Isatin chloride: a phantom. Reactions of 2-(2,2-dichloro-2,3-dihydro-3-oxoindol-1-yl)-3*H*-indol-3-one

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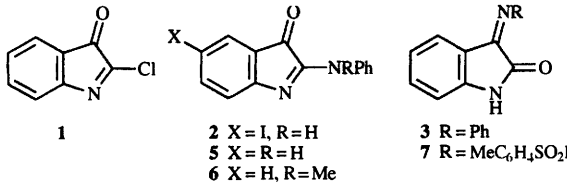
It is shown that 2-chloro-3*H*-indol-3-one 1 and analogues have never actually been isolated and that their reactions, reported over 115 years in 40 papers and 4 patents, are those of more or less impure 2-(2,2-dichloro-2,3-dihydro-3-oxoindol-1-yl)-3*H*-indol-3-one 14. Several reactions of the parent compound and its 5,5′-dimethyl and 5,5′-dibromo derivatives are reported, especially a reaction with dry methanol leading to the known indoloquinazoline 25 ('methylisatoid') and to the known alkaloid tryptanthrin 21 *via* a photolabile orthoester.

Introduction

In 1878[1] and 1879[2] A. Baeyer, investigating the synthesis of indigo, warmed isatin (indole-2,3-dione) with phosphorus pentachloride either alone[1] or in benzene.[2] He obtained a product which yielded indigo on treatment in air with various reducing agents (yellow phosphorus, zinc in ethanol or acetic acid, ammonium sulfide, hydrogen iodide in acetic acid). The intermediate was characterized in the second paper as a brown crystalline mass melting with decomposition around 180 °C and unstable to heat (100 °C), to water (yielding isatin), to moist air and to recrystallization. It also contained phosphorus; this was assumed to be present as phosphoryl chloride and the elementary analyses were adjusted accordingly. Baeyer had little doubt that he had obtained 'Isatinchlorid' **1** (since variously named isatin α-chloride, 2-chloro-3-oxoindolenin, 2-chloropseudoindol-3-one and—the modern name—2-chloro-3*H*-indol-3-one). Later[3] he obtained from 5-bromoisatin an analogue which could be recrystallized in small amounts.

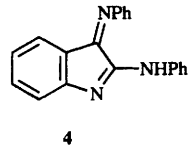
Baeyer's view of his product's structure was generally accepted, even 'confirmed', on the basis of interpretations of its reactions. Structure **1** has electrophilic centres at the 2- and 3-positions, and most of the reported reactions were with nucleophiles (amines, thiols, phenols and 'active methylene' compounds in general). One expects an imido chloride function to react faster than a ketone with nucleophiles and the products, especially with carbon nucleophiles, tended to be formulated as 2-substituted indol-3-ones. Since Baeyer 37 papers and 4 patents, from 26 research groups, have been published on 'isatin chloride' and on analogues from other isatins.



1

2 X = I, R = H
5 X = R = H
6 X = H, R = Me

3 R = Ph
7 R = $MeC_6H_4SO_2NH$



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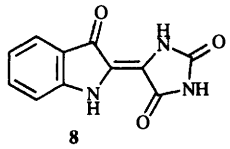

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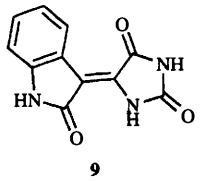

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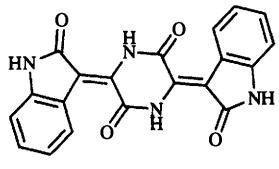
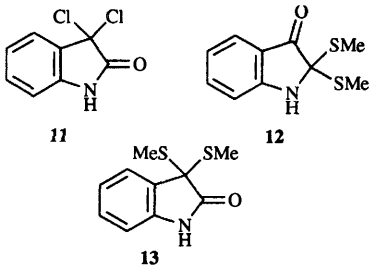


10

The first signs of ambiguity came from reactions with amines. Borsche *et al.*[4] heated the 'isatin chloride' from 5-iodoisatin with aniline in benzene and obtained a violet–black product assumed to be the 2-anil **2**. Callow and Hope[5] heated 'isatin chloride' with 1 equiv. of aniline in benzene and obtained the known yellow isatin-3-anil **3**; with excess of aniline the 2,3-dianil **4** was isolated. Grimshaw and Begley[6] added 'isatin chloride' and several of its substitution products to excess of aniline at room temperature and obtained the isatin 2,3-dianils, hydrolysable to the 2-anils by acid. From '4-methylisatin chloride' and '4-chloroisatin chloride' the 2-anils were said to be formed directly, without dianils. Aurich and Grigo[7] added 2 equiv. of aniline slowly to a cold solution of 'isatin chloride' in tetrahydrofuran and isolated the known 2-anil **5** in 2% yield along with a larger amount of the 2,3-dianil **4**. Pummerer[8] boiled 'isatin chloride' in benzene with *N*-methylaniline and obtained the violet 2-methylanilinoindol-3-one **6**. Moriconi and Murray[9] obtained isatin 3-tosylhydrazone **7** from their preparation of 'isatin chloride' and tosylhydrazine.

