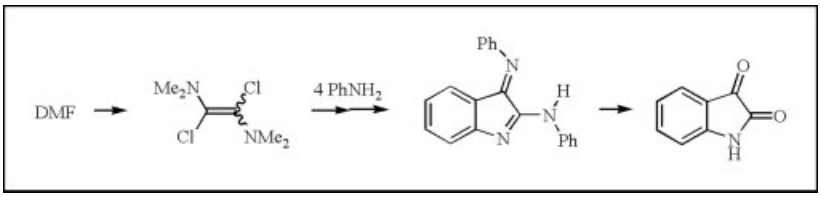
From DMF to Isatine: A Novel and General One-Pot Synthesis of Isatine and Its N-Unsubstituted Derivatives *via* Nucleophilic Substitution Reactions on 1,2-Bis(dimethylamino)-1,2-dichloroethene

Stefan M. Huber,* André Hennig, Frank G. Pühlhofer, and Robert Weiss*

Institut für Organische Chemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Henkestraße 42, 91054 Erlangen, Germany
*E-mail: weiss@chemie.uni-erlangen.de or stefan.m.huber@web.de

Additional Supporting Information may be found in the online version of this article.
Received June 5, 2008
DOI 10.1002/jhet.8
Published online 13 May 2009 in Wiley InterScience (www.interscience.wiley.com).



3-Imino-2-amino-isatines were obtained by a one-pot reaction of an excess of aniline (or its derivatives) with 1,2-bis(dimethylamino)-1,2-dichloro-ethene (prepared *in situ* from DMF). Subsequent hydrolysis yielded the corresponding isatine derivatives in reasonable to high yields. DFT calculations with regard to the mechanisms of this reaction sequence are presented.

J. Heterocyclic Chem., **46**, 421 (2009).

INTRODUCTION

Isatine **4** and its derivatives play an important role in the pharmaceutical and dye industry. Drugs containing isatine units cure diseases such as epilepsy [1], tuberculosis [2], and bulimia [3]. Isatin derivatives are furthermore employed as antibacterial [4] or antifugal [5] compounds or to treat inflammations [6].

Because of its importance, various synthetic routes to isatine and its derivatives have been developed. Although the large-scale synthesis of unsubstituted isatine is accomplished by oxidation of indigo [7], several methods are known for the preparation of isatine derivatives on the laboratory or pharmaceutical scale. Among these are the classical methods by Sandmeyer [8] and Gassman and von Bergen [9] as well as a more recent methodology developed by Meth-Cohn and Goon [10], the latter of which is restricted, however, to *N*-methyl isatines. Yet, most of these methods involve harsh conditions, expensive chemicals, and require multiple steps, including the isolation of several intermediates.

In the course of our investigations of nucleophilic substitution reactions on 1,2-bis(dimethylamino)-1,2-bisonioethenes [11], we have developed a new versatile one-pot synthesis of N-unsubstituted isatine derivatives, starting from the common solvent DMF and involving mostly customary chemicals, as described in more detail below.

RESULTS AND DISCUSSION

In the early 1980s, Boehme and Sutoyo [12] reported on the dimerization of deprotonated chlorochlorides deriving from DMF (and other formamides), yielding 1,2-bis(dimethylamino)-1,2-dichloro-ethene **1** (Scheme 1).

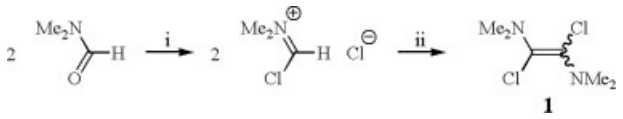
We found that treatment of a solution of **1** in THF with an excess of aniline did not result in the formation of the anticipated tetraaminoethene **2** (Scheme 2). Instead the known [13] isatine derivative **3** was isolated after stirring the reaction mixture for 24 h at room temperature and subsequent exposure to aerial oxygen. Apart from spectroscopic data, the structure of **3** was further confirmed by single-crystal X-ray crystallography, which was in perfect agreement with the already published structural analysis of **3** [14].

Indole derivative **3** could be isolated in 65% yield over all steps (*i.e.*, based on the amount of DMF used) by simple recrystallization from ethanol. Hydrolysis of **3** to isatine **4** could be achieved by treating **3** with conc. HCl in glacial acetic acid (yield: 71 %) [15]. Thus, a novel synthetic route to isatine **4** from DMF could be developed, which requires only the isolation of intermediate **3** *via* recrystallization (as ethene **1** can be prepared from DMF in a one-pot reaction and can be treated *in situ* with aniline to give the isatine precursor **3**).

To examine the range of application of our method, we reacted several aromatic amines of different electronic nature with ethene **1**. Results are shown in Table 1.

In all cases, the corresponding N-unsubstituted isatines **4a–g** could be obtained by recrystallization from ethanol. Although reaction conditions were not specifically optimized for the different aniline derivatives, reasonable overall yields (based on the amount of DMF) could be achieved in most cases. Still higher yields

Scheme 1. Synthesis of **1** by deprotonation of a chlorochloride derived from DMF; (i) $C_2O_2Cl_2$, 0 °C and (ii) Hünig's base ($NEtiPr_2$).



should be within reach by further optimization of the reaction procedure. Based on these (few) orientating experiments, no definitive statement can be made concerning the influence of the various substituents X, Y, and Z on the overall yield. It seems, though, that the presence of electron-withdrawing groups leads to a lower yield of the corresponding intermediate of type **3**. This would be in accordance with the reaction mechanism proposed below. Yet, in our experiments we also observed that addition of the bromo- and fluoro-substituted aniline derivatives to a solution of ethene **1** resulted in a stronger increase of temperature and a faster optical change of the solution (compared with the other derivatives).

