

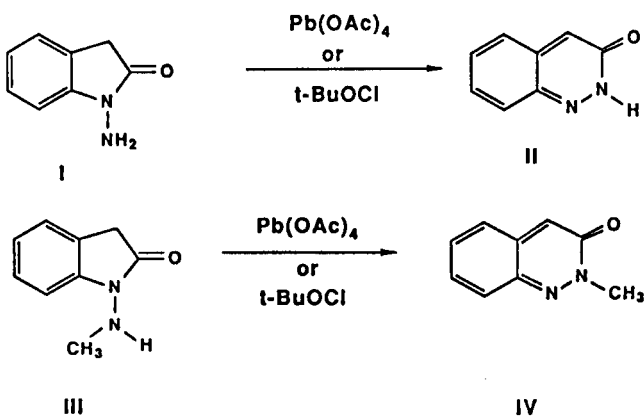
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Several 2-substituted-3(2*H*)-cinnolinones have been synthesized by a ring expansion of the respective 1-substituted-2-indolinones *via* an oxidative-rearrangement with *t*-butyl hypochlorite.

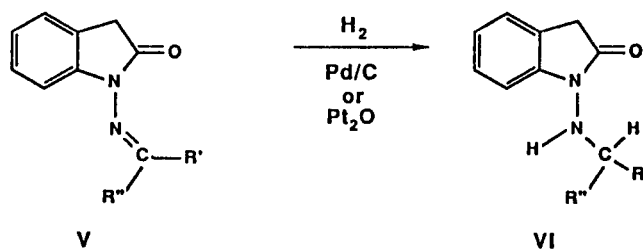
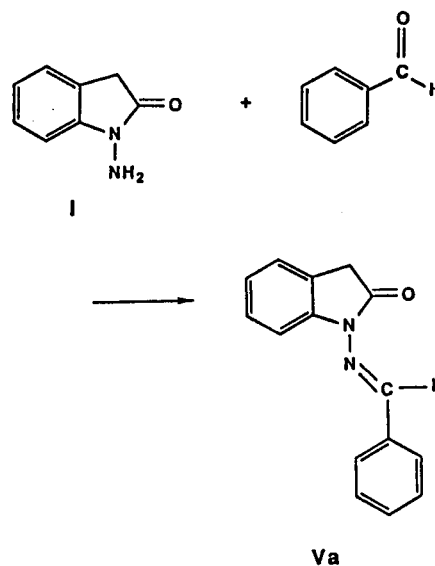
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Although several methods for the synthesis of substituted 3(2*H*)-cinnolinones have been reported, few, if any, can be classified as general methods. As part of the reinvestigation of the structure of "Neber's lactam" the oxidative-rearrangement of 1-amino-2-indolinone (1-amino oxindole) (**I**) to 3(2*H*)-cinnolinone (**II**) with lead tetraacetate (78% yield) was reported [1]. An improved route for the oxidative-rearrangement of **I**, treatment with equimolar amounts of *t*-butyl hypochlorite, has been reported by Baumgarten, Wittman and Lehmann [2] to produce nearly quantitative yields of **II**. The general usefulness of *t*-butyl hypochlorite was shown by the oxidative-rearrangement of 4- and 6-chloro-1-amino-2-indolinones to the corresponding 3(2*H*)-cinnolinones [2]. The reaction of 1-(*N*-methylamino)-2-indolinone (**III**) with lead tetraacetate or an equivalent amount of *t*-butyl hypochlorite gave 2-methyl-3(2*H*)-cinnolinone (**IV**) [3]. This publication describes the oxidative-rearrangement of various 1-substituted-amino-2-indolinones to 2-substituted-3(2*H*)-cinnolinones with one equivalent of *t*-butyl hypochlorite. This method of synthesis seems to be reasonably general.