For carbon nucleophiles Katritzky *et al.*[10] showed that condensation of 'isatin chloride' with hydantoin in acetic acid containing some acetic anhydride, a condensation previously carried out by Hill and Henze,[11] gave a violet–red product **8** different from the condensation product **9** obtained with isatin. When reactions of the same type (with 1,4-diacetylpiperazine-2,5-dione, 2-indanone *etc.*) were performed in *N*,*N*-dimethylformamide with triethylamine as catalyst, the products from 'isatin chloride' and isatin were the same and resulted from condensation at the 3-position of isatin. The structure **10** of the piperazinedione product was proved by X-ray crystallography. Since no drying of the solvent was mentioned, the authors' suggestion that hydrolysis of 'isatin chloride' to isatin could have preceded condensation (which then also generates water) seems reasonable.

All the work hitherto described was done with preparations made more or less according to Baeyer's recipe: that is, unstable preparations containing unknown proportions of unknown impurities. Hantzsch[12] found that when isatin and phosphorus pentachloride interacted at room temperature in benzene an alternative product, 3,3-dichloroindol-2-one **11**, was formed.



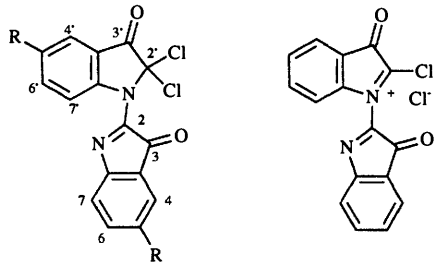
11 12 13

We repeated the experiment and isolated this oxindole in 19% crude yield; presumably, it is also formed during the Baeyer procedure. Hantzsch found it to be unstable when heated alone (20% weight loss at 100 °C in 11 h), but recrystallizable from boiling benzene. Thus, it or its decomposition products might be present in Baeyer's product, the instability of which seems to have discouraged successors from attempting purification.

The first achievement of a pure preparation is due to Baker and Duke.[13] Unlike all predecessors they used a dilute (4%) solution of isatin in benzene and a long period of reflux (6 h). They then distilled off benzene and recrystallized the residue twice from benzene. Their red crystalline product, after drying, decomposed at 200–204 °C and gave analytical figures correct for the chloroindolone **1**. It reacted, for example, with methanethiol in benzene to form 2,2-bis(methylthio)-2,3-dihydroindol-3-one **12**; in the presence of water, the reaction yielded the isomer **13**, presumably formed *via* hydrolysis to isatin. Other reactions with thiols were also studied. This outstanding work is described misleadingly elsewhere.[10c]

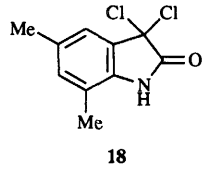
Results and discussion

We repeated Baker and Duke's preparation and were able to obtain large (but thin) red crystals. The compound is a benzene solvate that loses benzene slowly in air. In this form it is not sensitive to quick handling in moist air and it is stable on dry storage. It seems that impurities affect profoundly the sensitivity of 'isatin chloride'. Satisfactory ^{1}H and ^{13}C NMR spectra were obtained without trouble, and showed the presence of 8 different hydrogens and 16 different carbons. A single-crystal X-ray crystallographic analysis completed the identification of the product as 2-(2,2-dichloro-2,3-dihydro-3-oxoindol-1-yl)-3*H*-indol-3-one (**14**; Fig. 1). To verify that this compound is



14 R = H
15 R = Me
16 R = Br

17



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not the abnormal artefact of an unusually prolonged reaction period, we repeated a procedure[6] typical of Baeyer's recipe (1 h reflux). Examination of the dark product by NMR showed it to be principally **14**; around 25% of the signal, excluding benzene,

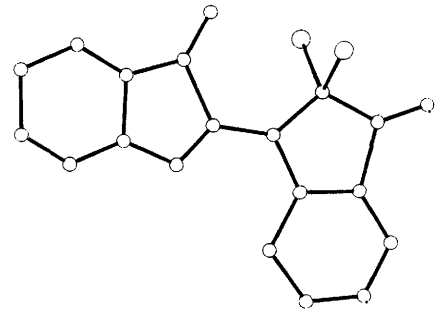
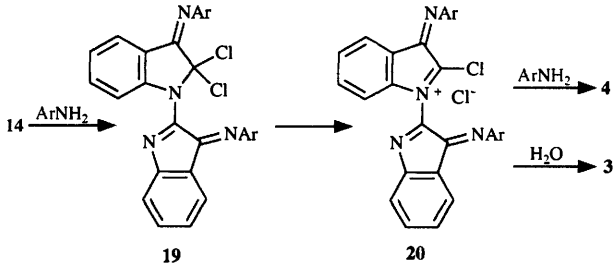


Fig. 1 X-Ray crystal structure of 2-(2,2-dichloro-2,3-dihydro-3-oxoindol-1-yl(-3*H*-indol-3-one

had different origins. Products made by Baker and Duke's procedure from 5-methylisatin and 5-bromoisatin were shown by their spectra to be analogues **15** and **16** of the parent compound. There can be little doubt that other 'isatin chlorides' are of the same type.

