The Cleavage of Heterocyclic Compounds in Organic Synthesis II [1] Use of 5-Nitroisatine for Synthesis of Various Nitrogenous Heterocycles

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The reactions of 5-nitroisatine were studied with nucleophiles like heterocyclic amines and alkaline hydroxide. With the use of alkaline hydroxide it was converted into 2-amino-5-nitrophenylglyoxylic acid **2**, with piperidine, morpholine and carbethoxypiperazine to its amides **4a-4c** or by oxidation to 5-nitroanthranilic acid **7**. This acid was used for synthesis of 3-hydroxy-6-nitro-2-phenyl-1*H*-quinolin-4-one **10**. Semicarbazone of 5-nitroisatine **11** was converted to 5-(2-amino-5-nitrophenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione **12**. Cyclocondensation of this compound to afford 8-nitro-2,3-dihydro-5*H*-[1,2,4]triazino-[5,6-*b*]indol-3-one **13** was unsuccessful.

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Introduction.

Isatines are very well known compounds that possess several reactive sites. Previously we have described the use of isatines for the synthesis of polynuclear-condensed heterocycles of a triazine type like *e.g.* triazinoindoles as well as non-condensed triazines such as 6-azauraciles and their thioanalogues [2]. They can also be used for the preparation of anthranilic acid, which may be used as a starting material for the synthesis of 2-phenyl-3-hydroxy-4(1*H*)-quinolinones [3].

Compounds that include a triazine ring in their structure are known to exhibit virostatic, coccidostatic or cancerostatic activities. They have also been used to study protein synthesis or to determine their influence on cell metabolism [4-9]. 6-Azauraciles have been reported to possess herbicidal effects [10].

The derivatives of quinolinones are known for their inhibition activity of bacterial as well as eucaryotic topoisomerase [11-14]. Derivatives of 3-hydroxy-4(1*H*)-quinolinones were also reported as inhibitors of the reverse transcriptase, enzyme responsible for multiplying the HIV virus [15].

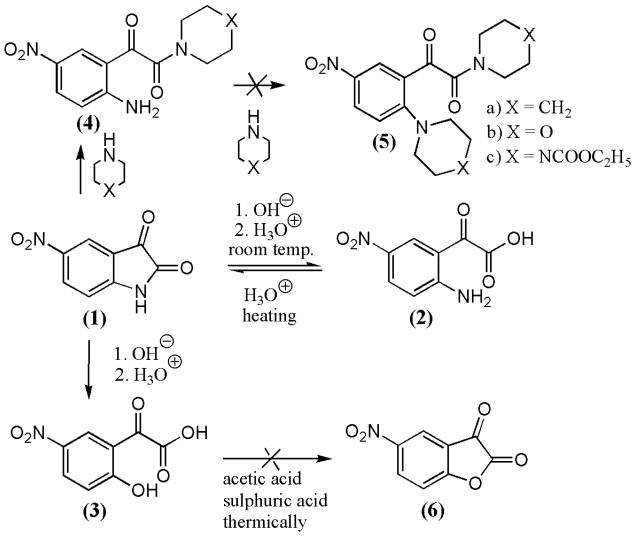
Now we have been interested in the conversion of 5-nitroisatine to the appropriate isatinic acid in alkaline solution, the amino group of which is sensitive to nucleophilic attack. We focused on studying the stability of 5-nitroisatine and its derivatives in alkaline solutions and on the preparation of various types of heterocycles as well.

Results and Discussion.

The reaction of 5-nitroisatine **1** with hydroxide anion as a nucleophile affording the 2-hydroxy-5-nitrophenylglyoxylic **3** acid has been already described [16]. We were interested in the stability of 2-amino-5-nitrophenylglyoxylic acid **2** as the intermediate of this reaction. Unlike other isatinic acid salts, the salt of acid **2** affords stable isatinic acid after acidification. Then we focused on the substitution of the amino group by other nucleophiles like piperidine, morpholine and *N*-ethoxycarbonylpiperazine. In all cases the appropriate amides of 2-amino-5-nitrophenylglyoxylic acid **4** were formed. Prolonged reaction time as well as excess of appropriate cyclic amine did not cause substitution reaction to amides **5**

The decreased nucleophility of the oxygen atom of the phenolic hydroxy group in compound **3** is responsible for non-reactivity of this acid to yield the benzofurane derivative **6**. All reactions are described in Scheme 1.