In contrast, when adding *N*-methyl aniline to a solution of **1**, no indications of such a cyclization reaction could be observed. Instead, the corresponding bis (dimethylamino)-bis(methyl-phenylamino)-ethene was detected by mass spectrometry (as well as its bis-oxidized form). Obviously, both chloro-substituents had been substituted by *N*-methyl aniline. Thus, only primary anilines are applicable for the synthesis of isatine derivatives according to our new method. A possible reason for this limitation is given below. In the case of secondary aniline derivatives, it should in principle be possible to isolate the corresponding tetraamino-ethenes (*cf*. Scheme 2).

During the course of our investigations, some intermediates could be detected, which shed some light on the mechanism of the formation of **3** from ethene **1**. It was observed that a clear, red solution of **3** in THF was only obtained after exposure of the reaction mixture to aerial oxygen. Under inert gas conditions, addition of aniline to ethene **1** resulted in an orange suspension. Although the solid compound could be isolated, it

Scheme 2. Reaction of **1** with an excess of aniline; (i) conc. HCl in glacial CH_3COOH.

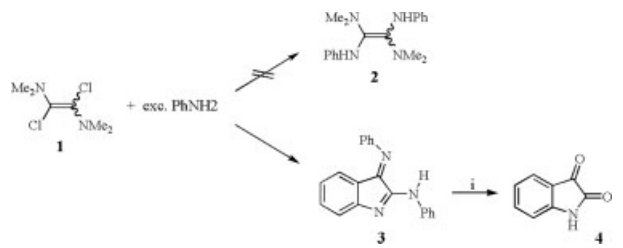
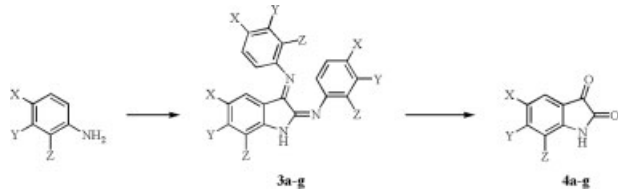


Table 1

Synthesis of isatine derivatives **3a–g** and isatines **4a–g**.

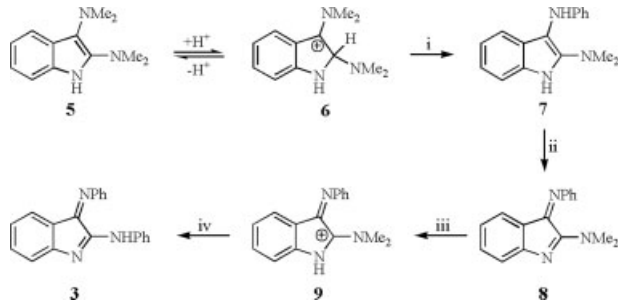


	X	Y	Z	**3** (%)[a]	**4** (%)[b]
a	H	H	H	65	71
b	CH_3	H	H	25	68
c	OCH_3	H	H	65	66
d	H	Br	H	18	93
e	F	H	H	28	85
f	$COOCH_3$	H	H	–	10
g	H			–	31

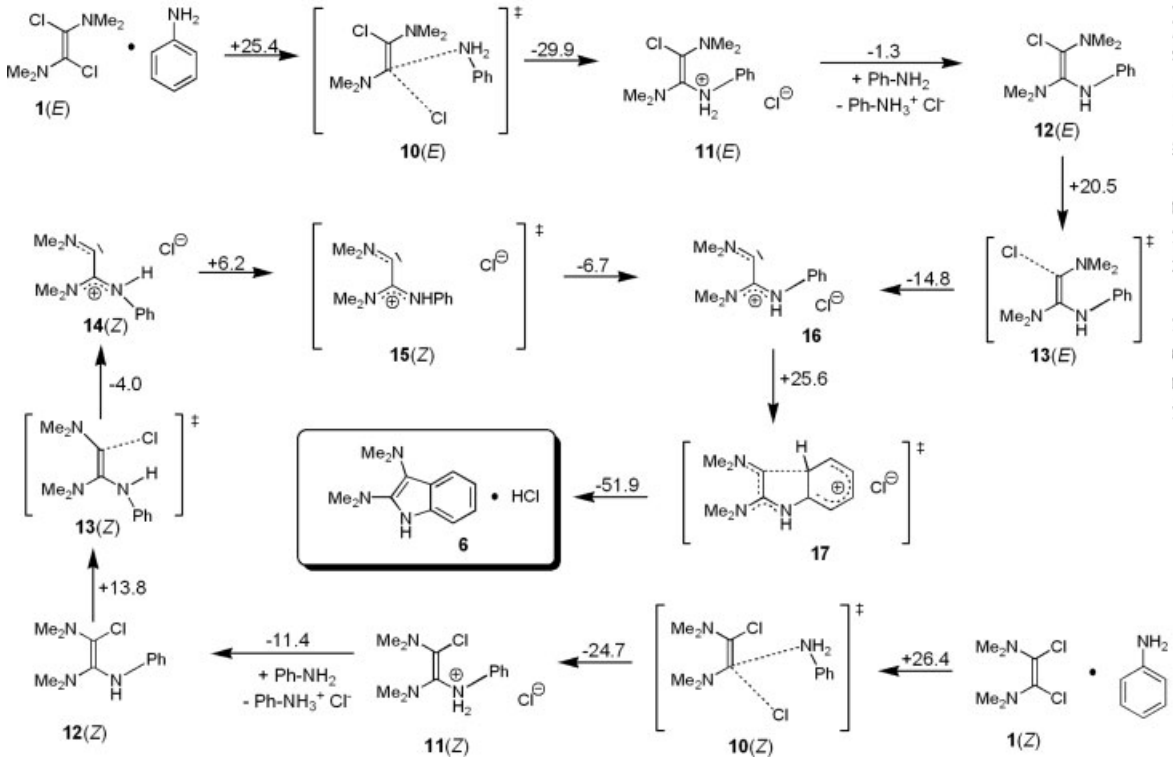
[a] Yields for **3a–g** are based on the amount of DMF.
[b] Yields for **4a–e** are based on the amount of **3a–e** and for **4f,g** on the amount of DMF, as intermediates **3f,g** were not isolated.