Imido chlorides show reactions similar to those of acid chlorides which are known to combine with weak bases, *e.g.* quinoline,[14] yielding thermally unstable adducts. Indolone **1**, an imido chloride, might well enter an equilibrium with a self-adduct **17**; but, if the properties of other imido chlorides are any guide, that equilibrium should strongly favour dissociation. However, **17** is unusual in that the collapse of its ion-pair to the neutral molecule **14** relieves considerable strain in a tight five-membered ring, and although this process should be reversible the overall equilibrium may, especially in the absence of a solvent promoting ionization, still favour the dimeric form. That seems to be the case: the NMR spectra of compounds **14**, **15** and **16** even in the somewhat polar solvent deuteriochloroform showed no indication of dissociation. The coplanarity of the connected ring systems may also contribute stability. From 5,7-dimethylisatin, where a 7′-methyl group would prevent coplanarity, the only compound isolated was the 'Hantzsch' product 3,3-dichloro-2,3-dihydro-5,7-dimethylindol-2-one **18**. In another effect of this coplanarity the carbonyl oxygen at position 3 is 'locked' between the two chlorine atoms, raising a barrier to free rotation and placing the nitrogen atom at position 1 close to the 7′-hydrogen. This proximity is known[15] to produce a large downfield shift in the ^{1}H NMR signals of hydrogen atoms similarly situated. One-proton signals, at δ 8.68, 8.49 and 8.63 in **14**, **15** and **16** respectively, are far downfield of any other signal. Their counterparts at position 7, exposed to no such proximity effect, are among the highest-field signals in the spectra.

The identification of Baeyer's product as essentially dimeric does seem to throw light on some of its reactions, particularly with aromatic amines. In the absence of ionic dissociation the most reactive electrophilic centres in the dimer **14** are probably the carbonyl groups, and the first product of reaction with primary amines in less polar solvents would then be Schiff bases formed at positions 3 and/or 3′ (*e.g.* **19**, Scheme 1). The water

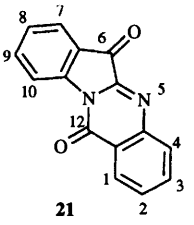


19 **20**

Scheme 1

liberated by this condensation could promote ionization; the ion-pair **20** could then react at positions 2 and 2′ sequentially

with excess of amine[5,6] to yield the dianils (*e.g.* **4**) or, when amine is limited, with water to yield the 3-monoanil **3**.[5] With a secondary amine,[8] Schiff bases are not formed and reaction is at the 2 and 2′ positions, presumably after ionization. With aniline in the somewhat more polar tetrahydrofuran, ionization competes with Schiff base formation and yields a small amount of 2-anil.[7] When the 3 and 3′ positions are hindered by 4,4′-substituents, larger amounts of 2-anils can be formed.[6] In the highly polar solvent acetonitrile Bergman *et al.* obtained a high yield of the alkaloid tryptanthrin **21** from reaction of Baeyer's



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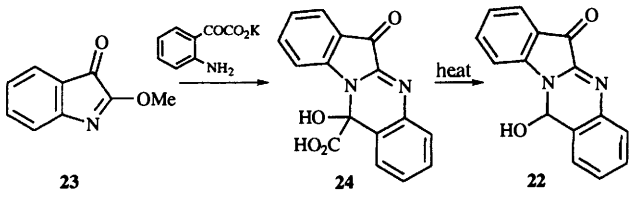
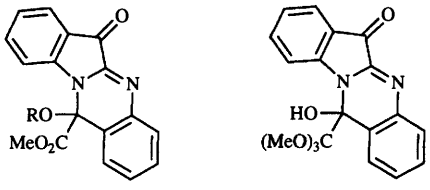


23 **24** **22**



25 R = H
26 R = Me

27

product with anthranilamide.[16] Here, ionization should predominate and no reaction at the 3 and 3′ positions was noted. The above is a simplified view of reactions that may actually be more complex in sequence and timing. The reactivity of **14** will be discussed later in another context.

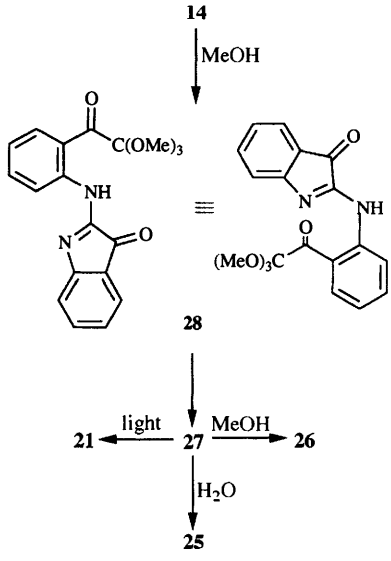
Our interest in 'isatin chloride' originated from a wish to make several grams of the indoloquinazolinone **22** without using the messy, but still unique, preparation of 2-methoxyindol-3-one **23** from isatin–silver and iodomethane. The indoloquinazolinone **22** was made[17] from the indolone **23** by a condensation with potassium isatinate in dimethylformamide yielding the easily decarboxylated acid **24**. This acid could also be obtained by mild alkaline hydrolysis of 'methylisatoid' **25**, its methyl ester, which is formed from two molecules of indolone **23** in 90% acetic acid or even in moist air.

Having established the structure **14** for 'isatin chloride' we looked for ways to convert it into the indoloquinazolinone **22** and found three fairly direct procedures the simplest of which, in 15% yield, was to stir the chloride with aqueous sodium hydrogen carbonate and to acidify and warm the resulting solution. Carbon dioxide was evolved in the final stage and the synthesis presumably proceeded through the acid **24**, as did a reaction of the chloride **14** with potassium isatinate in hot dimethylformamide that also yielded **22**, in 20% yield. Direct condensation of chloride **14** with 2-aminobenzaldehyde in acetonitrile gave a 22% yield of **22**: the sensitivity of the aldehyde to both acid and base limited the scope for improvement. A better though less direct procedure was then found.