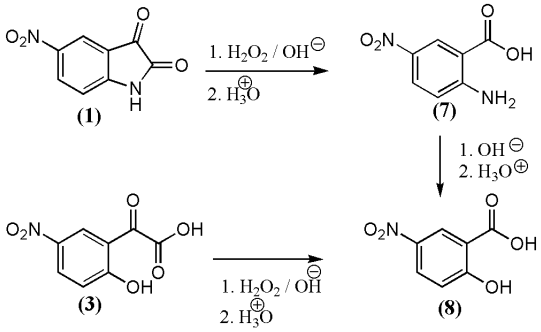
Scheme 1



The sensitivity of 5-nitroisatine to hydroxide anion substitution limited the easy preparation of 5-nitroanthranilic acid **7**. According to the described procedure for its preparation [17], we detected 5-nitrosalicylic acid **8**, in reaction mixture as a side product of nucleophilic substitution. Accordingly, we have modified this oxidation process.

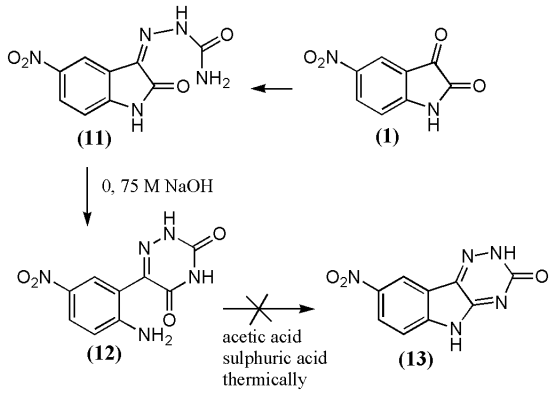
5-Nitroanthranilic acid **7** when treated with sodium hydroxide has been described to afford the 5-nitrosalicylic acid **8** without any details [18]. We wish to describe the precise conditions for this reaction. The novel preparation of compound **8** is based on oxidation of substituted glyoxylic acid **3** with use of hydrogen peroxide (Scheme 2).

Scheme 2



The reaction of 5-nitroanthranilic acid **7** with α-bromoacetophenone afforded the appropriate phenacylester **9**, cyclization of which led to the formation of 2-phenyl-3-hydroxy-6-nitro-4(1*H*)-quinolone **10** (Scheme 3).

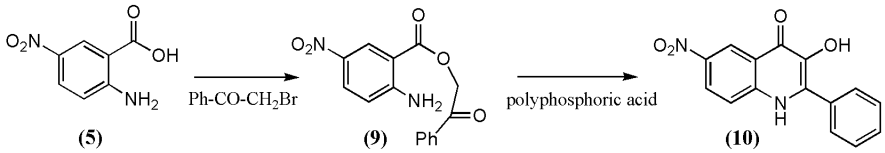
Scheme 4



EXPERIMENTAL

Melting points were determined on a Boetius stage apparatus. Infrared spectra (KBr disks) were acquired with an ATI Unicam Genesis FTIR instrument. NMR spectra of solutions in DMSO-d_6 (TMS as internal standard) were measured on a Bruker Avance 300 spectrometer (300 MHz). Elemental analyses were obtained with an EA 1108 Elemental Analyzer (Fison Instrument).

Scheme 3



The semicarbazone of 5-nitroisatine **11** was prepared in acetic acid medium. The presence of only one isomer, probably *Z* as known for the semicarbazone of isatine [19], of the product was detected in accordance with the NMR spectrum. We attempted to convert the double bond to the *E* configuration by refluxing in ammonium hydroxide or sodium bicarbonate. This conversion was unsuccessful. When **11** was treated with a 0.75 *M* solution of sodium hydroxide 5-(2-amino-5-nitro)-6-azauracil **12** was prepared. Higher concentration of alkaline hydroxide led to a complex mixture of unidentified compounds.

The cyclocondensation reaction of 6-azauracile **12** to 8-nitro-2,3-dihydro-5(*H*)-[1,2,4]triazino[5,6-*b*]indole-3-one **13** was complicated by its low solubility in acetic acid and hydrochloric acid. Heating compound **12** in concentrated sulphuric acid at 70 °C for two hours or boiling compound **12** in *N*-methylpyrrolidone did note result in formation of triazino[5,6-*b*]indole **13**. The reactivity of compound **12** is probably diminished by low basicity of the primary amino group (Scheme 4).