proved to be very sensitive to oxygen and could not be characterized by NMR spectroscopy. Its mass spectrum, however, showed a peak at $m/z = 252$, in accord with structure **7** (Scheme 3). When the colorless solid was dissolved in CH_2Cl_2 and stirred on air, the solution turned red rapidly. Apparently, oxidation to **8** had taken place, as evidenced by a mass peak at $m/z = 250$ (substitution at position C2 of the heterocycle can be ruled out due to the fact that its oxidation would produce an anti-aromatic intermediate). Compound **8** could be isolated and characterized by NMR spectroscopy. As expected, its methyl groups show a coalescence phenomenon at about −10°C. Incidentally, analogous compounds could also be detected during the preparation of

Scheme 3. Proposed mechanism of the formation of 3 (starting after cyclization to 5) according to experimental hints; (i) + $PhNH_2$, - $HNMe_2$, (ii) oxidation by air, (iii) + H^+, and (iv) + $PhNH_2$, - $HNMe_2$.



Scheme 4



compounds **3d–f**. In the case of compound **3d**, a heterocyclic intermediate containing two dimethylamino groups (analogous to **5** in Scheme 3) could also be detected in the reaction mixture *via* mass spectrometry.

Thus, it seems plausible that the primary product of the ring closure reaction leading to **3(a)** is intermediate **5**. After subsequent substitution of the dimethylamino group at C2 by aniline, oxidation by aerial oxygen leads to the (experimentally isolated) compound **8**. Further substitution of the second NMe_2 group by aniline finally yields isatine derivate **3**. This mechanism is shown in Scheme 3.

When *N*-methyl aniline instead of aniline is used in the reaction with ethene **1**, the corresponding *N*-methylated intermediate **7** cannot be oxidized *via* formal H_2 abstraction, and thus only primary amines are applicable as reactants.

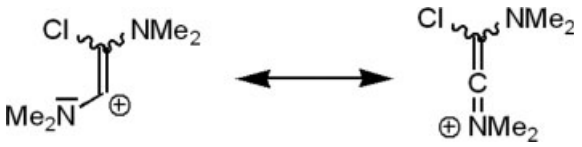
No experimental data could be obtained regarding the mechanisms of the ring closure, ultimately leading to compound **5**. Therefore, DFT calculations were carried out to gain some insight into the first steps of the formation of the isatine derivative from ethene **1**.

Computational section. The reaction sequence starting from ethylene derivative **1** and aniline to yield the isatine derivative **5** includes several mechanistic key steps. To analyze and characterize those steps, DFT-computations were performed using the Gaussian 98W suite of programs (for further details see Supporting Information). Scheme 4 shows the complete reaction path.

The first key step of the reaction sequence is the substitution of chloride in **1** by aniline. In principle such substitutions at vinyl-like carbon centres can proceed in two different ways: (a) *via* an addition/elimination mechanism under formation of an intermediate in analogy to the S_NAr mechanism (subsequently called **A**) or (b) *via* an elimination/addition mechanism in analogy to the S_N1 mechanism (subsequently called **B**) [16,17]. Reactions according to **A** were found for ethylene derivatives carrying strong electron withdrawing substituents. In contrast, ethylene derivatives with electron donating substituents show reactions according to **B**. Ethylene derivative **1** has two –I-acceptor substituents (chlorine) and two donor substituents (NMe_2). Hence, in principle both alternative mechanisms are to be considered. Because **1** is synthesized *in situ*, a mixture of the *E*- and *Z*-isomer enters the reaction sequence (this problem will be addressed later). Both forms need to be analyzed computationally.

Because of the gas phase conditions in the computations, the formation of ions (as in **B**) will not be favored. Hence, the corresponding reaction barriers should be overestimated in comparison to the real

Scheme 5. Partial formation of ketene-iminium structure in the transition state.



substitution conditions in polar solvents. Even with this handicap, the reaction barrier in **B** was found to be 26.4 kcal/mol for the *Z*-form and 25.4 kcal/mol for the *E*-isomer. A reaction according to **A**, or alternatively *via* a S_N2-in-plane mechanism, could not be determined computationally, but the corresponding reaction barrier was found to be at least 50 kcal/mol for both isomers. NBO analyses of the corresponding transition structures clearly explain this result. The cation in **10**, formed by elimination of chloride from **1**, is stabilized by partial formation of a ketene-iminium structure (*cf*. Scheme 5). The electron distribution of the N—C—π-bond [18] indicates the partial bond formation, whereas the C—C—π-bond is not influenced at all. N—C—C angles are 176° (*Z*-form) and 156° (*E*-form).

The bond lengths between the formally cationic carbon centre and both the chloride ion (351 and 315 pm) and the aniline (355 and 261 pm) indicate the formation of a nearly uncoordinated ketene-iminium-system.

