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Studies of the Reaction between Indole-2,3-diones (Isatins) and Secondary Aliphatic Amines

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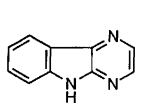
Simple secondary aliphatic amines react with isatin to yield, depending on the structure, either 2-amino-phenylglyoxamides, such as 2-amino-*N,N*-dimethyl-phenylglyoxamide, or dialkylammonium salts of 2-aminophenylglyoxylic acids. Reaction of isatin with *N,N'*-dimethylethylenediamine gave an unusual 2:1 product, whose structure has been determined by X-ray crystallography.

We have recently shown[1] that 5*H*-pyrazino[2,3-*b*]indole (**1**) can be synthesized from **2**, which in turn is readily available from *N*-acetylisatin (**3b**) and ethylenediamine. In this reaction an *N*-acetylated isatin is required because interaction between isatin (**3a**) and ethylenediamine will yield the 2:1 condensation product **4**. No intermediate 1:1 product could be isolated. A few higher homologues of **4** (with longer aliphatic chains) have been described in the literature.[2]



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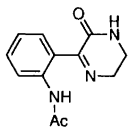

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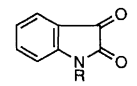
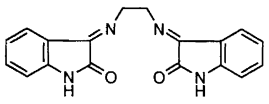


3a R=H
3b R=Ac
3c R=COOCH$_2$Ph



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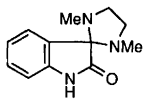

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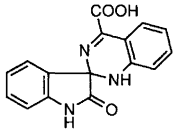
In connection with the development of the preparative method for **2** the interaction of various substituted derivatives of ethylenediamine, e.g., *N,N'*-dimethyl-ethylenediamine, with isatin were studied and as the two reactants mentioned gave, in addition to the expected[3–5] spiro product **5**, an unusual 2:1 product in which a methyl group had been transformed into a methylene group, it was considered of interest to investigate this compound in more detail. In order to obtain background information for the structure elucidation, we decided also to study the interactions of isatin with some simple monofunctional secondary amines.

The interaction of isatin and ammonia and various amines have been reported[3–6] in a large number of papers. The attack normally starts at the 3-position of the isatin, and many primary amines, like *tert*-butylamine, simply yield the 3-imines.[3] A particularly interesting compound,[6] isamic acid **6**, has been obtained from isatin and ammonia. Reaction of cyclic secondary amines with isatin under Dean–Stark conditions with toluene or benzene as solvents gave for example **7** and **8** in modest yields.[7,8] Heating (ca. 100 °C) of **7** gave the highly resonance-stabilized dye **9** of isatin blue type. Reactions between isatin and simple non-cyclic secondary amines have not been reported despite the fact that diethylamine is an important catalyst[9,10] for condensations of isatin with, for example, ketones.



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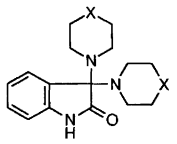
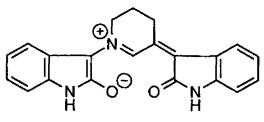


7 X=CH$_2$
8 X=O



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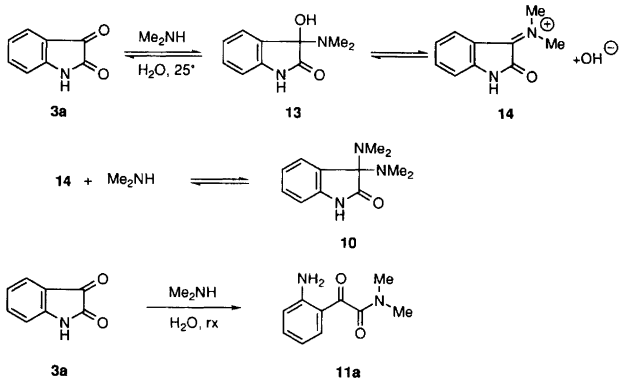
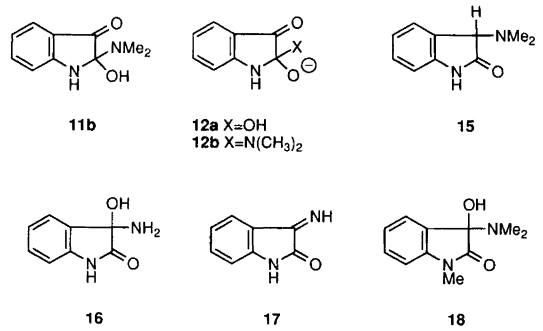
Results and discussion

When added to an aqueous solution of dimethylamine, isatin quickly dissolved and within a few minutes a precipitate of the kinetic product **10** was formed. Continued interaction (made quicker by heating) resulted in the dissolution of **10** and formation of the ring-opened product **11a**. The results are summarized in Scheme 1.