2-Amino-5-nitrophenylglyoxylic Acid (**2**).

The 5-nitroisatine (**1**) (0.5 g, 2.6 mmol) was dissolved in a solution of KOH (0.2 g, 3.6 mmol) in water (5 ml) at room temperature. After 30 minutes the solution was acidified with hydrochloric acid (0.3 ml). The resulting solid was collected by filtration, washed with water and dried in air to yield 0.5 g of orange powder, mp 221-223 °C; ir: NH_2 3426, 3322; CO 1702; ^{1}H NMR: δ 6.95 (d, 1H, J = 9.6 Hz, H3); 8.13 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.7 Hz, H4); 8.39 (s , 2H, NH_2); 8.41 (d, 1H, J = 2.7 Hz, H6).

Anal. Calcd. for $C_8H_6N_2O_5$: C, 45.72; H, 2.88; N, 13.33. Found: C, 45.66; H, 2.79; N, 13.47.

2-Hydroxy-5-nitrophenylglyoxylic Acid (**3**).

A solution of 5-nitroisatine (**1**, 4 g, 20.8 mmol) and sodium hydroxide (5.6 g, 129 mmol) in water (100 ml) was refluxed for four hours. After cooling the solution was acidified with hydrochloric acid to pH 2. The resulting precipitate was collected by filtration, washed with water and dried to yield a brown solid, 2 g (45.5 %). The filtrate was extracted with ethylacetate to yield another 2.2 g (50 %) of product, mp 265-268 °C (lit [16]: 259-260 °C); ir: ArH 3110; CO 1654; ^{1}H nmr: δ 7.17 (d, J = 9 Hz, 1H, H3), 8.41 (dd, J_1 = 9 Hz, J_2 = 3 Hz, 1H, H4), 8.51 (d, J_1 = 3 Hz, H6).

Anal. Calcd. for $C_8H_5NO_6$: C, 45.51; H, 2.39; N, 6.63. Found: C, 45.44; H, 2.11; N, 6.72.

1-(2-Amino-5-nitro-phenyl)-2-piperidin-1-yl-ethane-1,2-dione (**4a**).

A solution of 5-nitroisatine (**1**) (0.4 g, 2.1 mmol) in methanol (10 ml) was mixed with piperidine (0.5 ml, 5 mmol) and heated to the boiling point. After cooling the resulting solid was collected by filtration, washed with small amount of methanol and air-dried to yield 0.34 g (58.9 %) of compound **4a**, mp 193-197 °C ; ir: NH_2 3376, 3201; CO 1642; ^{1}H nmr: δ 1.43 (m, 2H, CH_2); 1.61 (m, 4H, CH_2); 3.26 (m, 2H, CH_2); 3.61 (m, 2H, CH_2); 6.97 (d, 1H, J = 9.3 Hz, H3); 8.13 (dd, 1H, J = 9.3 Hz, J_2 = 2.7 Hz, H4); 8.22 (d, 1H, J = 2.7 Hz, H6); 8.41 (s, 2H, NH_2).

Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.21; H, 5.63; N, 14.99.

1-(2-Amino-5-nitro-phenyl)-2-morpholin-1-yl-ethane-1,2-dione (**4b**).

A solution of 5-nitroisatine (**1**, 0.46 g, 2.4 mmol) in methanol (10 ml) was mixed with morpholine (0.5 ml, 5.7 mmol) and heated to the boiling point. After cooling the resulting solid was collected by filtration, washed with small amount of methanol and air-dried to yield 0.61 g (91 %) of product **4b**, mp 208-211 °C; ir: NH_2 3387, 3195; CO 1630; ^{1}H nmr: δ 3.34 (m, 2H, CH_2), 3.54 (m, 2H, CH_2), 3.68 (m, 4H, CH_2), 6.97 (d, 1H, J=9 Hz, H3), 8.13 (dd, 1H, J_1=9 Hz, J_2=2.5 Hz, H4), 8.27 (d, 1H, J=2.5 Hz, H6), 8.45 (brs, 2H, NH_2).

Anal. Calcd. for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 15.05. Found: C, 51.91; H, 4.83; N, 14.97.

