Reduction Products of 3(2*H*)-Cinnolinones

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Reduction of 3(2*H*)-cinnolinone with zinc and ammonium hydroxide forms 1,4-dihydro-3(2*H*)-cinnolinone which rapidly rearranges to 1-amino-2-indolinone (1-aminooxindole) in acid solution. 1,4-Dihydro-2-methyl-3(2*H*)-cinnolinone is formed from 2-methyl-3(2*H*)-cinnolinone under the same conditions, but its rearrangement to 1-(*N*-methylamino)-2-indolinone (1-(*N*-methylamino)oxindole) in acid solution is much slower.

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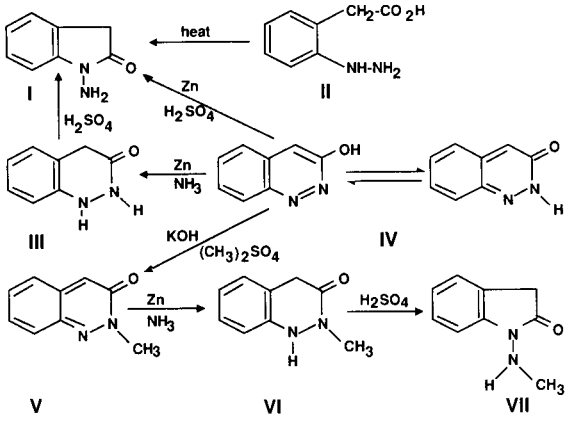
Neber and coworkers [1,2] have reported the preparation of 1-amino-2-indolinone (1-aminooxindole) (**I**) by the thermal cyclization of *o*-hydrazinophenylacetic acid (**II**). Neber's group [3] and his student, Bössel [4], also reported the preparation of 1,4-dihydro-3(2*H*)-cinnolinone (**III**) by reduction of 3(2*H*)-cinnolinone (**IV**) with zinc and sulfuric acid. A reinvestigation [5] of this work has shown that products **I** and **III** as reported by Neber and coworkers are identical and their structure is **I**.

Reduction of 2-methyl-3(2*H*)-cinnolinone (**V**) with zinc and ethanolic ammonia gave a dihydroderivative to which Alford and Schofield [6] assigned the structure 1,4-dihydro-2-methyl-3(2*H*)-cinnolinone (**VI**). A reinvestigation of this work by Ames and Kucharska [7] proved conclusively that the original structure assignment was correct and the reduction product was not 1-(*N*-methylamino)-2-indolinone (**VII**).



This article describes the results of reduction reactions carried out on **IV** and **V** with zinc and sulfuric acid and zinc and ammonium hydroxide.

The preparation of 3(2*H*)-cinnoline (**IV**) was carried out as described in an earlier communication by this investigator [8]. An initial attempt to reduce **IV** by adding ammonium hydroxide to a refluxing solution of **IV** and zinc in ethanol failed. However, when the method of Ames and Kucharska [7] was adopted and a few drops of hydrobromic acid was added to the refluxing solution several minutes before the ammonium hydroxide addition was started the reduction proceeded rapidly to give 1,4-dihydro-3(2*H*)-cinnolinone (**III**), whose structure was determined by elemental analysis and ir [9], in 56% yield. It is presumed that the hydrobromic acid cleaned the surface of the zinc so that reaction with ammonium hydroxide could occur.

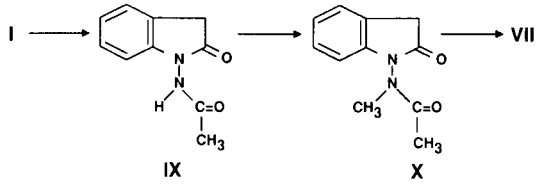
1,4-Dihydro-3(2*H*)-cinnolinone (**III**) has also been prepared by the reduction of 3(2*H*)-cinnolinone (**IV**) with zinc and sulfuric acid in a two phase system [10].

1,4-Dihydro-3(2*H*)-cinnolinone (**III**) was rapidly converted in quantitative yield to the isomeric 1-amino-2-indolinone (**I**) when heated to reflux in a sulfuric acid-ethanol mixture. Winters, Aresi, and Nathansohn [10] also noted the same result with dilute hydrochloric acid, but observed no noticeable change with ammonium hydroxide or sodium hydroxide. They proposed a hydrolysis and recondensation scheme or an intramolecular rearrangement to explain the results. This author prefers the hydrolysis and recondensation scheme. The formation of **I** can be attributed to two factors. In acidic solution, protonation of the hydrazine group would occur at the more basic β-nitrogen atom (**VIII**). This would sharply reduce the nucleophilic reactivity of that nitrogen and allow cyclization at the normally less nucleophilic α-nitrogen to form the five-membered ring in preference to the six-membered ring. Once formed, the disubstituted amide **I** is less susceptible to acidic hydrolysis than the monosubstituted amide **III**. Hydrolysis of diacetylphenylhydrazine in sulfuric acid yields α-acetylphenylhydrazine [11]. Further evidence for the stability of disubstituted amides toward hydrolysis was observed in the reduction of 2-methyl-3(2*H*)-cinnolinone (**V**). This reaction suggests that in the reaction of **IV** with zinc and sulfuric acid that **IV** is initially reduced to **III** with subsequent hydrolysis and recondensation to give **I**.