The chloride **14** reacted at room temperature with an excess of dry methanol and gave a mixture of three related products which were easily separated on alumina. One product was the known 'methylisatoid' **25**, a second and major product was its *O*-methyl ether **26**. The third, bright red product was the orthoester **27**. When the unseparated mixture was heated in 90% acetic acid the product was pure 'methylisatoid' **25** in 80% overall yield. Acidic hydrolysis of an orthoester to an ester is unremarkable, and the apparent demethylation of the methyl ether **26** would actually be a replacement of methoxy by hydroxy by way of an immonium cation. The already reported[17] conversion of **25** into indoloquinazolinone **22** was improved and gave in a simple procedure a 76% yield of recrystallized material. Thus a convenient preparation of **22** from isatin was completed.

The orthoester **27** was stable in the dark, but unstable in diffuse daylight, especially in solution. A solution in deuteriochloroform became almost colourless in a few days, depositing a new substance which proved to be the known alkaloid tryptanthrin **21**, and the ^1H and ^{13}C NMR spectra of the solution showed resonances attributable to dimethyl carbonate and methanol; if so, the overall change is an oxidation. Comparable instability was not seen in the congeners **25** and **26** and this photolysis seems unexampled.

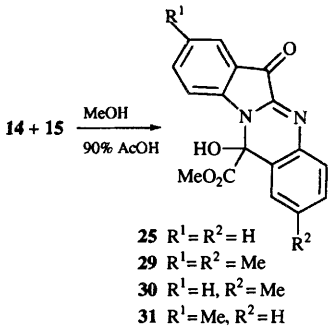
Appearance of the three products **25**, **26** and **27** in the reaction of the chloride **14** with methanol can be explained simply by supposing a triple reaction at position 2′, probably preceded by ionization at the same position. The product **28** (Scheme 2)



Scheme 2

is a tautomer of the orthoester **27** and its conversion to **27** should be very fast. In the methanolic hydrogen chloride now composing the reaction medium (since hydrogen chloride is necessarily formed at a very early stage), replacement of the hydroxy group in **27** by a methoxy group would be unremarkable. The water thus liberated (and traces of water already present) would hydrolyse both methylated and unmethylated orthoesters, leading to the esters **26** and **25**.

This explanation is too simple. When methanol reacted with an equimolar mixture of the chloride **14** and its dimethyl homologue **15** (Scheme 3) and the total product was hydrolysed in 90% acetic acid, the result was not a mixture of two 'methylisatoids' **25** and **29** but of four, in comparable amounts (**25**, **29**, **30** and **31**). Thus, at some stage, a displacement at position 2 had cleaved each molecule into two parts which were shuffled before being recombined at a later stage of the process. Ionization as a first step still seems necessary, but a total reversion of the ion-pair **17** to two molecules of 2-chloroindol-3-one by nucleophilic attack of chloride ion at position 2 seems unlikely here: methanol is present in much higher concentration and is the more active nucleophile. The products are then one molecule of 2-methoxyindol-3-one **23** *plus* one molecule of 2-chloroindol-3-

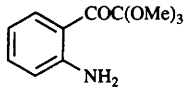


25 $R^1 = R^2 = H$
29 $R^1 = R^2 = Me$
30 $R^1 = H$, $R^2 = Me$
31 $R^1 = Me$, $R^2 = H$

Scheme 3

one, or two molecules of methoxyindolone, depending on whether an attack of methanol on the 2′ position precedes the attack on the 2 position. If 2-chloroindol-3-one is formed as one product it should react rapidly with methanol to give, initially, 2-methoxyindol-3-one. Shuffling has now occurred not only between different molecules of starting material but between the two indole moieties of individual molecules.

One of us has discussed[17] the mechanism whereby two molecules of 2-methoxyindol-3-one **23** yield 'methylisatoid' **25** with limited amounts of water: one molecule is hydrolysed to methyl isatinate, which reacts as an amine with a second molecule of the imido-ester **23** to yield an amidine tautomeric with 'methylisatoid'. If one adapts this mechanism to a medium of acidic dry methanol, the intermediate corresponding to methyl isatinate becomes its orthoester **32**. Reaction of this with 2-methoxyindol-3-one, followed by tautomeric rearrangement, would lead to the orthoester **27** from which the other two products would be derived as already indicated.



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Scheme 4

We have shown here that the reactions of 'isatin chloride', like its structure, are more complex than had been imagined. Some of the complications having now been explored, it should become possible to apply this useful intermediate more intelligently.

Experimental

Melting points, taken using an Electrothermal apparatus, are uncorrected. Infra-red spectra were taken in paraffin mulls, NMR spectra in $CDCl_3$. Chemical shifts (δ) are given in ppm relative to Me_4Si; J values are given in Hz. In the ^{13}C NMR spectra, multiplicity of peaks in brackets refers to C–H coupling. Phosphorus pentachloride was a 95% grade from Aldrich Chemical.

