Studies of the reactions between indole-2,3-diones (isatins) and 2-aminobenzylamine

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Received 16 September 2002; revised 21 November 2002; accepted 12 December 2002

Abstract—Reflux of equimolecular amounts 2-aminobenzylamine and isatins in acetic acid produced indolo[3,2-c]quinolin-6-ones in good yields. A proposed mechanism involving initial formation of a spiro compound is given. This isolable intermediate subsequently rearranges via a sequential isocyanate ring opening and a cyclization process to a urea derivative which finally cyclized to the indolo[3,2-c]quinolin-6-ones. The urea derivative could be prepared separately and cyclized selectively to indolo[3,2-c]quinolin-6-one. Reaction of N-acetylisatin with 2-aminobenzylamine at room temperature yielded the 1,4-benzodiazepinone 3-(2-acetamidophenyl)-1,5-dihydro-1,4-benzodiazepin-2-one whereas its isomer 2-(2-acetamidophenyl)-4,5-dihydro-1,4-benzodiazepin-3-one was obtained from 2-(2-acetylaminophenyl)-N-(2-aminobenzyl)-2-oxoacetamide in acetic acid at room temperature. The previously unknown linear isomer of indolo[3,2-c]quinolin-11-one, i.e. indolo[2,3-b]quinolin-11-one, has been prepared by thermal (260 °C) cyclization of methyl 2-phenylamino indole-3-carboxylate, which in turn was prepared in two steps from methyl indole-3-carboxylate. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Several members of the tetracyclic ring system 6H-indolo-[2,3-b]quinoxaline (1a) (Fig. 1), first synthesized1 in 1895 by Schunck and Marchlewski from isatin (indole-2,3-diones, 2a) and o-phenylenediamine, have been intensely studied2 because some derivatives with basic side-chains in the 6-position, such as 2,3-dimethyl-6-(2-dimethylamino-ethyl)-6H-indolo[2,3-b]quinoxaline (1b), exhibit potent antiviral activity,3 against e.g. HSV-1, CMV and VZV. Compound 1b and its congeners have no effects on virus polymerases. It is believed rather to act via inhibition of the decapsidation process of the virus.4 In this context the propensity of 1b to reversibly intercalate with DNA might play a role.5,6

In connection with efforts to synthesize analogues of 1b, the interactions of various diamines with isatin and N-acetylisatin (2b) have been studied.7 In this paper we report the outcome of reactions between 2-aminobenzylamine and isatin as well as between N-acetylisatin.

2. Results and discussion

The condensation between isatin and o-phenylenediamine can, depending on the solvent, give rise to three different products (1a, 3 or 4).8–10 In acidic solvents, like acetic acid, the linear product 1a is the dominating product. The spiro compound 3 (Fig. 2) reportedly has been obtained in a high yield when the reaction was performed in N-methyl-2-pyrrolidone, whereas the ring-opened quinoxaline 4 was the major product when THF or benzene was used as solvent. In some papers9,10 compound 4, with a carbonyl absorption at 1670 cm⁻¹ in the IR spectrum,10 incorrectly has been assigned the structure of 5a, with a carbonyl band

Figure 1.

Keywords: diazepines; indoles; quinolinones.

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The condensation of isatin with o-phenylenediamine in refluxing methanol has been reported to produce a mixture of 1a (39%), 4 (30%) and only traces of the spiro compound 3. Now, in a similar experiment using 2-aminobenzylamine as partner to isatin, the spiro compound 7a (which can be considered as a higher homologue of 3) was obtained as the sole product, whilst none of the possible 2,3-condensation products (8a–b) nor the ring-opened products 9 and 10 were observed (Fig. 3). Not surprisingly, the formation of the 6-membered ring in 7a is more favored compared to that of the seven-membered ring in the other at least theoretically possible products (8a,b, 9 and 10). When the reaction was performed at ambient temperature instead of refluxing methanol the yield of 7a increased from 53 to 67%. The IR spectrum of 7a exhibits a characteristic carbonyl at 1706 cm\(^{-1}\) and the \(^1\)H NMR spectrum features signals at 4.36 and 3.78 ppm from the methylene group and a signal at 3.15 ppm from the NH in the 3-position in the tetrahydroquinazoline ring, which all couple with each other. The \(^13\)C NMR spectrum includes a quaternary signal at 68.7 ppm from the carbon atom in the spiro center (Scheme 2). A disubstituted derivative of 7a, compound 11, obtained from isatin and 2-amino-5-chloro-o-phenyl-benzylamine, has been briefly described previously in the literature.

The literature methods for the synthesis of 4 are relatively complicated but it has now been found that treatment of an alkaline water solution of isatin with o-phenylenediamine at 60°C for 1 h followed by adjustment of the pH to ca. 5 gave 4 in high yield and purity. The quinoxalinone 4 could be diazotized and reduced with \(\text{H}_3\text{PO}_2\) giving the known parent quinoxalinone 6, thereby unequivocally establishing the structure of 4 (Scheme 1).

Figure 2.

![Figure 2](image)

**Scheme 1.** (a) (i) NaOH, 60°C, 2 h, (ii) pH 5.5, room temperature, 48 h. (b) (i) aq. 20% HCl, NaNO\(_2\), 3°C, 5 min, (ii) \(\text{H}_3\text{PO}_2\), reflux, 2–3 min.

![Scheme 1](image)

**Scheme 2.** (a) Methanol, room temperature, 48 h.

![Scheme 2](image)

Figure 3.
When 2-aminobenzylamine was refluxed with isatin in acetic acid (rather than methanol), neither of the two possible 2,3-condensation products $8a$ and $8b$ (Fig. 3) nor the two possible tautomers $12a$ and $12b$ were observed. Instead a product, $A$ ($C_{15}H_{10}N_2O$), was formed easily in a good yield together with traces of the spiro compound $7a$. Product $A$ was initially assigned structure $16a$ because repetition of a literature method involving condensation of the anion of oxindole and methyl 2-aminobenzoate gave an identical product. Further studies however revealed that both products are in fact the angular molecule $13a$ rather than the linear, i.e. $16a$ (Scheme 4). The angular products obtained now are also identical with products obtained by other established procedures published by us and others.\textsuperscript{14--16}

As indicated in Scheme 3 ring opening of the intermediate, probably after protonation of the anilinic nitrogen atom in the tetrahedral intermediate, takes preference over elimination of water. The known molecule $15$\textsuperscript{17} could be independently synthesized and cyclized (exclusively) to the angular isomer $13a$. In this context there are several precedents in the literature of related ring-openings that should be noted. Thus Fryer et al. found in 1968 that compound $17$ gave the angular salt $18$ when heated under acidic conditions (HCl),\textsuperscript{18} and Abramovitch and Hey reported in 1954 that the nitro compound $19$ upon reduction with tin in hydrochloric acid gave, after ring-opening, the quinolone derivative $20$.\textsuperscript{19} (Fig. 5).