VIII

The preparation of 2-methyl-3(2*H*)-cinnolinone (**V**) was carried out essentially as described by Alford and Schofield [6] although procedural improvements were made which are described in the experimental section. Reduction of 2-methyl-3(2*H*)-cinnolinone (**V**) with zinc and sulfuric acid gave 1,4-dihydro-2-methyl-3(2*H*)-cinnolinone (**VI**) when the reaction time was kept short. Periods of reflux lasting several hours gave a mixture of **VI** and **VII**. The presence of **VII** was ascertained from infrared studies of the reaction product. Likewise, when **VI** was heated to reflux in a sulfuric acid-ethanol mixture for several hours, the presence of **VII** could be detected in the infrared spectrum of the reaction mixture. However, when the reflux period was extended to one week, **VI** was converted to **VII** in quantitative yield. These results seem to confirm the belief that when **IV** and **V** are treated with zinc and sulfuric acid they are initially reduced to **III** and **VI** respectively and that subsequent hydrolysis and recondensation lead to **I** and **VII** respectively. Apparently the slow hydrolysis and recondensation of **VI** is due to its disubstituted amide structure.

An authentic sample of **VII** was prepared by reacting **I** with acetic anhydride to give 1-acetamido-2-indolinone (**IX**), treatment of **IX** with dimethylsulfate in a basic solution to give 1-(*N*-methylacetamido)-2-indolinone (**X**) and acidic hydrolysis of **X**.



EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The ir spectra were determined in potassium bromide pellets.

3(2*H*)Cinnolinone (**IV**).

This material was prepared from isatin by the procedure previously reported by this author [8].

1,4-Dihydro-3(2*H*)-cinnolinone (**III**).

To a solution of 15 g (0.103 mole) of 3(2*H*)-cinnolinone (**IV**) in 300 ml of 95% ethanol was added 37.5 g (0.57 g-atom) of zinc dust and 25 drops of 48% hydrobromic acid. The mixture was heated and stirred at the reflux temperature for several minutes and then 225 ml of concentrated ammonium hydroxide was added over a 1-hour period. The yellow solution became virtually colorless within 20 minutes after the addition began. The reaction mixture was filtered and the filtrate evaporated to dryness on a rotary evaporator. The product was less colored when the rotary evaporator was flushed with nitrogen. The residue was heated to boiling with 300 ml of ethyl acetate and filtered. The filtrate was reduced in volume to 150 ml and chilled. The light yellow product, 8.4 g (56%), 159-165°, was collected by filtration. Recrystallization from methanol narrowed the mp range to 160-165° (lit [10] mp 167-168°); ir (potassium bromide): cm^{-1} (NH) 3420, 3190, (C=O) 1662 sh, 1653 sh, 1647 sh, 1641 [9]. Further attempts to purify the product were fruitless. It apparently undergoes air oxidation very rapidly in solution.

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.86; H, 5.54; N, 19.07.

1-Amino-2-indolinone (**I**).

(a) From 3(2*H*)-Cinnolinone (**IV**).

The procedure described by Baumgarten, Creger, and Zey [5] was used.

(b) From 1,4-Dihydro-3(2*H*)-cinnolinone (**III**).

A solution of 3 g of 1,4-dihydro-3(2*H*)-cinnolinone (**III**) in 120 ml of 95% ethanol and 51 ml of 6 *N* sulfuric acid was heated at the reflux temperature for 2 hours. The mixture was cooled and neutralized with ammonium hydroxide. The ethanol was removed on a rotary evaporator and the resulting aqueous mixture extracted with 3-50 ml portions of chloroform. Evaporation of the chloroform gave a quantitative yield of light-yellow product, mp 114-120°, whose infrared spectrum was identical with that of 1-amino-2-indolinone (**I**) prepared by the zinc-sulfuric acid reduction of 3(2*H*)-cinnolinone (**IV**) [5]; ir (potassium bromide): cm^{-1} (NH) 3290, 3205, 3195 sh, (C=O) 1720, 1707 sh [9].

2-Methyl-3(2*H*)-cinnolinone (**V**).

