (s, 1H, 2-H), 7.11–7.41 (m, 10H), 9.1 (s, NH). ^{13}C NMR δ: 36.0 (t), 39.4 (d), 43.7 (t), 97.6 (d), 123.1 (d), 124.5 (d), 126.6 (d), 127.0 (d), 128.5 (d), 129.3 (d), 139.1 (s), 143.9 (s), 161.2 (s), 195.2 (s). *Anal*. Calcd for $C_{18}H_{17}NO$: C 82.10; H 6.51; N 5.32. Found: C 81.86; H 6.58; N 5.09.

N,4-Diphenyl-6-chloro-3-hydroxyoxindole (39). The procedure described for **31** was used. Yield: 66%, mp 198°C dec. IR 3300–3100, 1718, 1593, 1571, 1499, 1411, 1356, 1235, 1093, 868 cm^{-1}. ^1H NMR δ: 5.40 (s, 1H, 3-H), 6.62 (d, 1H, 4-H, $J = 1.8$), 7.14 (d, 1H, 6-H, $J = 1.8$), 7.38–7.71 (m, 10H). ^{13}C NMR δ: 68.1 (d), 107.8 (d), 123.1 (d), 124.2 (s), 126.8 (d), 127.7 (d), 128.3 (d), 128.5 (d), 128.6 (d), 129.8 (d), 133.8 (s), 133.9 (s), 137.6 (s), 141.1 (s), 146.1 (s), 175.5 (s). *Anal*. Calcd for $C_{20}H_{14}ClNO_2$: C 71.60; H 4.19; N 4.16. Found: C 71.43; H 4.31; N 4.11.

Preparation of 4-chloroisatin and 6-chloroisatin by Sandmeyer synthesis. Chloral hydrate (33.0 g, 0.2 mol) was dissolved in water (450 mL), and sodium sulfate decahydrate (200 g) was added followed by 3-chloroaniline (25.4 g, 0.2 mol) dissolved in water (80 mL) plus conc. hydrochloric acid (15 mL), which resulted in partial precipitation of 3-chloro-anilinium sulfate. Finally, hydroxylamine hydrochloride (16.5 g, 0.22 mol) in water (60 mL) was added. The mixture was heated to 55°C and then kept between 65 and 70°C for 10 min. During that period, the organic sulfate dissolved and was gradually replaced by the desired oxime. The reaction was finalized by a heating period (10 min) at 70–75°C. The precipitate was collected, washed with water, and dried. For the second step, the oxime was added in portions to sulfuric acid (180 mL) at 60°C. The temperature rose slightly and was kept at 65–70°C. After completed addition, the temperature was kept at 80°C for 10 min. The red reaction mixture was allowed to cool and added to crushed ice. The precipitate formed was collected after 1 h and dissolved in 5% sodium hydroxide, whereupon to pH was adjusted to 8–9 and the mixture was filtered. The filtrate was acidified with acetic acid, and the orange-red solid formed of 4-chloroisatin was collected, 16.7 g (47%). 4-Chloroisatin **36** gave the following data, mp 257–258°C (lit. [27] mp 256.5–258°C). IR 3280, 1731, 1608, 1439, 1245, 1160, 915 cm^{-1}. ^1H NMR δ: 6.83 (dd, 1H, 7-H, $J_1 = 0.8$, $J_2 = 8.3$), 7.01 (dd, 1H, 5-H, $J_1 = 0.8$, $J_2 = 8.3$), 7.52 (dd, 1H, 6-H, $J_1 = J_2 = 8.3$), 11.2 (s, 1H, NH). ^{13}C NMR δ: 110.9 (d), 114.7 (s), 123.6 (d), 131.1 (s), 139.0 (d), 152.1 (s), 158.6 (s), 181.2 (s).

6-Chloroisatin (33). The mother liquor from the preparation earlier was acidified with hydrochloric acid, and the orange solid formed was collected after 1 h, 7.7 g (22%), mp 258–259°C (lit. [27] mp 258–259°C). IR 3180, 1742, 1715, 1609, 1443, 1326, 1207, 1098, 1064, 953, 920, 892 cm^{-1}. ^1H NMR δ: 6.87 (d, 1H, 7-H, $J_1 = 2.0$), 7.05 (dd, 1H, 5-H, $J_1 = 2.0$, $J_2 = 8.1$), 7.47 (d, 1H, 4-H, $J_2 = 8.1$), 11.2 (s, 1H, NH). ^{13}C NMR δ: 112.2 (d), 116.6 (s), 122.7 (d), 126.1 (d), 142.4 (s), 151.8 (s), 159.4 (s), 183.6 (s).

Indirubin (46). 3-Oxo-2-(2-oxo-3-indolylidene)-indole. 3-Hydroxyoxindole (1.49 g, 10 mmol) was dissolved in acetonitrile (35 mL) and oxalyl chloride (3.0 mL) added. The mixture was heated at reflux for 2 h and then left in repos for 24 h. The dark violet-red solid was collected and identified as indirubin [29] 0.99 g (76%) mp >260°C. ^1H NMR δ: 6.89 (d, 1H), 7.00 (dd, 2H), 7.23 (dd, 1H), 7.35 (d, 1H), 7.40–7.65 (m, 2H), 8.76 (d, 1H, 4-H), 10.9 (s, 1H, NH), 11.0 (s, 1H, NH). ^{13}C NMR δ: 107.5 (s), 110.5 (d), 114.3 (d), 119.9 (s), 122.1 (d), 122.2 (d), 122.3 (s), 125.2 (d), 125.5 (d), 130.1 (d), 138.0 (d), 139.2 (s), 141.8 (s), 153.4 (s), 171.8 (s), 189.5 (s). These spectroscopic data are in principal agreement with the data in the literature [48] except that the signal at 189.5 ppm in the ^{13}C NMR spectrum was not reported. This signal emanates from the carbonyl group in 3-position of the indole ring. The doublet at 8.76 ppm in the ^1H NMR spectrum emanates from the hydrogen atom in 4-position in the indole ring. In the literature, this signal was incorrectly assigned as one of the NH groups. This reassignment is in principle in agreement with work published by Adachi e*t al*. [49].

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