Hydrogenation of the condensation product from oxindole (2-indolinone) and pyridine-2-carboxaldehyde ($21$) gave a product that was at first believed to be $22$, but was later shown to be $23$ (with the ortho amidine $24$ as a likely intermediate).\textsuperscript{20} (Fig. 6)
Now it became of interest to synthesize and study the true linear isomer 16a (in fact all literature reports describing its purported synthesis deal with the angular isomer). After several unsuccessful attempts the desired compound could be prepared as outlined in Scheme 5. By reaction of the ester 25 with N-chlorosuccinimide (NCS) a reactive chloroindolenine could be prepared and subsequently reacted with an aniline in the 2-position of the indole and final cyclization. This methodology originally developed by Booker-Milburn et al. for introduction of allyloxy functions in the 2-position of indoles worked very well also for introduction of anilino functions. By subsequent treatment with refluxing diphenyl ether the linear analogues 16a–c could be obtained in reasonable yields. No undesired rearrangements to angular isomers were observed under these conditions. Attempts to rearrange 16a under basic as well as acidic conditions failed, thus showing that it is the intermediates (in e.g. Scheme 3) that are critical for the outcome and not the linear indoloquinolinones themselves.

It should be added that Kikumoto and Kobayashi, who reduced the epoxide 28 with tin dichloride in a mixture of concentrated hydrochloric acid and ethanol, obtained a product with composition C_{15}H_{12}N_{2}O. The IR spectrum of this material, claimed to be the linear isomer 16a, featured a carbonyl band at 1700 cm⁻¹, which is not in consonance with the structure of 16a, which absorbs at 1639 cm⁻¹. The product obtained by the Japanese workers could now be identified as 29a, a known compound that is obtained when 29b is reduced with zinc in a mixture of concentrated hydrochloric acid and ethanol. (Fig. 7)

More recently other workers have suggested the formation of structures like 30 upon reduction of e.g. 28. These results could not be confirmed in our laboratory. Attempts to cyclize 31a, prepared from 31b, to 30 failed. De Diesbach described in 1951 the reduction of 32 and its subsequent facile cyclization to yield a purported mixture of 13a and 16a. The reported individual components were however never separated and characterized. We have repeated this experiment and conclude that the angular isomer 13a is the sole product. More recently (1980) derivatives of 16a...
were claimed as the products when derivatives of isatoic anhydride and 3-mercaptomethyloxindole was condensed with NaH as the base. However all these products were later demonstrated to be angular (Fig. 8).26

In spite of the fact that the parent compound of 16a (i.e. 33) has been known since at least 1897, very few established derivatives substituted in the 6-membered heterocyclic moiety have been described.27–29 However, Seidel described a long time ago, the preparation of 34 by condensing isatin with oxindole under alkaline conditions.30 This reaction has now been confirmed (Scheme 6). Treatment of this acid with diazomethane gave the corresponding methyl ester (35), which gave NMR-data in agreement with a product previously reported via a complex procedure involving treatment of the precursor 36 with AlCl₃ in methylene chloride.31 Seidel has also reported the interesting N-methylated derivative 37, which was obtained as a side-product in a complex industrial process (not repeated by us).30 (Fig. 9).

![Scheme 6](image)

Figure 8.

![Scheme 7](image)

Figure 9.

In spite of the fact that the parent compound of 16a (i.e. 33) has been known since at least 1897, very few established derivatives substituted in the 6-membered heterocyclic moiety have been described.27–29 However, Seidel described a long time ago, the preparation of 34 by condensing isatin with oxindole under alkaline conditions.30 This reaction has now been confirmed (Scheme 6). Treatment of this acid with diazomethane gave the corresponding methyl ester (35), which gave NMR-data in agreement with a product previously reported via a complex procedure involving treatment of the precursor 36 with AlCl₃ in methylene chloride.31 Seidel has also reported the interesting N-methylated derivative 37, which was obtained as a side-product in a complex industrial process (not repeated by us).30 (Fig. 9).
The monochloro derivative 38 could be prepared starting from 2,4-dichloroquinoline and benzotriazole which gave, when heated at 110°C until the exothermic reaction had ceased, a 3:1 mixture of the regioisomers 39 and 40 that subsequently was treated with hot polyphosphoric acid (PPA). The linear analogue was separated by crystallization as its N-acetyl derivative (41) after treatment with hot acetic anhydride. The acetyl group could be removed easily with dilute hydrochloric acid. The chloro derivative 38 could be correlated with its parent compound 33 by treatment with Raney nickel in hot dioxane. The chloro substituent was reluctant to participate in nucleophilic substitutions and treatment with sodium hydroxide in DMSO somewhat surprisingly gave the thiomethyl derivative 42. On the other hand compound 16a could also be converted to 38 by treatment with POCl₃. The desired product 16a was finally obtained by treatment of 38 with water in hot DMSO (Scheme 7).

At this point it was argued that 16a under acidic conditions might yield the intermediate outlined in Scheme 1 and hence rearrange to 13a. This was however found not to be the case. The well-known parent compound of 16a (i.e. 33) has been oxidized to the corresponding N-oxide 43 (Fig. 10) by Kikumoto. We have repeated this experiment and conclude that the structure assigned is correct. Deoxygenation of 43 with zinc in acetic acid gave 33 back.

The indoloquinolin-6-one 13a can also be obtained by refluxing the spiro compound 7a in acetic acid or, in higher yield, when 7a was refluxed in acetic acid with an additional equivalent of 2-aminobenzylamine. These results indicate that 7a is a precursor of 13a. As a synthetic route to the tetracyclic ring system 13a our new method has considerable advantages over the previously known procedures because the fast one-step procedure is operationally simple. Reactions of 2-aminobenzylamine with some substituted isatins gave similar results (13b–d). The product from 5-methylisatin and 2-aminobenzylamine was initially considered to have structure 44 (Fig. 11) (i.e. with the isatin as the source of the indole moiety of the ring system). However a strong NOE between the protons indicated in structure 13b strongly suggested that in fact the indole moiety is formed from 2-aminobenzylamine.

A mechanistic rationalization of the ready formation of 13a from isatin and 2-aminobenzylamine is given in Scheme 8, starting with the formation of the 6-membered spiro compound 7a followed by an isocyanate ring opening. Such ring openings are known in the literature. Subsequently a cyclisation between the amine formed and the

![Figure 10](image_url)

![Figure 11](image_url)

**Scheme 8.** Mechanistic rationalization of the formation of indolo[3,2-c]quinolin-6-one from isatin and 2-aminobenzylamine.
isocyanate group will occur, followed by a ring opening of the spiro intermediate leading to the 2-substituted indole derivative 45a, finally followed by a regioselective cyclization to the indolo[3,2-c]quinoline-6-one 13a.