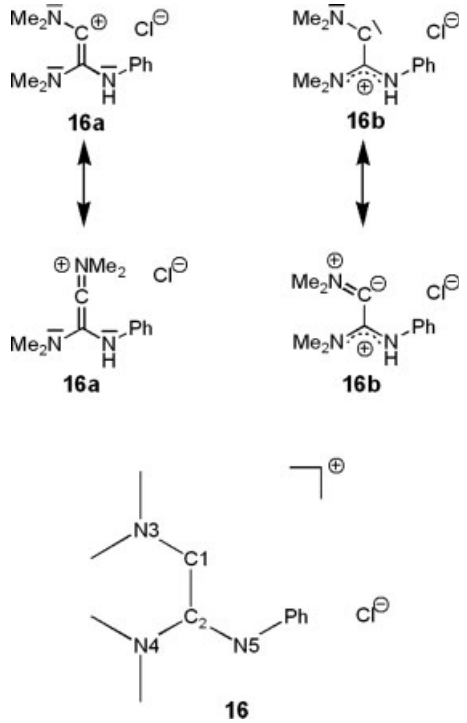
The second key step of the reaction sequence is the substitution of the second chlorine substituent in **12** under formation of the five-ring system **5**. Since **12** carries three donor substituents and only one chlorine substituent, the exchange reaction should proceed *via* the same mechanism as for derivative **1**, or even *via* formation of a ketene-iminium species as an intermediate, and not as a transition structure. Both isomers of **12** can be transformed into the same salt-like structure **16** (*via* transition state **13** (*E*-form) or two transition states **13** and **15**, with one connecting, energetically not favored intermediate **14** (*Z*-form)). This result simplifies the problem of the *E*- and *Z*-isomers because the question of *E* or *Z* does not occur in **16**. The (highest) reaction barrier for this transformation is 21 kcal/mol and the salt **16** is energetically not favored in comparison to **12** (6 kcal/mol for the *E*-isomer, 9 kcal/mol for the *Z*-isomer, respectively). But it should always be taken into account that these energies will be much lower for the experimental reaction due to solvent effects. Those will make structures **12** and **16** energetically at least comparable or even favor the salt **16**. The chloride ion in **16** is stabilized *via* several hydrogen bonds in the gas phase.

Nevertheless, this result brings up another interesting question: What is the electronic nature of **16**? Is this intermediate a cation stabilized *via* a ketene-iminium contribution (**16a**) or must it be seen as a donor–acceptor substituted carbene **16b** (*cf*. Scheme 6) Analysis of bond lengths, bond angles, and tetrahedral angles in context with NBO analysis answers this question (Scheme 6).

The representative bond lengths clearly show that **16** is not a ketene-iminium species. Additionally, NBO analysis identifies a lone pair located at C1 with a hybridization of $sp^{1.65}$ and partial formation of a double bond between C1 and N3 with a density distribution of 26% (C1) and 74% (N3). Hence, the best representation of the nature of **16** is that of a donor–acceptor substituted carbene **16b**, which is stabilized by partial formation of an iminium structure as is shown in Scheme 6.

Because of this electronic nature the subsequent ring formation could occur *via* nucleophilic attack of the carbenes lone pair toward the aniline's π* system or alternatively *via* nucleophilic attack of the aniline's π systems toward to unoccupied orbital of the carbene. The calculated barrier for the ring closure is 25.6 kcal/mol (B3LYP/6-311+G**). NBO analysis of the corresponding transition state **17** shows that the unoccupied orbital at the carbene centre is nucleophilically attacked by the aniline's π system. In the transition state **17**, the new C—C—σ bond starts to form (density distribution: 33% on C1 and 67% on the aromatic centre) and the

Scheme 6. Electronic nature of 16 and geometry at B3LYP/6-311+G**. Selected bond lengths [pm] and angles [°]: C1-C2=146; C1-N3=129; C2-N4=134; C2-N5=135; C2-C1-N3=118; C1-C2-N4=119; C1-C2-N5=122; N4-C2-N5=119; C1-C2-N4-N5=176; N3-C1-C2-N4=107; N3-C1-C2-N5=78.



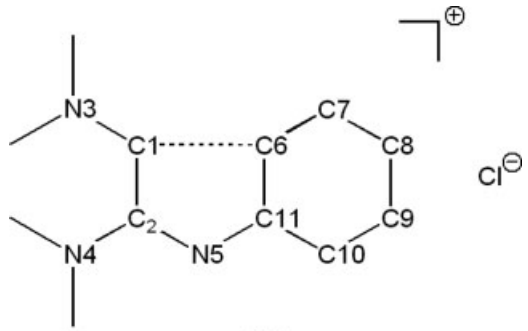
ethylene's C—C—π bond is ''rebuilt'' (density distribution: 46% on C1 and 54% on C2). The C1-N3 double bond, responsible for the partial ''iminium character'' of **16**, is reduced to a distribution of 18% on C1 and 82% on N3. Figure 1 gives representative geometry parameters for **17**.

Retrosynthetical analysis.. Examined from a retrosynthetical point of view, formation of isatine **4** is achieved by the reaction of aniline with C_2O_2 (in combination with an oxidation reaction), which is unstable under normal reaction conditions [19] (Scheme 7). Thus, ethene **1** acts as a synthetic equivalent of C_2O_2.

By substitution of both chloro-substituents of ethene **1**, followed by subsequent oxidation and hydrolysis, the synthesis of further, structurally different diketones appears to be feasible.

CONCLUSIONS

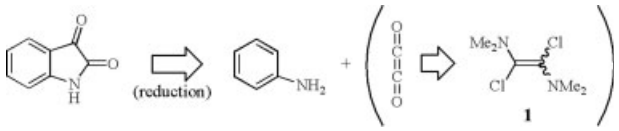
A new synthetic route to *N*-unsubstituted isatines has been presented, which is based on the reaction of ethene **1** with aniline derivatives. The isatine precursors **3a–g** are obtained under mild reaction conditions in a one-pot reaction starting from DMF. Apart from the respective substituted aniline, only standard chemicals such as oxalyl chloride or Hünig's base are employed as reactants, and isolation of the isatine precursors is accomplished by simple recrystallization. In general, reasonable overall yields could be achieved (especially for anilines with electron-donating substituents). Taking all that into account, the method presented in this article shares most of its advantages with the introduced method by Meth-Cohn and Goon [10] but in addition offers the possibility to synthesize N-unsubstituted isatine derivatives. Our method thus seems to have all prerequisites to evolve as a versatile isatine synthesis, especially for small or medium scale amounts.