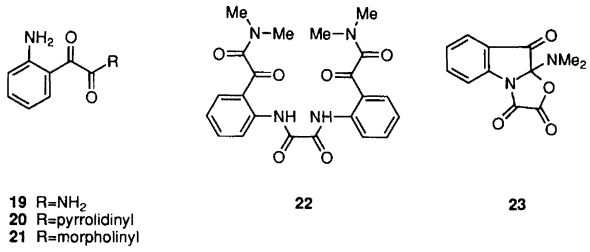


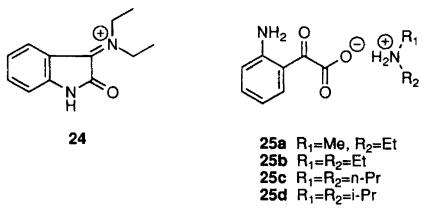
Scheme 1.

Equilibria involving addition of dimethylamine to the 2-position (e.g., **12b**), might also be involved, particularly in the final ring opening. In the base-induced (OH^-) cleavage of isatin evidence has been obtained[11] for the involvement of this type of species, namely **12a**. The intermediates (**13** and **14**) can be intercepted[12] by catalytic hydrogenation which will yield 3-dimethylaminoindol-2-one (**15**). An intermediate similar to **13**, namely **16**, has previously been isolated by Reissert and Hoppmann[13] by mild interaction of isatin and ammonia. This adduct readily eliminates ammonia giving back isatin, but can also be transformed into the imine **17**, which eventually gives rise to isamic acid **6**. In connection with the present work the adduct **18** (isolated by treatment of *N*-methylisatin and dimethylamine) was found to be stable in the presence of its mother liquor. Attempted drying or dissolution in for example $CDCl_3$ quickly reformed *N*-methylisatin and no signals emanating from **18** could be observed in the NMR spectra. However it was possible to obtain an IR spectrum of the compound in KBr.



The isolable intermediate **10**, obtained by treatment of isatin with dimethylamine, has never been described before, whereas the *N,N*-dimethylglyoxamide **11a** recently has been prepared[14,15] from isatin in a three-step procedure involving a reaction of the sodium salt of isatin with $PhCH_2OCOCl$ to give **3c**, followed by nucleophilic ring-opening with dimethylamine. In the final step the activating and protecting group was eliminated by catalytic hydrogenation. By this route the Australian workers have prepared several related compounds including **19** and **20**. No doubt these compounds are more readily available by the direct route now described.



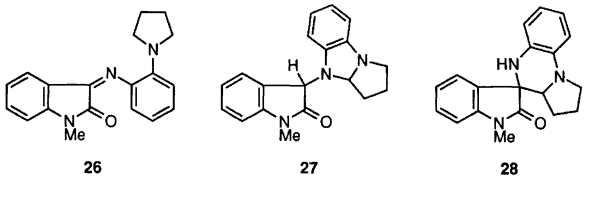


The glyoxamide **11a** featured, due to restricted rotation around the amide bond, two separate signals from the methyl groups in the ^1H NMR (3.07 and 2.93 ppm) as well as in the ^{13}C NMR (37.1 and 33.8 ppm) spectrum. The two carbonyl groups gave rise to signals at 194.1 and 167.3 ppm, respectively. The NMR studies gave no support for the co-occurrence of the ring-tautomer **11b**, and reaction of **11a** with oxalyl chloride immediately gave the corresponding bis-amide **22** and not the oxazolidinedione derivative **23**. In this context it is noteworthy that some related reactions leading to oxazolinediones have recently been studied by Bergman and Stålhandske.[16] The bis-amide **22** was identical with a sample previously prepared[17] by ring-opening of 1,1′-oxalylbisisatin.

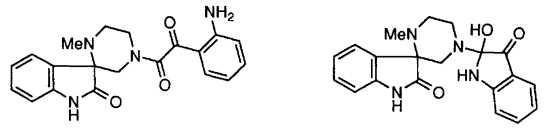
Aqueous piperidine resembles dimethylamine in its interaction with isatin giving **7** quickly and conveniently. Under forcing conditions **7** gave rise to isatin blue (**9**), which has been studied by several workers.[18] From morpholine both the 1:2 product **8** and the ring-opened product **21** can be isolated.