The correctness of this assignment was eventually confirmed by an independent synthesis from 46a and 46b, which in turn were obtained by Fischer indolizations of the phenylhydrazones of the corresponding 2-amino-acetophenones (Scheme 9).33

Compounds 45a and 45b could be independently synthesized from 46a and 46b and sodium cyanate under acidic conditions and then smoothly selectively cyclized to 13a and 13b, respectively. On the other hand cyclization of 46a, in dioxane, gave the known compound 47 (Scheme 10).14

Reaction of 2-aminobenzylamine with isatin in acetic acid at room temperature (as distinct from reactions at reflux)
gave a quite different product, namely the 2:1 product \(48a\), the structure of which has been determined with X-ray crystallography (Scheme 11 and Fig. 12). Compound \(13a\) could not be isolated when \(48a\) was heated to reflux in acetic acid, while addition of 1 equivalent of 2-aminobenzylamine to the reaction mixture gave traces of \(13a\). A plausible mechanism for the formation of \(48a\) is given in Scheme 12. Thus it is assumed that the spiro compound \(7a\) is in equilibrium with its chain tautomer \(49a\), which after ring opening will yield \(49b\). These two compounds will subsequently condense (giving \(50\)) which after cyclization and decarboxylation will yield the observed product \(48a\). A somewhat analogous series of transformations has been invoked by Wassermann to explain the formation of the alkaloid vasicine (\(51\)), when 2-aminobenzylamine was reacted with the vinyl vicinal tricarbonyl reagent (\(52\)). A molecule, \(53a\), structurally related to \(48a\) could readily be prepared in high yields by condensation of 2-aminobenzamide and isatin in acetic acid. The spiro carbon atoms in \(53a\) and \(53b\) resoned at 70.9 and 71.6 ppm, respectively, in their \(^{13}\)C NMR spectra. Interestingly \(53a\), is related with the classic, and during several decades controversial compound, \(54\) (Fig. 13).

It is well known that the relative reactivity of the two carbonyl groups in isatin and N-acetylisatin differ considerably and hence it was also of interest to study the reactions between N-acetylisatin and 2-aminobenzylamine. It is also well known that N-acetylisatin is readily ring opened by ammonia, amines and alcohols. For example when N-acetylisatin is refluxed in ethanol for 3 h, nucleophilic ring opening produces the ester \(55\), which readily reacts with ethylenediamine or \(o\)-phenylenediamine giving \(56\) or \(57\) in high yields. When the ester \(55\) was

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**Scheme 12.** A plausible mechanism for the formation of \(48a,b\).

**Figure 13.**
reacted with 2-aminobenzylamine in ethanol the aliphatic amine function reacted exclusively with the ester carbonyl group giving compound 58 in high yield. The \( ^1H \) NMR spectrum of 58 includes a methylene at 4.24 ppm, which couples to an NH at 9.09 ppm. The \( ^1H \) NMR spectrum also includes an NH signal at 10.52 ppm and an NH\(_2\) signal at 5.10 ppm (Fig. 14, Schemes 13 and 14).

When 2-aminobenzylamine was stirred at room temperature with N-acetylisaatin in acetic acid, the 3-(20-acetamido-phenyl)-1,5-dihydro-1,4-benzodiazepin-2-one 59 could be collected by filtration directly from the reaction mixture when the pH of the filtrate was increased to 9–10, a mixture of 59 and 60 was obtained. In none of these experiments the quinazolines 61 or 62 have been observed. The formation of the six-membered ring in the quinazolines might have been expected to be competitive to that of the seven-membered ring in 59 and 60, which indeed has been the case for some related compounds.\(^{41}\) The \( ^1H \) NMR spectrum of 60 included a broadened signal at 4.2 and 4.0 ppm from the methylene group and a signal at 9.01 ppm from the NH, which show a coupling that disappeared when the signal from the methylene group was irradiated. The \( ^1H \) NMR spectrum of 60 also included a singlet at 11.13 ppm from the NH in the acetamido group. The \( ^1H \) NMR spectrum of 59 included a singlet from the two methylene protons (4.66 ppm) and two \( ^1H \) singlets (11.12 and 10.86 ppm) from the two NH functions. Particularly compound 59 deserves interest as an analogue to the pharmacologically highly active 5-aryl-1,3-dihydro-1,4-benzodiazepin-2-one, e.g. diazepam 63. Deacetylation of 59 gave the amine 10, however attempts to generate the fused indoles 8a and/or 12a failed. No ring contractions (59–61 or 60–62) were observed during these deacetylations (Fig. 15).

![Scheme 13](image)

Scheme 13. (a) Ethanol, reflux, 3 h. (b) 2-Aminobenzylamine, ethanol, 5–25°C. (c) Acetic acid, room temperature, 168 h.

![Scheme 14](image)

Scheme 14. (a) Acetic acid, room temperature, 168 h. (b) KOH, ethanol, H\(_2\)O, reflux.

Figure 15.
3. Conclusions

In this paper we have shown that simple indole-2,3-diones can, when reacted with 2-aminobenzylamine in acetic acid be quickly and conveniently converted to indolo[3,2-c]-quinolin-6-ones 13a or, depending upon the conditions (choice of reactants) highly functionalized 1,4-benzodiazepin-2(2H)-one 59 and 1,4-benzodiazepin-3(3H)-one 60. The choice of solvent is of paramount importance, as demonstrated by the reaction of 2-aminobenzylamine and isatin in methanol, which yields the spirocyclic quinazoline derivative 7a that is believed to be an intermediate in the formation of 13a. We have also shown two alternative ways to form indolo[2,3-b]quinolin-11-one (16a) which to this day has been unknown.

4. Experimental

4.1. General

NMR spectra were recorded in DMSO-d$_6$ solutions at room temperature, unless otherwise stated, on a Bruker DPX 300 (300 MHz) spectrometer. J values are given in Hz and $\delta$ values are given in ppm. IR spectra are recorded on a Perkin–Elmer 1600 FTIR. Melting points were taken on a Büchi Melting Point B-545 apparatus and are uncorrected. Chromatography was performed on Merck silica gel 60, TLC analyses were run on Merck silica gel F$_254$ plates. The elemental analysis was performed by H. Kolbe Mikro-analytisches Laboratorium, Mülheim an der Ruhr, Germany. HRMS analyses were performed by E. Nilsson, University of Lund, Sweden. Solvents were of analytical grade and were used as received.