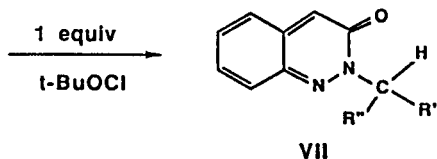


Neber and Keppler [4] reported the synthesis of 1-amino 3-benzal-2-indolinone by heating **I** with benzaldehyde under reflux in an ethanol solution. However, infrared analysis has shown the product to be 1-benzalamino-2-indolinone (**Va**) [1]. In this investigation, catalytic hydrogenation of **Va** with palladium on charcoal gave

1-benzylamino-2-indolinone (**VIa**). Oxidative-rearrangement of **VIa** with an equimolar amount of *t*-butyl hypochlorite gave 2-benzyl-3(2*H*)-cinnolinone (**VIIa**) which was identical to the product produced when 3(2*H*)-cinnolinone was reacted with benzyl chloride according to the method of Alford and Schofield [5].



- a  $\text{R}' = \text{H}, \text{R}'' = \text{C}_6\text{H}_5$
- b  $\text{R}' = \text{H}, \text{R}'' = \text{C}_6\text{H}_4\text{OCH}_3$
- c  $\text{R}' = \text{H}, \text{R}'' = \text{C}_6\text{H}_4\text{CH}_3$
- d  $\text{R}' = \text{R}'' = \text{CH}_3$



2-Benzyl-3(2*H*)-cinnolinone was prepared in 70% yield from **I**. The generality of the reaction was shown by the preparation of 2-*p*-methoxybenzyl-3(2*H*)-cinnolinone (**VIIb**) (71%), 2-*p*-methylbenzyl-3(2*H*)-cinnolinone (**VIIc**) (80%) and 2-isopropyl-3(2*H*)-cinnolinone (**VIIId**) (35%) in an analogous manner.

Table 1

## Infrared Spectra [a]

Compound	(C=O) region cm <sup>-1</sup>	(N-H) region cm <sup>-1</sup>
1-Benzalamino-2-indolinone <b>Va</b> [6]	1725	
1-( <i>p</i> -Methoxybenzalamino)-2-indolinone <b>Vb</b> [6]	1695	
1-( <i>p</i> -Methylbenzalamino)-2-indolinone <b>Vc</b>	1706	
1-Isopropylidenylamino-2-indolinone <b>Vd</b> [6]	1717	
1-Benzylamino-2-indolinone <b>VIa</b>	1683, 1703	3265
1-( <i>p</i> -Methoxybenzylamino)-2-indolinone <b>VIb</b>	1689, 1700	3255
1-( <i>p</i> -Methylbenzylamino)-2-indolinone <b>VIc</b>	1705	3259
1-Isopropylamino-2-indolinone <b>VIId</b>	1705	3275
2-Benzyl-3(2 <i>H</i> )-cinnolinone <b>VIIa</b> [6]	1642	
2- <i>p</i> -Methoxybenzyl-3(2 <i>H</i> )-cinnolinone <b>VIIb</b> [6]	1658	
2- <i>p</i> -Methylbenzyl-3(2 <i>H</i> )-cinnolinone <b>VIIc</b>	1641	
2-Isopropyl-3(2 <i>H</i> )-cinnolinone <b>VIIId</b> [6]	1655	

[a] Run using Perkin-Elmer model 257 double beam spectrometer in potassium bromide pellets except **VIId** which was determined neat.

## EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The ir are given in Table 1. The mass spectra of **II**, **VIIa**, **VIIb** and **VIIId** will be discussed in a later article. The tlc analyses were carried out on Analtech silica gel plates (250- $\mu$ m thickness) with fluorescent indicator. Flash chromatography purifications were carried out according to the procedure of Still, Kahn and Mitra [7]. The silica gel used was 40-63  $\mu$ m (230-400 mesh) silica gel 60 (E. Merck No. 9385) and the eluant was a mixture of ethyl acetate and hexane.

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

The procedure described by Baumgarten, Creger and Zey [1] for the reduction of 3(2*H*)-cinnolinone was used.

1-Benzalamino-2-indolinone (**Va**).

This compound was prepared in 92% yield from 1-amino-2-indolinone (**I**) according to the procedure described by Baumgarten, Creger and Zey [1], mp 118.5-120.5° (lit [1] mp 120.5-122°).