2-(2,2-Dichloro-2,3-dihydro-3-oxoindol-1-yl)-3*H*-indol-3-one 14

Isatin (20 g) and phosphorus pentachloride (26 g) were heated under reflux with dry benzene (600 ml) for 6 h. The solvent was evaporated, finally at low pressure, and the residue was twice recrystallized from dry benzene avoiding needless exposure to moist air, yielding thin, flat red platelets (11 g). A sample recrystallized a third time with slow cooling gave somewhat larger crystals, mp 179 °C (decomp.); mp 200 °C (decomp.) after drying at 60 °C *in vacuo* (lit.,[13] 200–204 °C); δ_H(360 MHz) 7.19 (1 H, app t, J 7.4, 5-H), 7.26 (1 H, d, J 7.3, 7-H), 7.35 (1 H, t, J 7.4, 5′-H), 7.355 (s, C_6H_6), 7.53 (1 H, t, J 7.1, 6-H), 7.57 (1 H, d, J 7.4, 4-H), 7.83 (1 H, dd, J 7.7, 8.5, H-6′), 7.94 (1 H, d, J 7.7, H-4′), 8.68 (1 H, d, J 8.5, H-7′) (Note: 1,3 couplings, though present, are unrecorded here); δ_C(90.36 MHz) 87.1 (s, C-2′), 117.9 (s), 119.2 (d), 120.7 (d), 121.1 (s), 125.58 (d), 125.63 (d), 126.61 (d), 126.87 (d), 137.6 (d), 138.9 (d), 150.3 (s), 155.0 (s), 159.4 (s, C-2), 185.47 and 185.60 (s, C-3, -3′). At low pressure, the crystals lost some benzene and disintegrated. They were kept in a closed bottle in dry air.

Crystal data for 14. $C_{16}H_8Cl_2N_2O_2 \cdot C_6H_6$, $M = 409.3$, orthorhombic, space group *Pnma* (No. 62), $a = 31.112(15)$, $b = 6.763(2)$, $c = 8.983(3)$ Å, $V = 1890$ Å^3, $Z = 4$, $D_x = 1.44$ g cm^{-3}, $F(000) = 840$. Monochromated Mo-Kα radiation, $\lambda = 0.710\,69$ Å, $\mu = 3.6$ cm^{-1}. Crystal size $0.3 \times 0.3 \times (<0.01)$ mm.

Cell dimensions and intensities were measured on an Enraf-Nonius CAD4 diffractometer at room temperature. There were 1971 unique reflections for $2 < \theta < 25°$ ($h = 0 \longrightarrow 37$, $k = 0 \longrightarrow 8$, $l = 0 \longrightarrow 10$) and of these 442 significant reflections with $I > 3\sigma(I)$ were used in the refinement. There was no correction for absorption and decay. The structure was solved by direct methods using SHELXS-86, and refined on F using the MolEN program package, with the Cl atom anisotropic and C, N and O atoms isotropic. H atoms were included in fixed calculated positions with $U_{iso} = 1.3\ U_{eq}$ for the parent atom. The final residuals were $R = 0.119$, $R_w = 0.125$, with $S = 2.5$, $(\Delta/\sigma)_{max}$ 0.04, $(\Delta\rho)_{max} \pm 0.7$ e Å^{-3}. The molecule lies with all atoms except Cl on the crystallographic mirror plane. The molecule of benzene solvate lies across the mirror plane.

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/61.

2-(2,2-Dichloro-2,3-dihydro-5-methyl-3-oxoindol-1-yl)-5-methyl-3*H*-indol-3-one 15

This compound was prepared from dry benzene (300 ml), 5-methylisatin (10 g) and phosphorus pentachloride (13 g) as described for compound **14**. Two recrystallizations from benzene gave red–brown needles (4.2 g), mp 213–215 °C (decomp.) (lit.,[6] mp 190–200 °C) of a benzene solvate (Found after drying: C, 60.5; H, 3.4; N, 7.8. $C_{18}H_{12}Cl_2N_2O_2$ requires C, 60.2; H, 3.4; N, 7.8%); δ_H(360 MHz) 2.35 (3 H, s, 5-Me), 2.49 (3 H, s, 5′-Me), 7.13 (1 H, d, J 7.7, H-7), 7.30 (1 H, dm, J 7.7, H-6), 7.355 (s, C_6H_6), 7.36 (1 H, m, H-4), 7.61 (1 H, dm, J 8.5, H-6′), 7.71 (1 H, m, H-4′), 8.49 (1 H, d, J 8.5, H-7′); δ_C(90.36 MHz) 20.8 and 21.0 (q, 5- and 5′-Me), 87.3 (s, C-2′), 117.9 (s), 118.8 (d), 120.3 (d), 121.3 (s), 126.1 (d), 126.2 (d), 128.4 (d, C_6H_6), 135.8 (s), 136.8 (s), 137.7 (d), 139.9 (d), 148.5 (s), 154.5 (d), 157.2 (s, C-2), 185.6 and 186.0 (2 s, C-3, -3′).

2-(5-Bromo-2,2-dichloro-2,3-dihydro-3-oxoindol-1-yl)-5-bromo-3*H*-indol-3-one 16

This compound was prepared from 5-bromoisatin (10 g), phosphorus pentachloride (9.4 g) and dry benzene (300 ml) as described for **14** and recrystallized twice from benzene. The red solvated needles (4 g) showed mp (after drying *in vacuo*) 242–245 °C (decomp.) [lit.,[6] mp 220–240 °C (decomp.)] (Found: C, 40.0; H, 1.3; N, 5.8. $C_{16}H_6Br_2Cl_2N_2O_2 \cdot 0.05C_6H_6$ requires C, 40.0; H, 1.3; N, 5.7%; residual benzene was detected by NMR); δ_H(360 MHz) 7.18 (1 H, d, J 6.7, H-7), 7.37 (s, C_6H_6), 7.69 (2 H, br s, H-4 and -6), 7.93 (1 H, d, J 7.3, H-6′), 8.07 (1 H, s, H-4′), 8.63 (1 H, d, J 7.3, H-7′).