4.1.1. 3-(2'-Aminophenyl)-quinoxaline-2(1H)-one (4). Isatin (3.75 g, 50 mmol) was dissolved in potassium hydroxide (aq., 8%, 80 mL), o-phenylenediamine (5.40 g, 50 mmol) was added and the mixture was heated (60°C) for 2 h (or until a clear solution was obtained). The pH was then adjusted to ca. 5.5 by addition of acetic acid. After 2 days at ambient temperature the yellow-orange solid formed was collected by filtration. Yield: 3.45 g (65%); mp: 174–175°C; IR (KBr) $\nu_{\text{max}}$: 3369, 3329, 3050, 1699, 1628, 1605, 1596, 802, 746 cm$^{-1}$; $^1$H NMR $\delta$: 10.14 (1H, s, NH), 7.05 (1H, d, J=7.9 Hz, Ph), 6.94–6.84 (2H, m, Ph), 6.70 (1H, d, J=7.9 Hz, Ph), 6.55–6.47 (2H, m, Ph), 6.43 (1H, s, Ph), 4.32 (1H, d, J=16.4, 8.8 Hz, CH$_2$), 3.76 (1H, dd, J=16.4, 6.0 Hz, CH$_3$), 3.04 (dd, J=8.5, 6.0 Hz, NH), 2.23 (3H, s, CH$_3$); $^{13}$C NMR $\delta$: 177.3 (s), 142.7 (s), 139.1 (s), 131.5 (s), 129.0 (s), 126.6 (d), 125.5 (d), 124.7 (d), 119.8 (s), 115.8 (d), 113.7 (d), 109.3 (d), 68.9 (s), 40.8 (t), 20.7 (q). Anal. calc. for C$_{18}$H$_{15}$N$_3$O: C, 72.43; H, 5.70; N, 16.72. Found: C, 71.78; H, 5.14; N, 16.64.

4.1.2. 3-Phenylquinoxaline-2(1H)-one (6). Compound 4 (1.18 g, 10 mmol) was dissolved in hydrochloric acid (20%, 10 mL) by stirring at 3°C. Solid sodium nitrite (0.69 g, 10 mmol) was added keeping the temperature at 3°C. After 5 min at this temperature the solid material was removed and the filtrate added to hot hypophosphorus acid (aq., 50%, 10 mL). After a short period (2–3 min) of boiling the mixture was cooled and the product collected by filtration. Yield: 0.52 g (47%); mp: 245–247°C; This product was identical with a sample of 3-phenylquinoxaline-2(1H)-one prepared by condensation of ethyl phenylglyoxylate according to the literature method.

4.1.3. 1,2,3,4-Tetrahydroquinazoline-2-spiro-3'-1H-indolin-2-one (7a). A mixture of isatin (2.94 g, 20 mmol) and 2-aminobenzylamine (2.44 g, 20 mmol) in MeOH (125 mL) was stirred at room temperature for 48 h, whereupon the reaction mixture was concentrated to 50 mL. The solid formed was collected by filtration. Yield: 3.39 g (67%); mp: 166–167°C (dec.); IR (KBr) $\nu_{\text{max}}$: 3379, 3316, 3189, 1706, 1623, 1476, 746 cm$^{-1}$; $^1$H NMR $\delta$: 10.29 (1H, s, NH), 7.4–7.2 (2H, m, Ph), 7.1–6.8 (4H, m, Ph), 6.6–6.4 (3H, m, Ph), 4.36 (1H, dd, J=8.8, 16.4 Hz, CH$_2$), 3.78 (1H, dd, J=6.0, 16.4 Hz, CH$_2$), 3.15 (1H, dd, NH, J=6.0, 8.8 Hz, CH$_2$); $^{13}$C NMR $\delta$: 177.2 (s), 142.6 (s), 141.5 (s), 131.4 (s), 129.4 (d), 126.5 (d), 125.4 (d), 123.9 (d), 121.5 (d), 119.7 (s), 115.9 (d), 113.7 (d), 109.4 (d), 68.7 (s), 40.7 (t). Anal. calc. for C$_{19}$H$_{18}$N$_3$O: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.78; H, 5.14; N, 16.64.

4.1.4. 1,2,3,4-Tetrahydroquinazoline-5-methyl-2-spiro-3'-1H-indolin-2-one (7b). A mixture of 5-methylisatin (3.22 g, 20 mmol) and 2-aminobenzylamine (2.44 g, 20 mmol) in MeOH (125 mL) was stirred at room temperature for 48 h, whereupon the reaction mixture was concentrated to 50 mL. The solid formed was collected by filtration. Yield: 3.45 g (65%); mp: 174–175°C; IR (KBr) $\nu_{\text{max}}$: 3369, 3329, 3042, 1699, 1628, 1605, 1496, 802, 747 cm$^{-1}$; $^1$H NMR $\delta$: 10.14 (1H, s, NH), 7.05 (1H, d, J=7.9 Hz, Ph), 6.94–6.84 (2H, m, Ph), 6.70 (1H, d, J=7.9 Hz, Ph), 6.55–6.47 (2H, m, Ph), 6.43 (1H, s, Ph), 4.32 (1H, d, J=16.4, 8.8 Hz, CH$_2$), 3.76 (1H, dd, J=16.4, 6.0 Hz, CH$_2$), 3.04 (dd, J=8.5, 6.0 Hz, NH), 2.23 (3H, s, CH$_3$); $^{13}$C NMR $\delta$: 177.3 (s), 142.7 (s), 139.1 (s), 131.5 (s), 130.4 (s), 129.5 (d), 126.6 (d), 125.5 (d), 124.7 (d), 119.8 (s), 115.8 (d), 113.7 (d), 109.3 (d), 68.9 (s), 40.8 (t), 20.7 (q). Anal. calc. for C$_{20}$H$_{19}$N$_3$O: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.49; H, 5.83; N, 15.77.

4.1.5. 1,2,3,4-Tetrahydroquinazoline-1-methyl-2-spiro-3'-1H-indolin-2-one (7e). Method A. A mixture of N-methylisatin (1.61 g, 10 mmol) and 2-aminobenzylamine (1.22 g, 10 mmol) in MeOH (60 mL) was stirred at room temperature for 48 h, whereupon the reaction mixture was concentrated to 30 mL. The solid formed was collected by filtration, washed with cold ethanol and dried. Yield: 1.82 g (68%).

Method B. A mixture of N-methylisatin (1.61 g, 10 mmol) and 2-aminobenzylamine (2.44 g, 20 mmol) in acetic acid (100 mL) was stirred at room temperature for 20 h, whereupon the mixture was poured into water and basified with NaOH (2 M). The solid thus formed was isolated by filtration and washed with water. Yield: 2.13 g (80%).
130.7 (s), 129.6 (d), 126.6 (d), 125.5 (d), 123.6 (d), 122.3 (d), 119.7 (s), 116.0 (d), 113.8 (d), 108.4 (d), 68.6 (s), 40.8 (t), 25.6 (q). Anal. calcd for C_{16}H_{12}N_{2}O: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.53; H, 5.77; N, 15.79.