17

Figure 1. Geometry parameters for **17** (lengths in pm, angles in °): C1-C2=141; C1-N3=132; C1-C6=197; C2-N4=136; C2-N5=137; N5-C11=137; C6-C7=142; C6-C11=142; C7-C8=138; C8-C9=141; C9-C10=139; C10-C11=140; C2-C1-N3=130; C2-C1-C6=95; C1-C2-N4=128; C1-C2-N5=112; N3-C1-N6=118; C1-C2-N4-N5=163; N3-C1-C2-N4=40; N3-C1-C2-N5=157; C2-C1-N3-C6=125; N4-C2-C1-C6=173; N5-C2-C1-C6=24.

Scheme 7. Retrosynthetical analysis.



EXPERIMENTAL

General. All operations in THF were carried out under a dry inert nitrogen atmosphere using standard Schlenk techniques. THF was distilled under nitrogen from sodium-benzophenone. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance spectrometer. The IR-spectra were taken on Bruker spectrophotometer in KBr pellets. Mass spectra were determined using a Micromass ZabSpec spectrometer. The elemental analyses were obtained on a EA 1110 CHNS analyzer.

General procedure for the preparation of 3a–e. A solution of 0.92 mL (12 mmol) DMF in 25 mL THF was cooled to 0°C, and under inert gas conditions, 1.03 mL (12 mmol) oxalyl chloride was added. After stirring for 2 h at room temperature, the suspension was again cooled to 0°C and a solution of 2.1 mL (12 mmol) Hünig's base (NEt*i*Pr$_2$) was added dropwise. After stirring for 1 h at 0°C and 2 h at room temperature, the precipitate was filtered off, and then 25 mmol of the corresponding aniline was added to the filtrate. After stirring for 16 h at room temperature, aerial oxygen was passed through the solution for several hours. The solvent was evaporated, the residue dissolved in 150 mL CH_2Cl_2 and washed twice with 50 mL H_2O. The organic phase was evaporated to dryness and the residue recrystallized from boiling ethanol.

2-Phenylamino-3-phenylimino-3H-indole 3a. Red solid; ^{1}H NMR ($CDCl_3$): δ = 6.64 (m, 2H, Phen), 7.05 (dd, *J* = 7.70 Hz, 1.1, 2H, Phen), 7.09 (t, *J* = 7.70 Hz, 1H, Phen), 7.23 (m, 3H, Phen), 7.42 (m, 4H, Phen), 7.85 (d, *J* = 7.70 Hz, 2H, Phen), 7.91 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 118.9 (CH Phen), 119.3 (CH Phen), 119.6 (C q), 122.8 (CH, Phen), 123.6 (CH, Phen), 125.8 (CH, Phen), 129.4 (CH, Phen), 129.6 (CH, Phen), 134.7 (CH, Phen), 138.5 (C q), 149.0 (C q), 158.3 (C q), 160.4 (C q), 162.9 (C q); IR (KBr): 3337, 164, 1629, 1597, 1574, 1545, 1481, 1440, 1320, 1300, 1244, 1226, 1192, 1146, 902, 785, 755, 715, 690, 582, 532, 509, 494 cm^{-1}; MS (FAB$^+$): *m*/*z*: 298[M$^+$+1]; elemental analysis calcd for $C_{20}H_{15}N_3$: C 80.78, H 5.08, N 14.13; found C 79.12, H 5.38, N 14.05.

3-(p-Tolylimino)-5-methyl-N-p-tolyl-3H-indole-2-amine 3b. Deep Red solid; ^{1}H NMR ($CDCl_3$): δ = 2.06 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 6.61 (s, 1H, Phen), 6.97 (d, *J* = 8.17 Hz, 2H, Phen), 7.05 (q, *J* = 7.81 Hz, 2H, Phen), 7.17 (d, *J* = 8.17 Hz, 2H, Phen), 7.23 (d, *J* = 8.05 Hz, 2H, Phen), 7.71 (d, *J* = 8.42 Hz, 2H, Phen), 7.83 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 20.6 (CH_3), 20.8 (CH_3), 118.7 (CH, Phen), 119.1 (CH, Phen), 119.2 (CH, Phen), 119.8 (C q,

Phen), 126.2 (CH, Phen), 129.8 (CH, Phen), 130.0 (CH, Phen), 132.0 (C q, Phen), 132.9 (C q, Phen), 134.9 (CH, Phen), 135.6 (C q, Phen),136.2 (C q, Phen), 146.3 (C q, Phen), 158.0 (C q), 160.7 (C q); IR (KBr): 3202, 3025, 2918, 1657, 1602, 1569, 1542, 1511, 1500, 1469, 1449, 1333, 1305, 1248, 1197, 1172, 1101, 1035, 939, 860, 840, 820, 735, 718, 578, 510cm^{-1}; MS (FAB$^+$): *m/z*: 340[M$^+$+1]; elemental analysis calcd for $C_{23}H_{21}N_3$: C 81.38, H 6.24, N 12.38; found C 80.86, H 6.24, N 12.33.