Reaction between diethylamine and isatin in water gave neither a precipitate of a 1:2 adduct nor a precipitate of a ring-opened product. Presumably steric hindrance (ethyl–ethyl interactions) will preclude any reaction beyond the 1:1 intermediate **24**. Formation of this cation (plus OH^-) accounts for the efficiency of diethylamine as catalyst in condensations between isatin and, e.g., ketones. Concentration of the reaction solution from

isatin and diethylamine eventually led to separation of the salt **25b**, which is formed relatively slowly by attack of OH^- on its counter-ion. Several other secondary amines, such as methylethylamine and dipropylamine gave analogous salts in high yields. These salts are soluble in several organic solvents and, for example, **25c** could be recrystallized from acetonitrile. In contrast with **11a**, the two alkyl groups in the salts **25b–d** gave rise to only one collection of signals in the ^1H and ^{13}C NMR spectra.

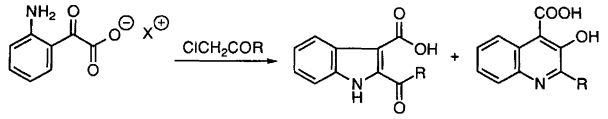


26 **27** **28**



29 **30**

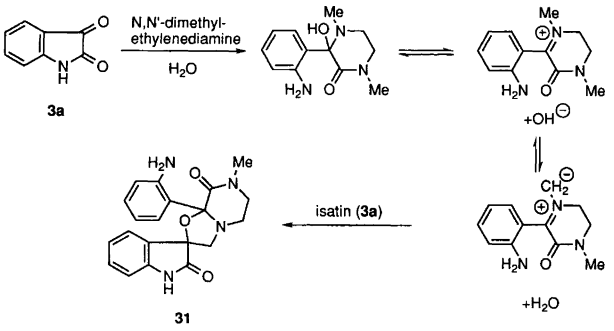
In contrast with the known[19] sodium salt of isatinic acid, the ammonium salts **25** are easy to obtain free from water and sodium hydroxide, hence they should be promising candidates for the synthesis[20] of 2-acylindoles via reaction with α-halo ketones. The potential for increased tendency to form 2-acylindole-3-carboxylic acids (which easily decarboxylate) rather than quinolines should be considerable (Scheme 2).



Scheme 2.

At this point we refocused our attention on the unusual 2:1 product obtained from *N,N'*-dimethylethylenediamine and isatin. The most pertinent piece of information obtained from the NMR spectra was the fact that one methyl group had been transformed into a methylene group. This fact alone, plus a related precedent in the literature[21] where the imine **26** was converted into the dihydrobenzimidazole derivative **27** and finally to the spiro compound **28**, suggested the tentative and seemingly mechanistically straightforward (intramolecular oxidation of an *N*-methyl group via an iminium ion) structure **29**, which, however, was discounted after consideration of the signals from the carbonyl groups (177.2 and 164.8 ppm) in the ^{13}C NMR spectrum as well as the position of carbonyl vibrations (1736 and 1641 cm^{-1}) in the IR spectrum. In this context the previously studied glyoxamine **11a** served as a model compound.

A large number of alternatives, including the ring tautomer of **29**, i.e. **30**, were now considered, but fortunately the compound could be obtained in crystalline form suitable for X-ray crystallography, which established the structure as the spiro compound **31**. A rationalization of its formation, involving an azomethine ylide intermediate and a cycloaddition to isatin in the final step, is given in Scheme 3.

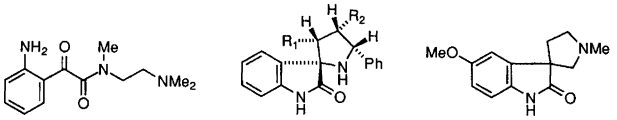


3a **31**

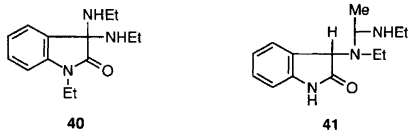
Scheme 3.

Reaction of isatin with *N,N,N'*-trimethylethylenediamine under similar conditions gave, as the final product, the ring-opened product **32** (i.e., analogous with **11a**). It was concluded that *N,N'*-dimethylethylenediamine and *N,N,N'*-trimethylethylenediamine both attack isatin initially at the 3-position according to the general Scheme 1. The highly nucleophilic (as compared with simple amines) ethylenediamines compete successfully with OH^- giving the ring-opened thermodynamic products (e.g., **32**). In the case of *N,N'*-dimethylethylenediamine this intermediate is capable of secondary reactions as outlined in Scheme 3.

A somewhat related result has been reported by Grigg *et al.*,[22] who found that isatin, benzylamine and methyl acrylate reacted to give a 5:2 mixture of the regioisomers **33a** and **33b**. More recently Palmisano[23] and Brown[24] in approaches to the alkaloid horsfiline (**34**) have reacted, in the crucial step, a suitable 3-alkylideneindolone with an azomethine intermediate.