4-[2-(2-Amino-5-nitro-phenyl)-2-oxo-acetyl]-piperazine-1-carboxylic Acid Ethyl Ester (**4c**).

A solution of 5-nitroisatine (**1**, 0.46 g, 2.4 mmol) in methanol (5 ml) was mixed with carbethoxypiperazine (0.5 ml, 3.4 mol). The resulting solid was collected by filtratioon, washed with a small amount of methanol and air-dried to yield 0.74 g (88 %) of product **4c**, mp 163-165 °C; ir : NH_2 3409, 3311; CO 1713; ^{1}H nmr: δ 1.18 (t, J=7 Hz, 3H, CH_3), 3.35 (m, 4H, CH_2), 3,49 (m, 2H, CH_2), 3,67 (m, 2H, CH_2), 4.02 (q, J=7 Hz, 2H, CH_2), 6.97 (d, J=9.5 Hz, 1H, H3), 8.13 (dd, J_1=9.5 Hz, J_2=2.5 Hz, H4), 8.25 (d, J=2.5 Hz, 1H, H6), 8.46 (brs, 2H, NH_2).

Anal. Calcd. for $C_{15}H_{18}N_4O_6$: C, 51.43; H, 5.18; N, 15.99. Found: C, 51.15; H, 5.22; N, 15.87.

5-Nitroanthranilic Acid (**7**).

The 5-nitroisatine (**1**) (0.5 g, 2.6 mmol) was dissolved in solution of KOH (0.6 g, 10.7 mmol) in water (10 ml) and cooled in an ice bath. Hydrogen peroxide 33 % (0.6 ml) was added dropwise. After 30 minutes the solution was warmed to room temperature and kept for the next two hours at which time the solution was acidified with 10 % sulphuric acid to pH 1-2. The resulting solid was collected by filtratoin, washed with water and dried to yield 0.46 g (98 %) mp 258-260 °C (lit.: [17] 254-255 °C ir: NH_2 3483, 3369; CO 1688; ^{1}H nmr: δ 6.87 (d, 1H, J = 9.3 Hz, H3); 7.86 (s, 2H, NH_2); 8.06 (dd, 1H, J_1 = 9.3 Hz, J_2 = 2.7 Hz, H4); 8.59 (d, 1H, J = 2.7 Hz, H6).

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.16, H, 3.32, N, 15.38. Found: C, 46.02, H 3.44, N, 15.11.

5-Nitro-2-hydroxybenzoic Acid (**8**).

Method A.

Compound **3** (0.8 g, 3.8 mmol) was dissolved in a 5% aqueous solution of potassium hydroxide (15 ml). Reaction mixture was cooled to 0 °C and 35 % solution of hydrogen peroxide (8.8 ml) was added. Reaction mixture was then left to stand at this temperature for 30 minutes and then another 2 hours at room temperature. The *pH* of the solution was then changed to 3-4 by adding a 5 % solution of sulfuric acid. The precipitated solid was collected by filtration, washed with 20 ml of cold water and dried to yield 0.5 g (72.5 %) of compound **6**.

Method B.

5-Nitroanthranilic acid (**1** g, 5.5 mmol) was dissolved in an aqueous solution of potassium hydroxide (50 ml). Reaction mixture was then refluxed for 60 minutes (with use of 5% KOH solution) or 12 hours (with use of 20% KOH solution). Then the reaction mixture was cooled to laboratory temperature and *pH* of the solution was changed to 3-4 by adding 5 % solution of sulfuric acid. The precipitated solid was collected by filtration, washed with cold water (100 ml) and dried to yield 0.8 g (79.4 %) of the product **6**, mp 226-230 °C (water) (lit.[18] 228 °C). ir: CO 1673; NO 1341; ^{1}H nmr: δ 7.13 (d, 1H, J = 9 Hz, H3); 8.31 (dd, 1H, J_1 = 9 Hz, J_2 = 3 Hz, H4); 8.54 (d, 1H, J = 3 Hz, H6).

2-Amino-5-nitrobenzoic Acid 2-Oxo-2-phenylethyl Ester (**9**).