3-(4-Methoxyphenylimino)-5-methoxy-N-(4-methoxyphenyl)-3H-indol-2-amine 3c. Violet solid; ^{1}H NMR ($CDCl_3$): δ = 3.57 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 6.54 (d, *J* = 2.45 Hz, 1H, Phen), 6.76 (dd, *J* = 8.43, 2.54 Hz, 1H, Phen), 6.94 (m, 4H, Phen), 7.06 (d, *J* = 8.95 Hz, 3H, Phen), 7.74 (m, 3H, Phen, NH); ^{13}C NMR ($CDCl_3$): δ = 55.5 (CH_3), 55.6 (CH_3), 112.4 (CH, Phen), 114.4 (CH, Phen), 114.5 (CH, Phen), 118.1 (CH, Phen), 118.8 (CH, Phen), 120.2 (C q, Phen), 120.3 (CH, Phen), 121.0 (CH, Phen), 132.0 (C q, Phen), 141.3 (C q, Phen), 155.2 (C q, Phen), 155.6 (C q, Phen), 156.1 (C q, Phen), 157.5 (C q, Phen), 158.0 (C q), 159.6 (C q); IR (KBr): 3338, 3000, 2946, 2829, 1632, 1608, 1579, 1542, 1506, 1468, 1435, 1299, 1285, 1238, 1212, 1184, 1172, 1132, 1106, 1038, 1024, 879, 852, 823, 801, 771, 739, 636, 589, 503 cm^{-1}; MS (FAB$^+$): *m/z*: 388[M$^+$+1]; elemental analysis calcd for $C_{23}H_{21}N_3O_3$: C 71.30, H 5.46, N 10.85; found C 70.68, H 5.45, N 10.57.

3-(3-Bromophenylimino)-6-bromo-N-(3-bromophenyl)-3H-indol-2-amine 3d. Red solid; ^{1}H NMR ($CDCl_3$): δ = 6.51 (d, *J* = 8.24 Hz, 1H, Phen), 6.83 (dd, *J* = 8.24, 1.65 Hz, 1H, Phen), 6.96 (m, 1H, Phen), 7.22 (m, 4H, Phen), 7.41 (m, 1H, Phen), 7.68 (m, 1H, Phen), 8.06 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 117.4 (CH, Phen), 117.7 (C q, Phen), 117.9 (CH, Phen), 121.8 (CH, Phen), 122.2 (CH, Phen), 122.7 (CH, Phen), 122.9 (C q, Phen), 123.1 (C q, Phen), 126.0 (CH, Phen), 126.3 (CH, Phen), 126.9 (CH, Phen), 128.8 (CH, Phen), 129.6 (C q, Phen), 130.5 (CH, Phen), 130.5 (C q, Phen), 130.8 (CH, Phen), 139.3 (C q, Phen), 149.5 (C q, Phen), 157.9 (C q), 159.3 (C q); IR (KBr): 3316, 1672, 1625, 1594, 1564, 1543, 1478, 1466, 1439, 1409, 1308, 1262, 1229, 1187, 1088, 1051, 1022, 994, 921, 872, 853, 808, 767, 738, 677, 657, 596, 424 cm^{-1}; MS (FAB$^+$): *m/z*: 532[M$^+$-2], 534[M$^+$], 536[M$^+$+2]; elemental analysis calcd for $C_{23}H_{21}Br_3N_3$: C 44.98, H 2.26, N 7.87; found C 44.30, H 2.77, N 7.48.

3-(4-Fluorophenylimino)-5-fluoro-N-(4-fluorophenyl)-3H-indol-2-amine 3e. Red solid; ^{1}H NMR ($CDCl_3$): δ = 6.44 (m, 1H, Phen), 6.83 (m, 2H, Phen), 7.01 (m, 5H, Phen), 7.15 (m, 2H, Phen), 7.78 (m, 2H, Phen); ^{13}C NMR ($CDCl_3$): δ = 112.6, 112.9 (CH, Phen), 115.5, 115.7 (C q, Phen), 115.8, 116.0 (CH, Phen), 116.2, 116.2 (C q, Phen), 116.3, 116.6 (CH, Phen), 119.4 (C q, Phen), 119.6, 119.7 (C q, Phen), 120.5 (CH, Phen), 120.6 (CH, Phen), 120.6 (CH, Phen), 120.7 (CH, Phen), 143.9 (C q), 157.3, 157.7 (C q, Phen), 159.7, 160.1 (C q, Phen), 162.1 (C q); IR (KBr): 3199, 1656, 1629, 1578, 1544, 1500, 1460, 1302, 1270, 1232, 1206, 1184, 1153, 1124, 890, 847, 826, 741, 581, 516, 498, 464 cm^{-1}; MS (FAB$^+$): *m/z*: 352[M$^+$+1]; elemental analysis calcd for $C_{23}H_{21}F_3N_3$x0.5 H_2O: C 66.66, H 3.64, N 11.66; found C 65.58, H 3.59, N 11.53.

General procedure for the preparation of 4a–e. A solution of 2.3 mmol of the isatin derivatives **3a–e**, 30 mL glacial acetic acid, 4 mL conc. HCl and 4 mL H_2O was refluxed for 20 min. After cooling to RT the solvent was evaporated to dryness *in vacuo*. The orange residue was then taken up in water, filtrated, washed with water and dried under vacuum.

Isatine 4a. Orange solid; ^{1}H NMR (Aceton-d_6): δ = 7.02 (d, *J* = 7.92 Hz, 1H, H4), 7.11 (t, *J* = 7.5 Hz, 1H, H5), 7.52 (d, *J* = 7.23 Hz, 1H, H7), 7.62 (t, *J* = 7.71 Hz, 1H, H6), 10.00 (s, 1H, NH); ^{13}C NMR (Aceton-d_6): δ = 113.3 (C7), 119.3 (C3a), 124.2 (C5), 125.7 (C4), 139.6 (C6), 151.8 (C7a), 160.2 (C2), 185.3 (C3); IR (KBr): 3192, 1730, 1618, 1461, 1332, 1202, 1144, 1096, 947, 771, 661, 638, 480, 456 cm^{-1}; MS (FAB$^+$): *m/z*: 148 [M$^+$+1]; elemental analysis calcd for $C_8H_5NO_2$ × 0.25 H_2O: C 63.37, H 3.66, N 9.24; found C 63.54, H 3.63, N 8.92.