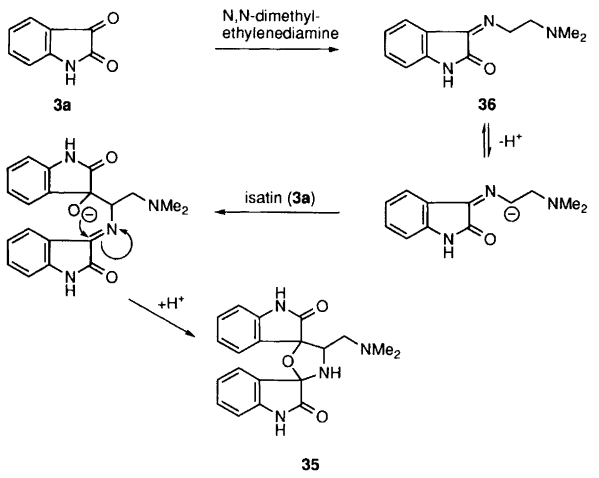
32 **33a** R_1=CO_2Me, R_2=H; **33b** R_1=H, R_2=CO_2Me **34**



40 **41**

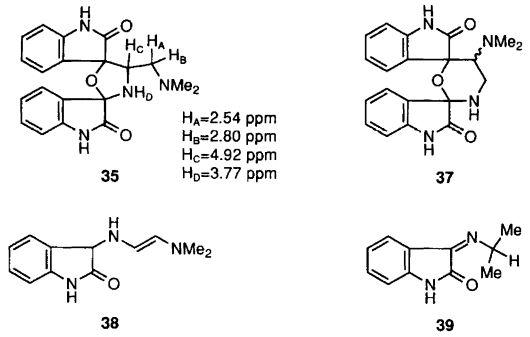
The reaction between isatin and *N,N*-dimethylethylenediamine also gave an unusual 2:1 product, which after consideration of the IR and NMR data has been given the tentative structure **35** featuring a central tetrahydro-1,3-oxazole ring as also does compound **31**

(Scheme 4). The unstable tetrahydro-1,3-oxazole **35** features several stereo centers and could not be obtained in crystalline form suitable for X-ray crystallography. The intermediate imine **36** could not be isolated.



Scheme 4.

The tetrahydro-1,3-oxazine **37** was for some time considered as the structure of the 1:2 product because the NMR signals from the methylene group showed a complicated coupling pattern indicating a cyclic structure. However, decoupling experiments established that the NH group (in the tetrahydro-1,3-oxazole ring) is coupled only with the methine proton, which in turn is coupled with both the diastereotopic protons H_A and H_B in the methylene group. Furthermore, formation of **37** would have required isomerization of the imine **36** to the enamine **38**, which is unlikely, as known imines (such as **39**) do not isomerize even under drastic conditions.[25]



Collection and refinement of X-ray diffraction data. A rebuilt and upgraded[26] Nicolet diffractometer equipped with Cu Kα radiation was used for the data collection. Three standard reflections measured every hour did not show any significant variations. The structure was solved by direct methods and refined by full-matrix least-squares. Atomic coordinates, thermal parameters, molecular geometries and structure factors have been deposited with the Cambridge Crystallographic Data Centre. Some data for the specimens and refinements are given below.

Compound **31**. A light yellow prismatic crystal of dimensions 0.05 × 0.10 × 0.25 mm obtained by recrystallization from acetonitrile was used for the data collection. Of the measured 2763 independent reflections, 1945 with $I > 3\sigma(I)$ were used in the refinements and gave $R = 0.045$ and $R_w = 0.054$ with 325 parameters.

A perspective view of molecule **31** is shown in Fig. 1 and selected distances and angles are given in Table 1. There are intermolecular N1–H···O3, N4–H···O3 and

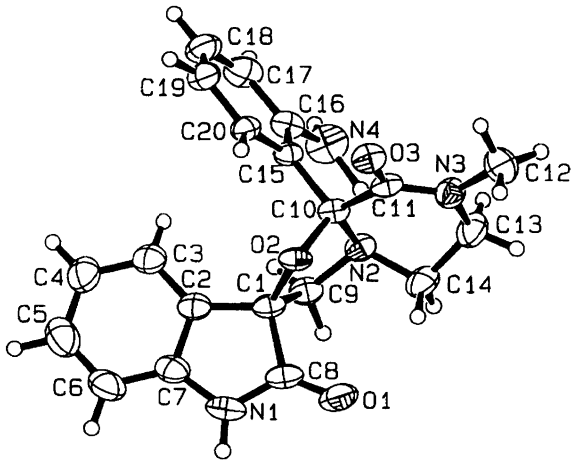


Fig. 1. ORTEP view of molecule **31** with numbering of the atoms. Thermal ellipsoids are drawn at the 40% probability level, hydrogen atoms are on an arbtirary scale.