4.1.6. 3-(2'-Aminophenyl)-4,5-dihydro-1,4-benzodiazepin-3(3H)-one (10). Compound 59 (2.93 g, 10 mmol) was added to 20% KOH (1:1, EtOH/H_2O, 25 mL). The solution was refluxed for 2 h and thereafter cooled in an ice-bath. Slow addition of acetic acid produced a yellow solid, which was collected by filtration. Yield: 1.60 g (64%); mp: 188–190°C; IR (KBr) \nu_{\text{max}}: 3394, 3272, 2839, 1655, 1613, 1490, 1252, 764, 742 cm^{-1}; ^1H NMR \delta: 11.04 (1H, s, NH), 7.41 (1H, d, J=7.5 Hz, Ph), 7.4–7.2 (2H, m, Ph), 7.2–7.0 (5H, m, Ph), 6.68 (1H, dd, J=8.3, 1.1 Hz, Ph), 6.45 (1H, m, Ph), 4.6 (2H, br s, CH_2); ^13C NMR \delta: 165.8 (s), 165.3 (s), 149.7 (s), 136.9 (s), 133.4 (s), 131.1 (d), 130.7 (d), 128.5 (d), 128.2 (d), 124.3 (d), 120.9 (d), 116.0 (d), 114.2 (s), 114.0 (s), 53.1 (t). Anal. calcd for C_{16}H_{12}N_{2}O: C, 72.10; H, 5.21; N, 16.72. Found: C, 71.62; H, 5.16; N, 16.57.

4.1.7. 5,11-Dihydro-indolo[3,2-c]quinolin-6-one (13a). Method A. A mixture of isatin (2.94 g, 20 mmol) and 2-aminobenzylamine (2.44 g, 20 mmol) was heated to reflux in acetic acid (100 mL) for 2 h, whereupon the reaction mixture was poured into water. The solid formed was collected by filtration. The crude product was flash chromatographed (MeOH/CHCl_3, 3/97), to give 13a as a beige solid. Yield: 0.065 g (70%).

Method B. A solution of 7a (503 mg, 2 mmol) in acetic acid (10 mL) was heated to reflux for 2 h, whereupon the reaction mixture was poured into water. The solid formed was collected by filtration. The crude product was flash chromatographed (MeOH/CHCl_3, 1/9), to give 13a as a beige solid. Yield: 0.261 g (51%); mp 342–343°C.

Method C. To a solution of 46a (0.620 g, 3.0 mmol) and acetic acid (5 mL) was sodium cyanate (0.210 g, 3.2 mmol) added and refluxed for 2 h. The solution was poured into ice-water and the formed solid was filtered by suction and washed with water. The solid was recrystallized from 2-propanol/methanol to give 13a. Yield: 0.540 g (78%).

Method D. Acetic acid (1.3 mL) and 45a (0.140 g, 0.53 mmol) was heated to reflux for 2 h, whereupon the reaction mixture was poured into water. The solid formed was collected by filtration and washed with water. The crude product was treated with ethyl acetate and filtered to give 13a as a pinkish solid. Yield: 0.261 g (51%); mp>360°C; IR (KBr) \nu_{\text{max}}: 3216, 1630, 1617, 1590, 1555, 1456, 1390, 812, 788, 748 cm^{-1}; ^1H NMR \delta: 12.50 (1H, s, NH), 11.36 (1H, s, NH), 8.19 (1H, d, J=8.0 Hz, Ph), 7.35–7.22 (4H, m, Ph), 2.41 (3H, s, CH_3); ^13C NMR \delta: 159.7 (s), 140.5 (s), 137.6 (s), 135.9 (s), 130.3 (s), 123.4 (d), 123.8 (d), 121.6 (d), 120.8 (d), 115.9 (d), 111.7 (s), 111.6 (d), 106.4 (s), 20.6 (q). Anal. calcd for C_{16}H_{12}N_{2}O: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.26; H, 4.94; N, 11.20.

4.1.8. 2-Methyl-5,11-dihydro-indolo[3,2-c]quinolin-6-one (13b). Method A. A mixture of 5-methylisatin (1.61 g, 10 mmol) and 2-aminobenzylamine (2.44 g, 20 mmol) was heated to reflux in acetic acid (100 mL) for 2 h. The reaction mixture was allowed to attain room temperature. The solid formed was collected and thereafter stirred for 30 min in a solution of NaHCO_3 and collected by filtration. Yield: 1.51 g (61%).

Method B. A solution of 7b (1.32 g, 5 mmol) in acetic acid (15 mL) was heated to reflux for 2 h. The reaction mixture was allowed to attain room temperature and the solid formed was collected by filtration. The crude product was treated in NaHCO_3 (10%) for 30 min and then filtered and washed with water, which gave 0.72 g of 13b. The filtrate was poured into water and a second crop of 13b was collected by filtration (0.25 g). Yield: 0.97 g (78%).

Method C. To a solution of 46b (0.650 g, 3.0 mmol) and acetic acid (5 mL) sodium cyanate (0.210 g, 3.2 mmol) was added and refluxed for 2 h. The solution was poured into ice-water and the formed solid was filtered by suction and washed with water. The solid was recrystallized from ethanol to give 0.370 g of 13b. A second crop was obtained by concentration of the mother liquor and purified by chromatography using methanol in chloroform giving 0.150 g of 13b. Yield: 0.520 g (72%).
4.1.10. 2,4-Dichloro-5,11-dihydro-indolo[3,2-c]quinolin-6-one (13d). A mixture of 5,7-dichloroisatin (2.16 g, 10 mmol) and 2-amino benzylamine (2.44 g, 20 mmol) was heated to reflux in acetic acid (100 mL) for 15 min. The reaction mixture was allowed to attain room temperature. The solid formed was collected by filtration. Yield: 2.00 g (66%); mp: >360°C; IR (KBr) νmax: 3398, 3082, 1644, 1608, 1419, 1367, 1330, 739 cm⁻¹; 1H NMR δ: 12.69 (1H, s, NH), 10.64 (1H, s, NH), 8.31 (1H, d, J=1.8 Hz, Ph), 8.20 (1H, d, J=7.9 Hz, Ph), 7.77 (1H, d, J=1.8 Hz, Ph), 7.63 (1H, d, J=7.9 Hz, Ph), 7.41 (1H, t, J=7.2 Hz, Ph), 7.29 (1H, t, J=7.2 Hz, Ph); 13C NMR δ: 159.1 (s), 138.9 (s), 137.8 (s), 132.9 (s), 128.4 (d), 125.4 (s), 124.8 (d), 123.8 (s), 121.4 (d), 120.9 (d), 120.7 (d), 120.1 (s), 114.5 (s), 111.9 (d), 107.3 (s). Anal. calcld for C15H10N2O: C, 76.91; H, 4.30; N, 11.96. Found: C, 75.76; H, 4.56; N, 11.84.