5-Methylisatine 4b. Orange/red solid; ^{1}H NMR (Aceton-d_6): δ = 2.29 (s, 3H, CH_3), 6.89 (d, *J* = 7.98 Hz, 1H, H7), 7.31 (s, 1H, H4), 7.41 (d, *J* = 8.01 Hz, 1H, H6), 9.87 (s, 1H, NH); ^{13}C NMR (Aceton-d_6): δ = 20.4 (CH_3), 113.2 (C7), 119.3 (C3a), 125.8 (C4), 133.9 (C5), 140.0 (C6), 149.7 (C7a), 160.4 (C2), 185.5 (C3); IR (KBr): 3286, 1743, 1626, 1491, 1438, 1399, 1304, 1195, 1127, 825, 738, 659, 552, 456 cm^{-1}; MS (FAB$^+$): *m/z* 161[M$^+$]; elemental analysis calcd for $C_9H_7NO_2$: C 67.08, H 4.38, N 8.69; found C 67.00, H 4.22, N 8.77.

5-Methoxyisatine 4c. Orange solid; ^{1}H NMR (DMSO-d_6): δ = 3.73 (s, 3H, OCH_3), 6.83 (d, *J* = 8.52 Hz, 1H, H7), 7.05 (d, *J* = 2.63 Hz, 1H, H4), 7.17 (dd, *J* = 8.52, 2.72 Hz, 1H, H6), 10.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 55.7 (OCH_3), 108.7 (C4), 113.3 (C6), 118.0 (C3a), 124.8 (C7), 144.6 (C7a), 155.3 (C5), 159.5 (C2), 184.6 (C3); IR (KBr): 3156, 3101, 1748, 1732, 1637, 1607, 1492, 1446, 1408, 1309, 1284, 1265, 1242, 1201, 1154, 1035, 982, 903, 825, 773, 740, 703, 657, 603, 459 cm^{-1}; MS (FAB$^+$): *m/z* 178 [M$^+$+H]; elemental analysis calcd for $C_9H_7NO_3$: C 61.02, H 3.98, N 7.90; found C 60.38, H 4.06, N 7.80.

6-Bromoisatine 4d. Yellow/orange solid; ^{1}H NMR (DMSO-d_6): δ = 7.07 (d, *J* = 1.47 Hz, 1H, H7), 7.25 (dd, *J* = 7.99, 1.57 Hz, 1H, H5), 7.43 (d, *J* = 7.97 Hz, 1H, H4), 11.16 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 114.9 (C7), 117.0 (C3a), 125.6 (C5), 126.2 (C3), 131.6 (C6), 151.5 (C7a), 159.3 (C2), 183.2 (C3); IR (KBr): 3172, 1744, 1716, 1609, 1443, 1327, 1262, 1246, 1206, 1100, 1053, 953, 907, 892, 789, 742, 663, 589, 511, 471 cm^{-1}; MS-EI: *m/z* 224 [M$^+$, ^{79}Br], 226 [M$^+$, ^{81}Br]; elemental analysis calcd for $C_8H_4NO_2Br$: C 42.51, H 1.78, N 6.20; found C 41.80, H 2.15, N 5.78.

5-Fluoroisatine 4e. Orange/red solid; ^{1}H NMR (DMSO-d_6): δ = 6.89 (dd, *J* = 8.8, 3.85, 1H, H7), 7.35 (dd, *J* = 7.14, 2.74 Hz, 1H, H4), 7.42 (m, 1H, H6), 11.03 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 111.30, 111.53 (C4), 113.46, 113.53 (C7), 118.47, 118.54 (C3a), 124.47, 124.71 (C6), 146.8 (C7a), 156.9 (C2), 159.35, 159.53 (C5), 183.9 (C3); ^{19}F NMR (DMSO-d_6): δ = 121.0 (m, C5F); IR (KBr): 3213, 1738, 1619, 1489, 1389, 1290, 1262, 1141, 1105, 912, 890, 847, 792, 739, 655, 604, 459 cm^{-1}; MS (FAB$^+$): *m/z* 166 [M$^+$+1]; elemental analysis calcd for $C_8H_4NO_2F$ × 0.5 H_2O: C 55.18, H 2.89, N 8.04; found C 54.29, H 3.09, N 7.29.

General procedure for the preparation of 4f,g. A solution of 0.92 mL (12 mmol) DMF in 25 mL THF was cooled to 0°C and under inert gas conditions 1.03 mL (12 mmol) oxalyl chloride were added. After stirring for 2 h at room temperature, the suspension was again cooled to 0°C and a solution of 2.1 mL (12 mmol) Hünig's base (NEt*i*Pr$_2$) was added dropwise. After stirring for 1 h at 0°C and 2 h at room

temperature, the precipitate was filtered off, and then to the filtrate, 25 mmol of the corresponding aniline was added. After stirring for 16 h at room temperature, aerial oxygen was passed through the solution for several hours. The solvent was evaporated the residue was taken up in 36 mL glacial acetic acid, 5 mL conc. HCl and 5 mL H_2O. This solution was refluxed for 20 minutes. After cooling to RT the solvent was evaporated to dryness *in vacuo*. The orange residue was then taken up in water, filtrated, washed with water and dried under vacuum.