To a stirred solution of 22.5 g (0.154 mole) of 3(2*H*)-cinnolinone (**IV**), 9.9 g (0.177 mole) of potassium hydroxide, 87 ml of water, and 15 ml of 95% ethanol was added in one portion 21 ml (0.222 mole) of dimethyl sulfate. The solution became warm immediately and was allowed to stir 1.5 hours. The reaction mixture was extracted with chloroform and the chloroform evaporated on a rotary evaporator. The residue was dissolved in 160 ml of acetone, treated with decolorizing charcoal, and chilled. The golden-yellow product, 17.4 g, mp 132-134° (lit [6] mp 135.5-136.5°) was collected by filtration; ir (potassium bromide): cm^{-1} (C=O) 1664, 1657, 1647, 1629 sh [9]. Concentration of the filtrate gave another 2.3 g of product (total crude yield, 19.7 g (80%)). This product was sufficiently pure for most purposes but could be further purified by recrystallization from acetone.

1,4-Dihydro-2-methyl-3(2*H*)-cinnolinone (**VI**).

(a) Reduction of 2-Methyl-3(2*H*)-cinnolinone (**V**) in Basic Solution.

The material was prepared by the procedure of Alford and Schofield [6], mp 91-92.5° (lit [6] mp 91-92.5°).

(b) Reduction of 2-Methyl-3(2*H*)-cinnolinone (**V**) in Acidic Solution.

To a solution of 3.4 g (0.021 mole) of 2-methyl-3(2*H*)-cinnolinone (**V**) in 250 ml of 95% ethanol was added 8 g (0.122 g-atom) of zinc dust. The mixture was heated and stirred at the reflux temperature while 60 ml of 6 *N* sulfuric acid was added over a 20-minute period. Heating and stirring were continued another 5 minutes at which time the solution was colorless. The reaction mixture was filtered and the filtrate neutralized with ammonium hydroxide. The ethanol was removed on a rotary evaporator and the resulting aqueous mixture extracted with chloroform. Evaporation of the chloroform gave 3.25 g (96%) of a light-yellow product whose infrared spectrum was nearly identical with that of 1,4-dihydro-2-methyl-3(2*H*)-cinnolinone (**VI**) prepared by reduction of 2-methyl-3(2*H*)-cinnolinone (**V**) in basic solution; ir (potassium bromide): cm^{-1} (NH) 3215, 3177, 3127, (C=O) 1630, 1620, 1609, 1598 sh [9]. The spectrum gave no indication of the presence of 1-(*N*-methylamino)-2-indolinone (**VII**). Recrystallization from carbon tetrachloride gave 2.4 g (71%), mp 89-91° (lit [6] mp 91-92.5°).

Periods of reflux lasting several hours gave a mixture in which the presence of 1-(*N*-methylamino)-2-indolinone (**VII**) could be detected by infrared analysis.

1-Acetamido-2-indolinone (**IX**).

This material was prepared by the procedure of Neber and Keppler [2], mp 189.5-190.5° (lit [2] mp 186-187°); ir (potassium bromide): cm^{-1} (NH) 3245, (C=O) 1740, 1718 sh, 1670 [9].

1-(*N*-Methylacetamido)-2-indolinone (**X**).

This material was prepared by the procedure of Neber and Keppler [2], mp 146-146.5° (lit [2] mp 146°); ir (potassium bromide): cm^{-1} (C=O) 1735, 1685 [9].

1-(*N*-Methylamino)-2-indolinone (**VII**).

(a) From 1-(*N*-Methylacetamido)-2-indolinone (**X**).

A solution of 7.6 g (0.04 mole) of 1-(*N*-methylacetamido)-2-indolinone (**X**) in 120 ml of 95% ethanol and 51 ml of 6 *N* sulfuric acid was heated in a nitrogen atmosphere at the reflux temperature for 2 hours. The mixture was neutralized with ammonium hydroxide and the ethanol removed on a rotary evaporator. The resulting aqueous mixture was extracted with chloroform. Evaporation of the chloroform gave a dark-yellow oil which solidified on standing. The material was distilled using a spinning-band distillation column at 101-102°/2 torr to give 2.3 g (35%) of a colorless solid, mp 90-91°; ir (potassium bromide): cm^{-1} (NH) 3280, (C=O) 1699 sh, 1690 [9].

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.63; H, 6.01; N, 17.31.

(b) Acid Catalyzed Rearrangement of 1,4-Dihydro-2-methyl-3(2*H*)-cinnolinone (**VI**).

A solution of 2 g of 1,4-dihydro-2-methyl-3(2*H*)-cinnolinone (**VI**) in 40 ml of 95% ethanol and 17 ml of sulfuric acid was heated at the reflux temperature for one week in a nitrogen atmosphere. The mixture was cooled and neutralized with ammonium hydroxide. The ethanol was removed on a rotary evaporator and the resulting aqueous mixture extracted with 3-50 ml portions of chloroform. Evaporation of the chloroform gave a near quantitative yield of light-yellow product, mp 85-90°, whose infrared spectrum was identical with that of an authentic sample of 1-(*N*-methylamino)-2-indolinone (**VII**).

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