4.1.11. 5-Methyl-5,11-dihydro-indolo[3,2-c]quinolin-6-one (13e). Method A. A mixture of N-methylisatin (1.61 g, 10 mmol) and 2-amino benzylamine (2.44 g, 20 mmol) was heated to reflux in acetic acid (25 mL) for 2 h. The reaction mixture was allowed to attain room temperature and poured into water. The solid thus formed was collected by filtration. Yield: 2.02 g (81%).

Method B. A solution of 7c (0.53 g, 2 mmol) in acetic acid (10 mL) was heated to reflux for 2 h. The reaction mixture was allowed to attain room temperature and poured into water. The solid thus formed was collected by filtration, washed with water and purified by column chromatography (2/8 MeOH/CHCl₃). Yield: 0.36 g (73%).

Mp: 265–266°C (dec.) (lit.¹⁶ 265°C); IR (KBr) νmax: 3155, 1614, 1568, 1327, 742 cm⁻¹; 1H NMR δ: 12.55 (1H, s, NH), 8.30–8.23 (2H, m, Ph), 7.64–7.60 (3H, m, Ph), 7.41–7.34 (2H, m, Ph), 7.27 (1H, t, J=7.0 Hz, Ph), 3.74 (3H, s, CH₃); 13C NMR δ: 159.0 (s), 139.6 (s), 138.7 (s), 137.8 (s), 129.6 (d), 124.6 (s), 124.1 (d), 122.6 (d), 121.6 (d), 121.1 (d), 120.8 (d), 115.7 (d), 112.9 (s), 1117 (d), 105.9 (s), 28.5 (q).

4.1.12. 5,6-Dihydro-indolo[2,3-b]quinolin-11-one (16a). Method A. The ester (27a) (1 g, 3.76 mmol) in diphenyl ether (5 mL) was heated at reflux for 3 h 30 min, whereupon the reaction mixture was allowed to attain room temperature. The solid thus formed was isolated by filtration and washed with a large quantity of diethyl ether. Yield: 0.570 g (65%).

Method B. 11-Chloro-5H-indolo[2,3-b]quinoline (38) (0.100 g, 0.4 mmol) was dissolved in diphenyl ether (5 mL) and washed with 10% aqueous sodium bicarbonate solution. The reaction mixture was allowed to attain room temperature. Whereupon the solution of trichloroacetic acid (0.5 g, 3 mmol) and the appropriate aniline 26a–c (23.4 mmol) in dichloromethane (50 mL) was added and the reaction mixture was allowed to attain room temperature. After 2 h the reaction mixture was washed with 10% aqueous sodium bicarbonate solution and then with 1 M aqueous hydrochloric acid and finally washed with water. The resulting solution was dried, filtered and evaporated. The residue was chromatographed using hexane/ethyl acetate 8:2 as eluent.

4.2. General procedure for synthesis of 27a–c

To a solution of methyl indole-3-carboxylate (2.08 g, 11.9 mmol) and dichloromethane (50 mL) at 0°C under argon N,N-dimethylpiperazene (0.75 g, 6.56 mmol) and NCS (1.75 g, 13.1 mmol) were added. The reaction mixture was allowed to stand at 0°C for 2 h. Whereupon a solution of trichloroacetic acid (0.5 g, 3 mmol) and the appropriate aniline 26a–c (23.4 mmol) in dichloromethane (50 mL) was added and the reaction mixture was allowed to attain room temperature. After 2 h the reaction mixture was washed with 10% aqueous sodium bicarbonate solution and then with 1 M aqueous hydrochloric acid and finally washed with water. The resulting solution was dried, filtered and evaporated. The residue was chromatographed using hexane/ethyl acetate 8:2 as eluent.
2.4.4. 2-Nitrobenzyl-oxireno[α,3]oxindole (28). Sodium (1.52 g, 65 mmol) was dissolved in ethanol (75 mL) under N₂, whereupon isatin (4.41 g, 30 mmol) was added, which gave a red-violet solution. 2-Nitrobenzyl chloride (5.16 g, 30 mmol) in EtOH was then added at 15°C to the stirred solution. After 3 h at room temperature, water (300 mL) and acetic acid (10 mL) were added and the solid formed was collected after 2 h and recrystallized from EtOH. Yield: 6.60 g (78%); mp: 174–176°C (lit. 23 174–176°C); IR (KBr) νmax: 3300, 1737, 1702, 1622, 1528, 1470, 1342 cm⁻¹; ¹H NMR δ: 10.94 (1H, s, NH), 8.18 (H, d, J=8.2, 0.9 Hz, Ph), 8.00–7.93 (2H, m, Ph), 7.78–7.72 (1H, m, Ph), 7.20 (1H, dt, J=7.7, 1.1 Hz, Ph), 6.90 (1H, d, J=7.7 Hz, Ph), 6.64 (1H, dt, J=7.5, 1.1 Hz, Ph), 5.97 (1H, td, J=7.5, 0.6 Hz, Ph), 5.06 (1H, s, CH₂); ¹³C NMR δ: 171.6 (s), 146.6 (s), 143.6 (s), 134.8 (s), 130.5 (d), 130.1 (d), 130.0 (s), 129.0 (d), 124.7 (d), 122.0 (d), 121.5 (d), 120.1 (d), 110.7 (d), 63.6 (d), 61.5 (s).

2.4.5. 3-(2-Aminobenzoyl)-1H-indole (29a). An EtOH (4 mL) suspension of 28 (2.8 g, 10 mmol) was treated with SnCl₂ (8 g, 112.8 mmol) in concentrated HCl (7.5 mL). The mixture was heated for 1 h on a water bath. After cooling the mixture, now containing yellow crystals, was poured into NaOH (2 M,aq) and the solid thus formed was isolated by filtration. Yield: 1.20 g (50%); mp: 228–230°C (lit., 24 228–230°C); IR (KBr) νmax: 3405, 3340, 3131, 1700, 1601, 1458, 1337, 1232, 742 cm⁻¹; ¹H NMR δ: 10.51 (1H, s, NH), 7.55 (1H, s, CH), 7.46 (1H, d, J=7.7 Hz, Ph), 7.41 (1H, dd, J=7.7, 1.2 Hz, Ph), 7.2–7.1 (2H, m, Ph), 6.9–6.7 (3H, m, Ph), 6.61 (1H, d, J=7.7 Hz, Ph), 5.52 (2H, s, NH₂); ¹³C NMR δ: 168.8 (s), 147.9 (s), 142.2 (s), 133.2 (d), 131.0 (d), 129.2 (d), 129.2 (d), 125.9 (s), 122.2 (d), 121.5 (s), 120.7 (d), 117.9 (s), 115.5 (d), 115.4 (d), 109.6 (d).

4.2.6. 11-Chloro 6H-indolo[2,3-b]-quinoline (38). Method A. 11-Chloro N-acetylindolo[2,3-b]quinoline (0.295 g, 1.0 mmol) was refluxed in hydrochloric acid (2 M, 10 mL) for 30 h. The solution was allowed to attain room temperature and then basified with saturated sodium bicarbonate and thereafter filtered by suction, washed with water and dried. Yield: 0.238 g (94%).