5-Methyl-carboxylate-isatine 4f. Yellow/orange solid; ^{1}H NMR (DMSO-d_6): $\delta = 3.82$ (s, 3H, $COOCH_3$), 7.62 (d, $J =$ 8.67 Hz, 1H, H7), 7.91 (s, 1H, H4), 8.14 (dd, $J = 8.25$, 1.68, 1H, H6), 11.41 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): $\delta = 52.3$ (CH_3), 112.2 (C7), 118.0 (C3a), 123.8 (C5), 124.9 (C4), 138.9 (C6), 154.1 (C7a), 159.7 (COOMe), 165.2 (C2), 183.3 (C3); IR (KBr): 3255, 1763, 1731, 1703, 1618, 1493, 1431, 1393, 1250, 1199, 1133, 1086, 998, 948, 867, 818, 773, 747, 723, 679, 534, 465 cm^{-1}; MS (FAB$^+$): *m/z* 206 [M$^+$+1]; elemental analysis calcd for $C_{10}H_7NO_4 \times 0.5\ H_2O$: C 56.08, H 3.76, N 6.54; found C 56.63, H 3.62, N 6.87.

6,7-Benzoisatine 4g. Red/brown solid; ^{1}H NMR (Aceton-d_6): $\delta = 7.46$ (d, $J = 8.4$ Hz, 1H, H5), 7.54 (d, $J = 8.4$ Hz, 1H, H4), 7.61 (dt, $J = 7.03$, 1.03 Hz, 1H, H7/8), 7.72 (dt, $J =$ 6.93, 1.14 Hz, 1H, H7/8), 7.94 (d, $J = 8.18$ Hz, 1H, H 6/9), 8.23 (d, $J = 8.16$ Hz, 1H, H6/9), 10.65 (s, 1H, NH); ^{13}C NMR (Aceton-d_6): $\delta = 113.2$ (C3a), 119.8 (C5), 120.7 (C9a), 123.4 (C4/9), 123.7 (C4/9), 127.9 (C8), 129.9 (C6/7), 131.7 (C6/7), 139.7 (C5a), 153.1 (C9b), 160.9 (C2), 183.5 (C3); IR (KBr): 3197, 1741, 1628, 1580, 1531, 1464, 1419, 1387, 1305, 1177, 1077, 971, 895, 876, 829, 797, 774, 738, 715, 658, 558, 418 cm^{-1}; MS (FAB$^+$): *m/z* 198 [M$^+$+1]; elemental analysis calcd for $C_{12}H_7NO_2$: C 73.09, H 3.58, N 7.10; found C 73.46, H 4.37, N 7.71.

Acknowledgment. S.M.H. thanks the *Studienstiftung des Deutschen Volkes* for a doctoral scholarship.

REFERENCES AND NOTES

[1] Pandeya, S. N.; Smitha, S.; Stables, J. P. Arch Pharm Med Chem 2002, 4, 129.

[2] Pandeya, S. N.; Sriram, D.; Yogeeswari, P.; Ananthan, S. Chemotherapy 2001, 47, 266.

[3] Brewerton, T. D.; Zealberg, J. J.; Lydiard, R. B.; Glover, V.; Sandler, M.; Ballenger, J. C. Biol Psychiatry 1995, 37, 481.

[4] Breinholt, J.; Demuth, H.; Heide, M.; Jensen, G. W.; Moller, I. L.; Nielsen, R. I.; Olsen, C. E.; Rosendahl, C. N. Acta Chem Scand 1996, 50, 443.

[5] Cimanga, K.; de Bruyn, T.; Lasure, A.; van Poel, B.; Pieters, P. R. Planta Med 1996, 62, 22.

[6] Welstead, J. J Med Chem 1979, 22, 1074.

[7] (a) Henesey, F. J. Soc. Dyers Colour 1937, 53, 347; (b) Erdmann, O. E. J Prakt Chem 1841, 24, 1; (c) Laurent, A. J. Prakt. Chem. 1842, 25, 430.

[8] Sandmeyer, T. Helv Chim Acta 1919, 2, 234.

[9] Gassman, P. G.; von Bergen, T. J. J Am Chem Soc 1974, 96, 5508.

[10] Meth-Cohn, O.; Goon, S. Tetrahedron Lett 1996, 37, 9381.

[11] (a) Weiss, R.; Huber, S. M.; Heinemann, F. W.; Audebert, P.; Pühlhofer, F. G. Angew Chem 2006, 118, 8228–8231; (b) Weiss, R.; Huber, S. M.; Heinemann, F. W.; Audebert, P.; Pühlhofer, F. G. Angew Chem Int Ed 2006, 45, 8059–8062.

[12] Boehme, H.; Sutoyo, P. Tetrahedron Lett 1981, 22, 1671.

[13] (a) Callow, R. K.; Hope, E. J Chem Soc 1929, 1191; (b) Grimshaw, J.; Begley, W. J. Synthesis 1974, 496.

[14] Cardellini, L.; Carloni, P.; Damiani, E.; Greci, L.; Stipa, P.; Rizzoli, C.; Sgarabotti, P. J Chem Soc Perkin Trans 2 1994, 1589.

[15] Etienne, A. Bull Soc Chim Fr 1949, 515.

[16] Rappoport, Z. Acc Chem Res 1981, 14, 7–15.

[17] Rappoport, Z. Acc Chem Res 1992, 25, 474–479.

[18] The electron distribution is 31% on the carbon centre and 69% on the nitrogen centre for the Z-isomer (28% and 72% for the E-isomer).

[19] Nxumalo, L. M.; Ngidi, E. K.; Ford, T. A. J Mol Struct 2006, 786, 168 and references cited therein.