Table 1. Selected bond lengths (in Å) and angles (in °) for **31**.[a]

O1–C8	1.210(4)	C1–C2–C7	108.4(3)
O2–C1	1.430(3)	C2–C7–N1	109.9(3)
O2–C10	1.468(3)	C7–N1–C8	111.8(3)
O3–C11	1.234(3)	N1–C8–O1	126.7(3)
N1–C7	1.400(4)	N1–C8–C1	107.3(3)
N1–C8	1.358(4)	C8–C1–C2	102.3(2)
N2–C9	1.453(4)	C8–C1–C9	111.8(2)
N2–C14	1.468(4)	C9–N2–C10	102.9(2)
N3–C11	1.326(4)	N2–C10–O2	104.9(2)
N3–C12	1.463(4)	C10–O2–C1	108.0(2)
N3–C13	1.460(4)	O2–C1–C9	103.8(2)
N4–C16	1.373(4)	N2–C10–C15	112.7(2)
C1–C2	1.502(4)	N2–C10–C11	114.4(2)
C1–C8	1.441(4)	C10–C11–O3	118.7(3)
C1–C9	1.557(4)	C10–C11–N3	119.1(2)
C2–C7	1.391(4)	C11–N3–C12	120.0(3)
C10–C11	1.543(4)	C11–N3–C13	122.7(3)
C10–C15	1.527(4)	N3–C13–C14	109.4(3)
C13–C14	1.490(5)	C13–C14–N2	107.3(3)
C14–N2–C10	112.9(2)		
C14–N2–C9	114.3(2)		
C15–C16–N4	124.8(3)		

[a] $C_{20}H_{20}N_4O_3$, $M = 364.41$, space group $P2_1/n$, $a = 10.063(2)$, $b = 15.192(3)$, $c = 11.623(2)$ Å, $\beta = 91.92(3)°$, $V = 1776(1)$ Å^3, $Z = 4$, $D_c = 1.363$ g cm^{-3}, $2\theta_{max} = 120°$, $T = 295$ K.

intramolecular N4–H···N2 hydrogen bonds in the structure.

Conclusions

In this paper we have defined the type of product one should expect when isatin is reacted with simple aliphatic amines. In some cases, involving ethylenediamines, products with unexpected structures (such as **31**) have been isolated. In this context it is noteworthy that reactions between isatin and simple primary amines have, in addition to the expected 3-imines, resulted in unexpected and poorly characterized products. Thus Haslinger[27] isolated, for example, a 1:3 product from the reaction between isatin and ethylamine, initially given the unlikely structure **40** but later revised to **41** by Popp.[28] However, in the light of the results obtained in this work it seems desirable also carefully to reinvestigate the reaction pattern between isatin and simple primary amines.

Experimental

Melting points are uncorrected. NMR spectra were recorded on a Bruker AM 400 or a Bruker AM 250 instrument. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer. Flash chromatography was performed using Merck silica gel 60 (particle size 0.040–0.063 mm).

5. Isatin (2.94 g, 20 mmol) was added to a stirred solution of *N,N'*-dimethylethylenediamine (2.20 g, 25 mmol) in water (30 ml). The clear solution started to form a precipitate after ca. 1 h, which was collected after 24 h and recrystallized from acetonitrile. Yield: 2.40 g (64%); m.p. 176–177 °C (decomp.). IR (KBr): ν_{max} 2866, 2787, 1716, 1619, 1471, 1226, 1194, 750, 625 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.22 (s, 1 H, NH), 7.23 (dd, 1 H), 7.18 (d, 1 H), 6.97 (dd, 1 H), 6.77 (d, 1 H), 3.22 (m, 2 H, CH_2), 3.09 (m, 2 H, CH_2), 2.02 (s, 6 H, Me); ^{13}C NMR (DMSO-d_6): δ 176.7 (s), 143.6 (s), 129.8 (d), 126.0 (s), 125.4 (d), 121.8 (d), 109.4 (d), 85.5 (s), 50.3 (t), 35.2 (q). In connection with the recrystallization a tiny amount of compound **31** was also obtained.

3,3-Dipiperidinoindol-2-one (**7**). A solution of isatin (7.36 g, 50 mmol) in a mixture of piperidine (8 ml) and H_2O (32 ml) was stirred for 10 min at room temperature. The solid formed was collected by filtration. Yield: 6.85 g (46%). IR (KBr): ν_{max} 3282, 2926, 2801, 1722, 1682, 1619, 1470, 1222, 743 cm^{-1}.