3,3-Dichloro-2,3-dihydroindol-2-one 11

Isatin (5 g) and phosphorus pentachloride (10 g) were added to dry benzene (10 ml). A dark solution was formed after 0.5 h and crystallization began 1 h later. Next day the crystals were collected and washed with benzene. The sandy powder (1.31 g, 19%) was recrystallized three times (the first time with decolorizing carbon) from CH_2Cl_2; the colourless needles of oxindole

11 had mp 168 °C (decomp.) [lit.,[12] mp 165 °C (decomp.)]; δ_H(360 MHz) 7.03 (1 H, ddd, $J_{1,2}$ 7.85, H-7), 7.19 (1 H, dt, J 7.7, 1.0, H-5), 7.37 (1 H, dt, J 7.8, 1.3, H-6), 7.63 (1 H, dm, $J_{1,2}$ 7.6, H-4), 9.32 (1 H, br s, NH); δ_C(90.36 MHz) 74.6 (s, C-3), 111.4 (d, C-7), 124.3 (d, C-5), 125.0 (d, C-4), 129.7 (s, C-3a), 132.0 (d, C-6), 137.9 (s, C-7a), 171.2 (s, C-2).

3,3-Dichloro-5,7-dimethyl-2,3-dihydroindol-2-one 18

Dry benzene (250 ml), 5,7-dimethylisatin (8.6 g) and phosphorus pentachloride (10.2 g) were heated together under reflux for 6 h. The product was worked up as in previous examples; recrystallizations from benzene gave brown crystals (4.3 g) of a mixture. Sublimation at 110 °C and 0.1 mmHg gave the light orange oxindole **18** (no mp; decomp. around 200 °C) which appeared homogeneous by NMR; δ_H(360 MHz) 2.31 (3 H, s, 7-Me), 2.35 (3 H, s, 5-Me), 7.00 (1 H, s, 6-Me), 7.28 (1 H, s, 4-Me), 9.22 (1 H, br s, NH) (orientations were confirmed by NOE irradiation of the two methyl groups); δ_C(90.36 MHz) 16.2 (q, 7-Me), 21.0 (q, 5-Me), 75.3 (s, C-3), 120.5 (s, C-7), 122.8 (d, C-4), 129.3 (s, C-3a), 133.8 (d, C-6), 134.0 (s, C-7a), 134.1 (s, C-5), 171.4 (s, C-2).

6,12-Dihydro-12-hydroxyindolo[2,1-*b*]quinazolin-6-one 22

Method (*a*). Solvated chloro compound **14** (2 g) (0.33 g) was stirred with saturated aqueous sodium hydrogen carbonate (5 ml) for 2 d. The filtered solution was acidified (HCl) and heated briefly on a steam bath. The product was collected after cooling and was recrystallized from aqueous methyl sulfoxide, yielding orange platelets (0.03 g) of the indoloquinazolinone **22**; mp 241 °C (lit.,[17] 238–241 °C). The infra-red spectrum was identical with that of material obtained earlier.[17]

Method (*b*). The solvated chloro compound **14** (2 g) was added over 4 min to potassium isatinate (2.5 g) in dry dimethylformamide (5 ml) at *ca.* 90 °C. Carbon dioxide was evolved. After 30 min a little water was added; the crude product was filtered off after cooling and washed with aqueous sodium hydroxide (1 mol dm^{-3}) to dissolve isatin. The crystalline orange–yellow indoloquinazolinone **22** (0.6 g) had mp 241 °C and was identified by its IR spectrum.

Method (*c*). Solvated chloro compound **14** (0.33 g) was heated with 2-aminobenzaldehyde (0.24 g) in refluxing acetonitrile (4 ml) for 15 min. The solid obtained after filtration of the cooled solution was recrystallized twice from aqueous methyl sulfoxide, affording the indoloquinazolinone **22** (0.09 g), mp 241 °C, identified by its IR spectrum.

Method (*d*). Methylisatoid **25** (2.261 g; for preparation see below) was stirred under reflux (bath, 80 °C) with MeOH (20 ml), water (1 ml) and aqueous sodium carbonate (15 ml; 1.1 mol dm^{-3}) for 3 h. Water (6 ml) was added; 0.5 h later the MeOH was removed at low pressure and a little dark residue was filtered off. After addition of hydrochloric acid (22.5 ml; 2 mol dm^{-3}) the mixture was boiled for 15–20 min. Next day the cold mixture was made alkaline with sodium hydroxide and the product (1.47 g) was collected. Recrystallization from aqueous methyl sulfoxide gave 1.4 g, mp 241 °C, identical with earlier samples.