5-Nitroanthranilic acid (1 g, 5.5 mmol) was dissolved in dimethylformamide (10 ml) and potassium carbonate (540 mg, 4 mmol) was added to the solution. The reaction mixture was heated to 90° and stirred for 1 hour. Then the solution was cooled to 20° and α-bromoacetophenone (0.8 g, 4 mmol) was added. After stirring for 30 minutes the solution was poured into a 10 % solution of natrium bicarbonate (50 ml) in water and ice. The precipitated solid was collected by filtration, washed with water and dried to yield 0.8 g (51%) of product **7**, mp 223-226 °C (acetone); ir: NH_2 3438, 3316; CO 1696; ^{1}H nmr: δ 5.77 (s, 2H, CH_2); 6.93 (d, 1H, J = 9.3 Hz, H3); 7.59 (t, 2H, J = 8 Hz, H3´); 7.72 (t, 1H, J = 7.2 Hz, H4´); 7.83 (s, 2H, NH_2); 8.01 (d, 2H, J = 8 Hz, H2´); 8.12 (dd, 1H, J_1 = 9.3 Hz, J_2 = 2.7 Hz, H4); 8.72 (d, 1H, J = 2.7 Hz).

Anal. Calcd: for $C_{15}H_{12}N_2O_5$: C, 60.00, H, 4.03, N, 9.33. Found: C, 60.26, H 4.17, N, 9.61.

3-Hydroxy-6-nitro-2-phenyl-1*H*-quinolin-4-one (**10**).

Phenacylester of 5-nitroanthranilic acid **9** (0.5 g, 1.7 mmol) was added to polyphosphoric acid (5 g), at 120º and the reaction mixture was stirred for 1 hour at this temperature. The reaction mixture was then diluted with cold water (30 ml) and cooled to a room temperature. The pH of solution was adjusted between 7 and 8 by the addition of aqueous 10% sodium hydroxide solution and the precipitated solid was collected, washed with 50 ml of water and dried to yield 0.3 g (68%), mp above 360 °C (methylcellosolve); ir: NH 3425; C-H_{arom} 3106; CO 1642; ^{1}H nmr: δ 7.57 (m, 3H); 7.79 (dd, 2H, J_1 = 7.8 Hz, J_2 = 1.5 Hz, $H_{2\text{-phenyl}}$); 7.84 (d, 1H, J = 9.5 Hz, H8); 8.32 (dd, 1H, J_1 = 9.5 Hz, J_2 = 2.7 Hz, H7); 8.94 (d, 1H, J = 2.7 Hz, H5); 12.11 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{10}N_2O_4$: C, 63.83, H, 3.57, N, 9.92. Found: C, 64.24, H, 3.35, N, 10.18.

5-Nitroisatine Semicarbazone (**11**).

A solution of 5-nitroisatine (0.6 g, 3.1 mmol) in acetic acid (20 ml) was mixed with a solution of semicarbazide hydrochloride (0.35, 3.1 mmol) in water (10 ml). The solution was boiled for 10

minutes. After cooling the formed solid was collected by filtration, washed with water and air-dried to yield 0.7 g (91 %) of product **9**, mp 284 °C (acetic acid); ir: NH_2 3445, 3310; CO 1734; ^{1}H nmr: δ 7.13 (d, J = 9 Hz, 1H, H3), 8.25 (dd, J_1 = 9, J_2 = 3 Hz, 1H, H4), 8.54 (d, J = 3 Hz, 1H, H6), 11.56 (2 x brs, 1H, 2 x NH).

Anal. Calcd. for $C_9H_7N_5O_4$: C, 43.38; H, 2.83; N, 28.10. Found: C, 43.42; H, 2.63; N, 27.97.

5-(2-Amino-5-nitrophenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (**12**).

A solution of derivative **11** (0.2 g, 0.8 mmol) in 0.75 *M* sodium hydroxide (8 ml) was boiled for three hours. After cooling, the solution was filtered and acidified with hydrochloric acid. The resulting solid was collected by filtration, washed with water and air-dried to yield 0.15 g (75 %) of product **12**, mp 251-255 °C; ir: NH_2 3378, 3245; CO 1701, 1646; ^{1}H nmr: δ 6.76 (d, J = 9 Hz, 1H, H3), 6.88 (s, 2H, NH_2), 7.98 (dd, J_1 = 9, J_2 = 3 Hz, 1H, H4), 8.27 (d, J = 3 Hz, 1H, H6).

Anal. Calcd. For $C_9H_7N_5O_4$: C, 43.38; H, 2.83; N, 28.10. Found: C, 43.08; H, 3.11; N, 28.26.

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