3,3-Dimorpholinoindol-2-one (**8**) *and 1-(2-Aminophenyl)-2-morpholinoethanedione* (**21**). A solution of isatin (7.36 g, 50 mmol) in a mixture of morpholine (50 ml) and water (50 ml) was stirred at 50 °C for 12 h. The reaction mixture was allowed to attain room temperature. The solid formed was collected by filtration to give 4.08 g of **8** as a white solid. Water (100 ml) was added to the filtrate, after which it was stirred for 1 h. The solid formed was collected by filtration to give 3.28 g of **21** as a yellow solid.

8. Yield: 4.08 g (27%); IR (KBr): ν_{max} 3138, 3084, 2962, 2852, 1715, 1621, 1472, 1111, 746 cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.44 (br s, 1 H, NH), 7.21 (dd, 1 H), 7.15 (d, 1 H), 6.97 (dd, 1 H), 6.78 (d, 1 H), 3.47 (m, 8 H, CH_2), 2.47 (s, 8 H, CH_2). ^{13}C NMR ($CDCl_3$): δ 174.3 (s), 142.2 (s), 129.3 (d), 125.4 (d), 124.0 (s), 121.3 (d), 109.8 (d), 83.3 (s), 66.4 (t), 45.8 (t).

21. Yield: 3.28 g (28%); m.p. 117–119 °C (decomp.). IR (KBr): ν_{max} 3423, 3313, 1640, 1623, 1550, 1454, 1213, 1112, 741 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.45 (d, 1 H), 7.30 (dd, 1 H), 6.7–6.6 (m, 2 H), 6.37 (s, 2 H, NH_2), 3.8–3.7 (m, 4 H, CH_2), 3.63 (t, 2 H, CH_2), 2.35 (t, 2 H, CH_2). ^{13}C NMR ($CDCl_3$): δ 193.4 (s), 165.7 (s), 151.7 (s), 136.1 (d), 133.0 (d), 117.1 (d), 116.3 (d), 114.1 (s), 66.6 (t), 46.3 (t), 41.4 (t).

3,3-Di-(dimethylamino)indol-2-one (**10**). A solution of isatin (7.36 g, 50 mmol) in aqueous $NHMe_2$ (40%, 40 ml) was stirred for 10 min at room temperature. The solid formed was collected by filtration. Yield: 4.50 g (41%): m.p. 115–117 °C (decomp.). IR (KBr): ν_{max} 3262, 2945, 2865, 2783, 1732, 1698, 1616, 1459, 1194, 745 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.40 (br s, 1 H, NH), 7.3–7.2 (m, 2 H), 7.02 (dd, 1 H), 6.92 (d, 1 H), 2.32 (s, 12 H, Me). ^{13}C NMR ($CDCl_3$): δ 177.9 (s), 141.2 (s), 129.1 (d), 125.7 (s), 125.4 (d), 122.2 (d), 110.3 (d), 84.4 (s), 37.8 (q).

1-(2-Aminophenyl)-2-(dimethylamino)ethanedione (**11a**). A solution of isatin (7.36 g, 50 mmol) in aqueous $NHMe_2$ (40%, 40 ml) was refluxed for 10 min. The reaction mixture was allowed to attain room temperature. The solid formed was collected by filtration. Yield: 7.98 g (73%); m.p. 128–129 °C (lit. m.p. 129–131 °C).[14] IR (KBr): ν_{max} 3446, 3326, 1636, 1622, 1589, 1552, 1484, 1240, 1145, 762 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.38 (d, 1 H), 7.28 (dd, 1 H), 6.66 (d, 1 H), 6.61 (dd, 1 H), 6.73 (s, 2 H, NH_2), 3.07 (s, 3 H, Me), 2.93 (s, 3 H, Me). ^{13}C NMR ($CDCl_3$): δ 194.1 (s), 167.3 (s), 151.6 (s), 135.8 (d), 133.0 (d), 117.0 (d), 116.2 (d), 114.0 (s), 37.1 (q), 33.8 (q).

18. A suspension of *N*-methylisatin (8.06 g, 50 mmol) in aqueous $NHMe_2$ (40%, 40 ml) was stirred for 6 h. The solid formed was collected by filtration. Yield: 7.53 g (73%); m.p. decomp. IR (KBR): ν_{max} 3258, 2945, 2865, 2829, 2783, 1728, 1699, 1616, 1460, 1330, 746 cm^{-1}.

22. Compound **11a** (192 mg, 1 mmol) was dissolved in acetonitrile (8 ml). Addition of oxalyl chloride (87 µl, 1 mmol) immediately gave a white precipitate, which was collected by filtration to give compound **22**. Yield: 210 mg (95%); m.p. 264–265 °C (lit. m.p. 267–268°C).[17] IR (KBr): ν_{max} 3224, 1703, 1655, 1639, 1578, 1529, 1452, 1245, 755 cm^{-1}. ^1H NMR ($CDCl_3$): δ 12.98 (s, 2 H, NH), 8.93 (d, 2 H), 7.74 (d, 2 H), 7.70 (dd, 2 H), 7.26 (dd, 2H), 3.14 (s, 6 H, Me), 3.01 (s, 6 H, Me). ^{13}C NMR

($CDCl_3$): δ 195.0 (s), 165.8 (s), 158.6 (s), 140.2 (s), 136.6 (d), 133.7 (d), 124.3 (d), 121.0 (d), 119.4 (s), 37.2 (q), 34.1 (q).