Action of methanol on the chloro compound 14

The solvate **14** (0.5 g) was covered with dry MeOH (2.5 ml). An exotherm, beginning after a short delay, was controlled (to *ca.* 30 °C) by cooling in tap water. After 4 h, water and CH_2Cl_2 were added. The CH_2Cl_2 solution was washed with water, dried over magnesium sulfate and put on neutral alumina (10 g). The initial eluate (yellow) yielded, on evaporation and recrystallization from ethyl acetate, orange–yellow crystals of *methyl* 6,12-*dihydro*-12-*methoxy*-6-*oxoindolo*[2,1-b]*quinazoline*-12-*carboxylate* **26** (235 mg), mp 24–216 °C (Found: C, 67.1; H, 4.3; N, 8.6. $C_{18}H_{14}N_2O_4$ requires C, 67.1; H, 4.4; N, 8.7%); δ_H(500 MHz) 3.07 (3 H, s, ether Me), 3.71 (3 H, s, ester Me), 7.20 (1 H, dt, $J_{1,2}$ 7.5, $J_{1,3}$ 1), 7.23 (1 H, d of t, $J_{1,2}$ 8), 7.41 (1 H, dt, $J_{1,2}$ 7.5, $J_{1,3}$ 1.3), 7.52 (1 H, dt, $J_{1,2}$ 7.5, $J_{1,3}$ 1.3), 7.60 (1 H, dt, $J_{1,2}$ 8, $J_{1,3}$ 1.3), 7.61 (1 H, dd, $J_{1,2}$ 7.8, $J_{1,3}$ 1.5), 7.72 (1 H, dd, $J_{1,2}$ 7.8, $J_{1,3}$ 1.3), 7.82 (1 H, dm, $J_{1,2}$ 7.8); δ_C(125.76 MHz) 50.5 (q), 53.7 (q), 87.4 (s), 112.3 (d), 120.3 (s), 120.5 (s), 124.0 (d), 125.5 (d), 126.1 (d), 129.3 (d), 129.7 (d), 131.4 (d), 137.9 (d), 141.9 (s), 144.7 (s), 148.9 (s), 167.8 (s), 183.8 (s).

Eluate of a slower-running red band was rechromatographed on alumina (10 g); recrystallization from ethyl acetate then gave orange–red prisms (28 mg) of *trimethyl* 6,12-*dihydro*-12-*hydroxy*-6-*oxoindolo*[2,1-b]*quinazoline*-12-*orthocarboxylate* **27**, mp 204 °C (bubbling) (Found: C, 64.4; H, 5.0; N, 7.9. $C_{19}H_{18}N_2O_5$ requires C, 64.4; H, 5.1; N, 7.9%); δ_H(500 MHz) 3.14 (9 H, s, orthoester Me), 3.85 (1 H, s, OH, suppressed by addition of CD_3OD), 7.02 (1 H, dt, $J_{1,2}$ 7.5, $J_{1,3}$ 0.9), 7.30 (1 H, dt, $J_{1,2}$ 7.5, $J_{1,3}$ 1.3), 7.36 (1 H, dt, $J_{1,2}$ 7.5, $J_{1,3}$ 1.3), 7.45–7.52 (2 H, m), 7.65 (2 H, 2 dm superposed, $J_{1,2}$ 7.5), 7.73 (1 H, dt, $J_{1,2}$ 8.3, J' 0.8); δ_C(125.76 MHz) 51.6 (OMe), 89.3 (C-12), 113.2 (s, orthoester carbon), 117.7 (d), 120.3 (s), 122.3 (d), 124.1 (d), 127.1 (s), 127.2 (d), 127.6 (d), 127.65 (d), 129.9 (d), 136.7 (d), 141.9 (s), 146.2 (s), 153.0 (s), 185.8 (s, C-6). The mother liquor of recrystallization, and the NMR sample in $CDCl_3$, lost colour on storing in diffuse daylight for a few days and deposited yellow needles of 6,12-dihydroindolo[2,1-*b*]quinazoline-6,12-dione (**21**, tryptanthrin), mp 269–270 °C (lit.,[16] mp 268–269 °C); the NMR sample now showed the spectrum of tryptanthrin, superposable on the spectrum of a separately purified specimen and on the published high-resolution spectrum,[18] with additional singlet signals at δ 3.44 (MeOH) and 3.79 [$CO(OMe)_2$]; δ_C(125.76 MHz) 50.3 (MeOH), 54.9 [$CO(OMe)_2$] and 156.5 [$CO(OMe)_2$] along with the 15-line spectrum of tryptanthrin [δ_C 118.0 (d), 122.0, 123.9, 125.5 (d), 127.4 (d), 127.6 (d), 130.4 (d), 130.7 (d), 135.3 (d), 138.4 (d), 144.4, 146.4, 146.6, 158.3, 182.6]. From the original alumina column an orange band was eluted by 2.5% acetic acid in chloroform and this yielded methylisatoid **25**, identified by comparison with material from the following experiment.