Method B. 16a (0.046 g, 0.2 mmol) was refluxed in POCl₃ (1 mL) for 3 h. The reaction mixture was poured into water and basified with saturated sodium bicarbonate. The solid thus formed was isolated by filtration, washed with water and dried.

Yield: 0.048 g (97%); mp: 314–316°C; IR (KBr) νmax: 3426, 3144, 1613, 1572, 1405, 1250, 1236 cm⁻¹; ¹H NMR δ: 12.02 (1H, s, NH), 8.54 (1H, d, J=7.7 Hz, Ph), 8.37 (1H, dd, J=8.5, 0.9 Hz, Ph), 8.05 (1H, d, J=8.5 Hz, Ph), 7.82 (1H, m, Ph), 7.65–7.53 (3H, m, Ph), 7.31 (1H, m, Ph); ¹³C NMR δ: 152.5 (s), 146.6 (s), 141.6 (s), 134.0 (s), 129.6 (d), 129.0 (d), 127.5 (d), 124.0 (d), 123.6 (d), 123.4 (d), 121.3 (s), 120.1 (d), 119.2 (s), 115.1 (s), 111.1 (d).

4.3. Dechlorination of 11-chloro 6H-indolo[2,3-b]-quinoline (38) with Raney nickel

Compound 38 (0.253 g, 1.0 mmol) was refluxed with Raney nickel (2.0 g) in dioxane (15 mL) for 3 h. The mixture was filtered while hot and evaporated and treated with ethanol to give 6H-indolo[2,3-b]-quinoline (33). Yield: 0.202 g (92%); mp: 347–348°C (lit., 25 346°C); A sample prepared using a literature method 29 was identical with our product.

4.4. Synthesis of the ester 35

The acid 34 (0.262 g, 1.0 mmol) was added in portions at room temperature to diazomethane (1.2 mmol) dissolved in ether (40 mL) plus methanol (0.5 mL). The acid dissolved within 5 min and upon concentration and addition of petroleum ether the ester 35 was obtained as white crystals. Yield: 0.245 g (89%); mp: 258–259°C (lit., 31 >240°C); The spectral data were in agreement with those published. 31

4.4.1. 11-Chloro-5-acetylindolo[2,3-b]-quinoline (41). Benzotriazolone (5.95 g, 50 mmol) and 2,4-dichloroquinoline (9.90 g, 50 mmol) were heated at 110°C until the exothermic reaction finished. The solid formed was allowed to attain room temperature and PPA (70 g) was added and the mixture was heated at 130°C until the formation of N₂ had ceased whereupon the mixture was heated at 180°C for 5 min. The dark solution was allowed to attain room temperature whereupon it was poured into water. The solid thus formed was separated by filtration and was thoroughly washed with water. The crude solid was heated in NH₄OH at 100°C for 5 min and then cooled to room temperature.
A white solid was isolated by filtration, washed with water and heated to reflux in acetic anhydride (100 mL), filtrated hot and 41 was isolated by filtration after cooling to room temperature.

Yield: 1.65 g (11%); mp: 203–204°C; IR (KBr) \( \nu_{\text{max}} \): 1703, 1565, 1452, 1382, 1249, 1188, 764, 758, 750 cm\(^{-1}\); \(^1\)H NMR (75°C) \( \delta \): 8.67 (1H, d, \( J=8.4 \) Hz, Ph), 8.65 (1H, d, \( J=7.2 \) Hz, Ph), 8.42 (1H, d, \( J=8.4 \) Hz, Ph), 8.17 (1H, d, \( J=7.5 \) Hz, Ph), 7.93 (1H, t, \( J=7.5 \) Hz, Ph), 7.79 (1H, t, \( J=7.2 \) Hz, Ph), 7.71 (1H, t, \( J=7.2 \) Hz, Ph), 7.57 (1H, t, \( J=7.5 \) Hz, Ph), 3.22 (3H, s, \( CH_3 \)); \(^1^3\)C NMR (75°C) \( \delta \): 170.4 (s), 150.6 (s), 145.0 (s), 139.5 (s), 134.5 (s), 130.1 (d), 129.5 (d), 128.2 (d), 126.2 (d), 124.0 (d), 123.0 (d), 122.9 (d), 122.8 (s), 120.9 (s), 116.4 (d), 116.1 (s), 27.3 (t). Anal. calcd for \( C_{15}H_{13}N_3O \): C, 76.28; H, 3.76; N, 9.50. Found: C, 69.18; H, 3.66; N, 9.46.

4.4.2. 11-Thiomet-6H-indolo[2,3-b]-quinoline (42). Compound \( 38 \) (1.47 g, 5.0 mmol) and sodium acetate (2.0 g) were heated in DMSO at 165°C for 4 h. After cooling the mixture was poured into water and the solid obtained was recrystallized from acetonitrile to give 42. Yield: 0.80 g (63%); mp: 210–212°C; IR (KBr) \( \nu_{\text{max}} \): 3145, 1607, 1485, 1457, 1378, 1256, 1226, 746 cm\(^{-1}\); \(^1\)H NMR \( \delta \): 11.90 (1H, s, NH), 8.76 (1H, d, \( J=7.8 \) Hz, Ph), 8.65 (1H, d, \( J=8.5 \) Hz, Ph), 8.01 (1H, d, \( J=8.5 \) Hz, Ph), 7.75 (1H, m, Ph), 7.53 (2H, m, Ph), 7.29 (1H, m, Ph), 2.07 (3H, s, \( SC\)H); \(^1^3\)C NMR \( \delta \): 152.0 (s), 146.2 (s), 141.8 (s), 137.4 (s), 128.8 (d), 128.5 (d), 127.6 (d), 125.3 (d), 124.7 (d), 124.4 (d), 123.3 (d), 120.0 (d), 110.8 (s), 18.5 (t). Anal. calcd for \( C_{21}H_{16}S\): C, 76.65; H, 4.54; N, 10.58. Found: C, 72.91; H, 4.52; N, 10.36.