25a. Isatin (7.36 g, 50 mmol) was dissolved in water (60 ml) containing ethylmethylamine (5.91 g, 100 mmol). After a short period at reflux, evaporation gave the salt **25a**. Yield: 11.2 g (100%); m.p. 130–133 °C (decomp.). IR (KBr): ν_{max} 3417, 3290, 2990, 2731, 2495, 1673, 1618, 1571, 1555, 1226, 1160, 760, 740 cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.48, (d, 1 H), 7.18 (dd, 1 H), 7.08 (s, 2 H, NH_2), 6.71 (d, 1 H), 6.48 (dd, 1 H), 2.87 (q, 2 H, CH_2), 2.50 (s, 3 H, Me), 1.15 (t, 3 H, Me); finally one of the NH_2 could not be detected. ^{13}C NMR (DMSO-d_6): δ 199.5 (s), 170.6 (s), 151.6 (s), 133.7 (d), 133.6 (d), 116.3 (d), 114.1 (d), 113.5 (s), 43.0 (t), 31.6 (q), 10.7 (q).

The following salts were similarly prepared. The salt **25c** can easily be further purified by recrystallization from acetonitrile.

25b. Yield: 11.9 g (100%); m.p. 147–150 °C (decomp.). IR (KBr): ν_{max} 3414, 3282, 2988, 2733, 2515, 1634, 1580, 1552, 1421, 1228, 1157, 765, 742 cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.25 (s, 2 H, NH_2), 7.47 (d, 1 H), 7.18 (dd, 1 H), 7.07 (s, 2 H, NH_2), 6.71 (d, 1 H), 6.48 (dd, 1 H), 2.87 (q, 4 H, CH_2), 1.16 (t, 6 H, Me). ^{13}C NMR (DMSO-d_6): δ 199.5 (s), 170.5 (s), 151.6 (s), 133.7 (d), 133.6 (d), 116.3 (d), 114.0 (d), 113.5 (s), 41.1 (t), 10.9 (q).

25c. Yield: 13.3 g (100%); m.p. 154–157 °C (decomp.). IR (KBr): ν_{max} 3418, 3295, 2974, 2774, 2465, 1634, 1624, 1574, 1550, 1419, 1224, 1159, 756, 736 cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.31 (s, 2 H, NH_2), 7.46 (d, 1 H), 7.18 (dd, 1 H), 7.07 (s, 2 H, NH_2), 6.70 (d, 1 H), 6.47 (dd, 1 H), 2.78 (m, 4 H, CH_2), 1.60 (m, 4 H, CH_2), 0.87 (t, 6 H, Me). ^{13}C NMR (DMSO-d_6): δ 199.5 (s), 170.4 (s), 151.6 (s), 133.6 (d), 133.5 (d), 116.3 (d), 113.9 (d), 113.5 (s), 48.1 (t), 18.9 (t), 10.9 (q).

25d. Yield: 13.3 g (100%); m.p. 148–151 °C (decomp.). IR (KBr): ν_{max} 3461, 3341, 2980, 2738, 2521, 1629, 1568, 1551, 1416, 1224, 1159, 754, 731 cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.09 (s, 2 H, NH_2), 7.49 (d, 1 H), 7.17 (dd, 1 H), 7.09 (s, 2 H, NH_2), 6.71 (d, 1 H), 6.47 (dd, 1 H), 3.29 (m, 2 H, CH), 1.21 (d, 12 H, Me). ^{13}C NMR (DMSO-d_6): δ 199.4 (s), 170.2 (s), 151.6 (s), 133.6 (d), 133.5 (d), 116.3 (d), 113.9 (d), 113.5 (s), 45.8 (d), 18.5 (q).