Methyl 6,12-dihydro-12-hydroxy-6-oxoindolo[2,1-*b*]quinazoline-12-carboxylate 25

The chloride **14** (9.6 g) was mixed with MeOH (50 ml), cooled to subdue heating, left for 25 min, then shaken with water (200 ml) and chloroform (150 ml). The aqueous layer was extracted twice more with chloroform and the combined extracts were evaporated at low pressure. Acetic acid (45 ml) and water (5 ml) were added; the mixture was warmed at low pressure to remove residual volatiles and then boiled under reflux with more acetic acid (25 ml) and water (5 ml) for 1 h. Water (20 ml) was then added dropwise over 0.5 h to the boiling mixture. After cooling the orange crystals were collected, washed with 50% acetic acid and water, and dried (5.8 g). The product **25** (methylisatoid) was identical (TLC, IR) with previously prepared material.[17]

Methyl 6,12-dihydro-2,8-dimethyl-12-hydroxy-6-oxoindolo[2,1-*b*]quinazoline-12-carboxylate 29

The chloride **15** (1.07 g) was dissolved in dry MeOH (5 ml) with cooling to control the exotherm. After 3 h, potassium acetate (0.5 g), acetic acid (9 ml) and water (1 ml) were added and the MeOH was removed at low pressure. The mixture was heated with more water (2 ml) for 1.5 h on a steam bath, adding more water (7 ml) gradually after 1.5 h. The red product **29** was recrystallized from aqueous bis(2-methoxyethyl) ether, mp 242–244 °C (decomp.) (Found: C, 68.05; H, 4.75; N, 8.35. $C_{19}H_{16}N_2O_4$ requires C, 67.85; H, 4.8; N, 8.3%); δ_H(500 MHz) 2.37 and 2.38 (each 3 H, s, Ar-Me), 3.72 (3 H, s, OMe), 5.3 (1 H, br s, OH), 6.99 (1 H, d, J 8.2), 7.15 (1 H, ddd, $J_{1,2}$ 8.0), 7.25 (1 H, m), 7.37 (1 H, dm, $J_{1,2}$ 8.2), 7.44 (1 H, d, J 8.1), 7.54 (1 H, m).

Crossover experiment

The chlorides **14** (0.5 g) and **15** (0.535 g) were triturated

together, cooled in ice, treated with dry MeOH (5 ml), kept cold for a few min while the solids dissolved and cool during the ensuing exotherm. After 3 h, potassium acetate (0.5 g) and acetic acid (10 ml of 90%) were added, the MeOH was removed at low pressure, water (2 ml) was added and the mixture was heated (steam bath) for 1.6 h, adding more water at intervals (1 ml each at 20 min, 25 min and 40 min; 4 ml at 90 min). Crystallization began at 30 min. The orange–red crystals (0.63 g) were collected next day. The ^{1}H NMR spectrum (500 MHz) was complex but similar in character to the spectra of **25** and **29**; the aromatic methyl signal at δ 2.36 was not resolvable, but the ester methyl signal at δ 3.72 was resolved to four signals of comparable strength at δ 3.713, 3.720, 3.723 and 3.730. The mixture was not resolved by TLC on silica but by HPLC (column: 250 × 4.5 mm APEX ODS II; solvent: acetonitrile–propan-2-ol–water, 3:2:5; flow rate: 0.75 ml min^{-1}; detector: UV, 258 nm) it was cleanly resolved into four peaks of relative areas 20:32:17:29 (no other significant peak).

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References

1 A. Baeyer, *Ber. Dtsch. Chem. Ges.*, 1878, **11**, 1296.
2 A. Baeyer, *Ber. Dtsch. Chem. Ges.*, 1879, **12**, 456.
3 A. Baeyer, *Ber. Dtsch. Chem. Ges.*, 1879, **12**, 1309.
4 W. Borsche, H. Weussmann and A. Fritzsche, *Ber. Dtsch. Chem. Ges.*, 1924, **57**, 1770.
5 R. K. Callow and E. Hope, *J. Chem. Soc.*, 1929, 1191.
6 J. Grimshaw and W. Begley, *Synthesis*, 1974, 496.
7 H. G. Aurich and U. Grigo, *Chem. Ber.*, 1976, **109**, 200.
8 R. Pummerer, *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 338.
9 E. J. Moriconi and J. J. Murray, *J. Org. Chem.*, 1964, **29**, 3577.
10 (*a*) A. R. Katritzky, W.-Q. Fan, M. Szajda, Q.-L. Li and K. C. Caster, *J. Heterocycl. Chem.*, 1988, **25**, 591; (*b*) A. R. Katritzky, Q.-L. Li and W.-Q. Fan, *J. Heterocycl. Chem.*, 1988, **25**, 1287; (*c*) A. R. Katritzky, W.-Q. Fan, A. E. Koziol and G. J. Palenik, *J. Heterocycl. Chem.*, 1989, **26**, 821.
11 A. J. Hill and H. R. Henze, *J. Am. Chem. Soc.*, 1924, **46**, 2806.
12 A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1921, **54**, 1221.
13 J. T. Baker and C. C. Duke, *Aust. J. Chem.*, 1972, **25**, 2467; see also *Tetrahedron Lett.*, 1972, 307.
14 O. Eckstein, *Ber. Dtsch. Chem. Ges.*, 1906, **36**, 2135.
15 (*a*) G. W. Kirby, J. Michael and S. Nayaranaswami, *J. Chem. Soc., Perkin Trans. 1*, 1972, 203; (*b*) A. Maquestiau, Y. van Haverbeeke and R. N. Muller, *Bull. Soc. Chim. Belg.*, 1974, **83**, 259; (*c*) Sir J. Cornforth and M.-H. Du, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2183.
16 J. Bergman, J.-O. Lindström and U. Tilstam, *Tetrahedron*, 1985, **41**, 2897.
17 J. W. Cornforth, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2004.
18 M. Y. Jarrah and V. Thaller, *J. Chem. Res. (M)*, 1980, 2601.

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