4.4.3. [2-(1H-lndol-2-yl)phenyl]-urea (45a). To a solution of \( 46a \) (0.620 g, 3.0 mmol), methanol (30 mL) and hydrochloric acid (1 M (aq.), 5 mL) sodium cyanate (0.220 g, 3.3 mmol) was added at room temperature. After 22 h more sodium cyanate (0.220 g, 3.3 mmol) was added to the reaction mixture and the reaction was stirred at room temperature for 3 h. The solvent was concentrated to 5 mL and poured on water. The solid thus formed was filtered, washed with water, dried and purified by chromatography using hexane/ethyl acetate 6:4 as eluent to give \( 45a \) as a white solid. Yield: 0.250 g (34%); mp: >170°C (dec); IR (KBr) \( \nu_{\text{max}} \): 3488, 3334, 3190, 3054, 1726, 1656, 1579, 1442, 1253, 1043, 763, 744, 694 cm\(^{-1}\); \(^1\)H NMR \( \delta \): 11.35 (1H, s, NH), 7.98 (1H, d, \( J=8.3 \) Hz, Ph), 7.78 (1H, s, CH), 7.58 (1H, d, \( J=7.8 \) Hz, Ph), 7.43 (2H, m, Ph), 7.28 (1H, t, \( J=7.8 \) Hz, Ph), 7.05 (3H, m, Ph), 6.61 (1H, s, NH), 6.61 (2H, s, NH); \(^1^3\)C NMR \( \delta \): 170.3 (s), 156.1 (s), 137.2 (s), 136.6 (s), 134.7 (s), 129.3 (d), 127.9 (s), 123.2 (d), 122.2 (d), 121.3 (d), 120.0 (d), 119.1 (d), 1113 (d), 101.4 (d). HRMS (FAB): [M] found 251.1060. \( C_{13}H_{13}N_3O \) requires 251.1059.

4.4.4. [2-(1H-lndol-2-yl)-4-methylphenyl]-urea (45b). To a solution of \( 46b \) (0.660 g, 3.0 mmol), methanol (50 mL) and hydrochloric acid (1 M (aq.), 7 mL) sodium cyanate (0.220 g, 3.3 mmol) added at room temperature. After 22 h more sodium cyanate (0.220 g, 3.3 mmol) was added to the reaction mixture and the reaction was stirred in room temperature for 3 h. The solvent was concentrated to 5 mL and poured on water. The solid thus formed was filtered, washed with water, dried and purified by chromatography, using hexane/ethyl acetate 5:5, to give \( 45b \) as a white solid. Yield: 0.420 g (53%); mp: >180°C (dec); IR (KBr) \( \nu_{\text{max}} \): 3390, 3148, 3079, 2910, 1725, 1627, 1548, 1497, 1490, 1332, 1203, 1181, 813, 762 cm\(^{-1}\); \(^1\)H NMR \( \delta \): 10.63 (1H, br s, NH), 7.81 (1H, s, Ph), 7.54 (1H, s, Ph), 7.26–0.73 (8H, m, Ph), 6.55 (1H, d, \( J=8.0 \) Hz, Ph), 3.97 (1H, d, 13.2, CH\(_2\)); 3.88 (1H, d, 13.2, CH\(_2\)); 1.41 (2H, m, CH\(_2\)).
7.25 (1H, t, \(J = 13.50\)) Hz, Ph), 7.52 (1H, d, \(J = 7.6\) Hz, Ph), 6.97 (1H, dd, \(J = 6.7\), 1.4 Hz, Ph), 6.59 (1H, d, \(J = 8.0\) Hz, Ph). 13C NMR δ: 175.7 (s), 163.4 (s), 146.2 (s), 139.0 (s), 135.3 (d), 123.5 (s), 129.9 (d), 126.8 (d), 126.7 (s), 124.2 (d), 117.5 (d), 114.9 (s), 114.0 (s), 113.8 (d), 71.6 (s). Anal. calcd for C\(_{15}\)H\(_{12}\)N\(_3\)O\(_2\): C, 73.3; H, 4.96; N, 12.76. Found: C, 73.3; H, 4.95; N, 12.76.

4.4.11. 2-(2-Acetamidophenyl)-4,5-dihydro-1,4-benzodiazeepin-3(3H)-one (60). A solution of 55 (3.11 g, 10 mmol) in acetic acid (50 mL) was stirred at room temperature for 7 days. The solid formed was collected by filtration. Yield: 1.23 g (42%); mp: 250–255°C (dec); IR (KBr) \(v_{\text{max}}\): 3319, 3068, 2909, 2870, 1692, 1667, 1567, 1530, 1446, 1310, 778, 758, 744 cm\(^{-1}\). 1H NMR δ: 11.13 (1H, s, NH), 9.01 (1H, t, 6.2, NH), 7.84 (1H, d, \(J = 8.1\) Hz, Ph), 7.80 (1H, d, \(J = 7.7\) Hz, Ph), 7.6–7.4 (3H, m, Ph), 7.39 (1H, d, \(J = 7.4\) Hz, Ph), 7.3–7.2 (2H, m, Ph), 4.20 (1H, br s, CH\(_2\)), 4.00 (1H, br s, CH\(_2\) I, 2.11 (3H, s, CH\(_3\)). 13C NMR δ: 168.6 (s), 163.6 (s), 162.4 (s), 145.5 (s), 138.1 (s), 131.3 (d), 131.1 (s), 131.1 (d), 128.8 (d), 127.5 (s), 127.4 (d), 126.7 (d), 126.3 (d), 123.9 (d), 122.9 (d), 41.4 (t), 23.9 (q). HRMS (FAB): [M+H\(^+\)]\(^{1}\), found 294.1252. C\(_{17}\)H\(_{16}\)N\(_3\)O\(_2\) requires 294.1242.

4.5. Collection and refinement of X-ray diffraction data

The data collections for the compound 48a was performed with a Nicolet diffractometer equipped with Cu K\(_\alpha\) radiation and an Enraf-Nonius CAD4 diffractometer with Mo K\(_\alpha\) radiation. The data sets were corrected for absorption and the structures were solved by direct methods and refined by full-matrix least-squares including an extinction parameter for compound 48a. Only crystals of poor quality could be obtained from compound 48a and as the refinements gave rather high R-values and large standard deviations only crystal data is given below. The connectivity is, however, undoubtedly that shown for the compound.

Compounds 48a. A crystal of dimensions 0.25×0.25×0.40 mm\(^3\) was used for the data collection. Of the measured 2314 independent reflections, 1375 with \(I > 2\sigma(I)\) were used in the refinements and gave \(R = 0.065\) and \(R_{w} = 0.082\) with 309 parameters. C\(_{22}\)H\(_{16}\)N\(_8\)O\(_7\), \(M = 352.40\). Compound 48a, space group \(P_2_1/c\), \(a = 10.332(9), b = 14.938(4), c = 11.654(8)\) Å, \(\beta = 109.83(6)^\circ\), \(V = 1692(2)\) Å\(^3\), \(Z = 4, D_c = 1.383\) g cm\(^{-3}\), \(2\theta_{\text{max}} = 45^\circ\) (Mo K\(_\alpha\)), \(T = 150\) K.

Acknowledgements

We thank Professor E. W. Warnhoff, University of Western Ontario, London, Canada and Professor W. Stadlbauer, Karl Franzens University, Graz, Austria for kind submission of
samples of indolo[3,2-c]quinolin-6-one (13a). Financial support from the Swedish Natural Science Research Council and the Swedish Research Council for Engineering Sciences is gratefully acknowledged.

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