31. Isatin (7.35 g, 50 mmol), *N,N'*-dimethylethylenediamine (4.85 g, 55 mmol) and toluene (150 ml) was heated (4 h) at reflux using a Dean–Stark trap. Filtration, while hot, gave a dark crude solid (2.5 g) which was recrystallized twice from acetonitrile to yield **31**. Yield: 1.7 g (19%); m.p. 209–211 °C (decomp.). IR (KBr): ν_{max} 3433, 3328, 3269, 1736, 1641, 1608, 1493, 1470, 1447, 1332, 1191, 1142, 757 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.48 (s, 1 H, NH), 7.57 (d, 1 H), 7.13 (dd, 1 H), 7.05 (dd, 1 H), 6.75 (d, 1 H), 6.69 (dd, 1 H), 6.61 (d, 1 H), 6.50 (dd, 1 H), 6.06 (d, 1 H), 5.71 (s, 2 H, NH_2), 4.05 (dd, 1 H, CH_2), 3.72 (dd, 1 H, CH_2), 3.64 (d, 1 H, CH_2), 2.39 (d, 1 H, CH_2), 3.22 (d, 1 H, CH_2), 2.97 (d, 1 H, CH_2), 2.85 (s, 3 H, Me). ^{13}C NMR (DMSO-d_6): δ 177.2 (s), 164.8 (s), 148.2 (s), 142.1 (s), 130.2 (d), 129.5 (d), 129.4 (d), 128.8 (s), 125.0 (d), 121.7 (d), 121.5 (s), 116.2 (d), 114.9 (d), 109.5 (d), 101.7 (s), 80.0 (s), 62.4 (t), 48.1 (t), 46.2 (t), 34.0 (q).

32. Isatin (2.94 g, 20 mmol) was added to a solution of *N,N,N'*-trimethylethylenediamine (3.0 g, 30 mmol) in water (25 ml). After a reflux period of 3 min, the clear solution was set aside for 24 h, whereupon the crystals that formed were collected. Yield: 3.55 g (71%); m.p. 105–107 °C (decomp.). IR (KBr): ν_{max} 3426, 3301, 2821, 2765, 1638, 1621, 1551, 1483, 1454, 1239, 1164, 757 cm^{-1}. Major rotamer ^1H NMR (DMSO-d_6): δ 7.44–7.24 (m, 2 H), 7.35 (s, 2 H, NH_2), 6.81 (d, 1 H), 6.54 (t, 1 H), 3.19 (t, 2 H, CH_2), 2.99 (s, 3 H, Me), 2.34 (t, 2 H, CH_2), 1.98 (s, 6 H, Me). Minor rotamer ^1H NMR (DMSO-d_6): δ 7.44–7.24 (m, 2 H), 7.35 (s, 2 H, NH_2), 6.81 (d, 1 H), 6.54 (t, 1 H), 3.51 (t, 2 H, CH_2), 2.82 (s, 3 H, Me), 2.45 (t, 2 H, CH_2), 2.22 (s, 6 H, Me). ^{13}C NMR (DMSO-d_6): δ 193.3 (s), 193.6 (s), 166.9 (s), 166.8 (s), 152.2 (s, both rotamers), 135.5 (d, both rotamers), 132.9 (d), 132.8 (d), 116.8 (d, both rotamers), 114.8 (d), 114.5 (d), 112.6 (s), 112.5 (s), 56.6 (t), 55.4 (t), 45.1 (q), 44.9 (q), 42.8 (t), 34.4 (t), 31.3 (t).

35. *Method A.* Isatin (7.35 g, 50 mmol) was added to a stirred solution of *N,N*-dimethylethylenediamine (10 ml) in water (40 ml) at 40 °C, which resulted in the formation of a clear red solution. Within 2 h a sticky precipitate was formed which was collected, washed with water and dissolved in 2-propanol. After 24 h water was added until the solution became turbid, whereupon the vessel was set aside. The crystalline solid that formed was collected after 24 h. Yield: 3.50 g (38%).

Method B. Isatin (7.35 g, 50 mmol) was added to a stirred solution of *N,N*-dimethylethylenediamine (2.20 g, 25 mmol) in ethanol (50 ml) at room temperature, which resulted in the formation of a clear red solution. The reaction mixture was stirred for 5 days, after which the solid formed was collected by filtration. Yield: 3.78 g (41%); m.p. 153–155 °C (decomp.). IR (KBr): ν_{max} 3313, 3155, 3092, 2825, 1706, 1620, 1473, 1200, 761 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.32 (m, 2 H, NH), 7.29 (m, 2 H), 7.11 (m, 2 H), 6.87 (m, 2 H), 6.60 (m, 2 H), 4.92 (m, 1 H, CH), 3.77 (d, 1 H, NH), 2.80 (dd, 1 H, CH_2), 2.54 (dd, 1 H, CH_2), 2.21 (s, 6 H, Me). ^{13}C NMR (DMSO-d_6): δ 178.6 (s), 176.0 (s), 142.7 (s), 142.6 (s), 129.4 (d), 129.1 (d), 124.7 (s), 124.4 (d), 124.0 (d), 123.9 (s), 121.4 (2 C, d), 109.3 (d), 109.2 (d), 73.7 (s), 73.4 (d), 71.0 (s), 64.6 (t), 45.5 (q).

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