1-(*p*-Methoxybenzalamino)-2-indolinone (**Vb**).

This compound was prepared in 88% yield by a procedure similar to that used for **Va**. The colorless needles were recrystallized from ethanol, mp 131.5-132.5°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: C, 72.17, H, 5.30; N, 10.52. Found: C, 71.87; H, 5.21; N, 10.60.

1-(*p*-Methylbenzalamino)-2-indolinone (**Vc**).

This compound was prepared in 90% yield by a procedure similar to that used for **Va**. The colorless solid was recrystallized from ethyl acetate, mp 102.5-104°.

1-Isopropylidenylamino-2-indolinone (**Vd**).

Compound **I**, 3 g, was heated to the reflux temperature for 3 hours in 50 ml of acetone. The solvent was removed on a rotary evaporator. The solid was recrystallized from carbon tetrachloride to give **Vd** in 90% yield, mp 113-114.5°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O: C, 70.19; H, 6.42; N, 14.88. Found: C, 70.11; H, 6.21; N, 15.27.

1-Benzylamino-2-indolinone (**VIa**).

In a low pressure hydrogenation bottle, 2 g (0.0085 mole) of **Va** was dissolved in 25 ml of absolute ethanol. A small amount of 5% palladium on charcoal was added and the bottle was placed on a Parr hydrogenation apparatus under a hydrogen pressure of 45 psi. After several hours the catalyst was removed by vacuum filtration. The solvent was removed on a rotary evaporator to give a near quantitative yield of **VIa**. No impurities could be detected by tlc and the product was used in subsequent steps of the synthesis without further purification. An analytical sample was

purified by flash chromatography to give a colorless solid, mp 65-66°.

1-(*p*-Methoxybenzylamino)-2-indolinone (**V**ib****).

Compound **V**ib**** was prepared by the hydrogenation of **V**b**** according to the procedure described for **V**ia****. Purification by flash chromatography gave a colorless solid, mp 69-71°.

1-(*p*-Methylbenzylamino)-2-indolinone (**V**ic****).

Compound **V**ic**** was prepared by the hydrogenation of **V**c**** according to the procedure described for **V**ia****. Purification by flash chromatography gave a colorless solid, mp 79.5-80°.

1-Isopropylamino-2-indolinone (**V**id****).

Compound **V**id**** was prepared by the hydrogenation of **V**d**** according to the procedure described for **V**ia**** except that platinum oxide was used as the catalyst. The product was distilled at 84° (2 torr) on a Kugelrohr distillation apparatus to give a colorless oil which darkened upon standing.

2-Benzyl-3(2*H*)-cinnolinone (**V**ia****).

(a) Oxidative-Rearrangement of **V**ia****.

To a stirred solution of 0.25 g (0.00105 mole) of **V**ia**** in 25 ml of benzene was added dropwise (in ca. 15 minutes) 0.11 g (0.00105 mole) of *t*-butyl hypochlorite in 25 ml of benzene. The stirring was continued until tlc indicated the starting compound was no longer present. The solvent was removed on a rotary evaporator and the residue purified by flash chromatography to yield 0.19 g (76%) of yellow crystals, mp 146-147.5°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.20; H, 5.21; N, 12.11.

(b) From 3(2*H*)-cinnolinone.

To a stirred solution of 0.25 g (0.0017 mole) of **II** and 0.12 g of potassium hydroxide in 25 ml of ethanol, heated to the reflux temperature, was slowly added 0.22 (0.0017 mole) of benzyl chloride. The solution was stirred and heated overnight. The potassium chloride was removed by filtration and the solvent evaporated on a rotary evaporator. The residue was purified by

flash chromatography to yield 0.25 g (62%) of yellow crystals which were identical to the material prepared by the oxidative-rearrangement of **V**ia****.

2-(*p*-Methoxybenzyl)-3(2*H*)-cinnolinone (**V**ib****).

This compound was prepared in 81% yield by the oxidative-rearrangement of **V**b**** according to the procedure used for **V**ia****. The yellow crystals were purified by flash chromatography, mp 136-137°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.07; H, 5.51; N, 10.66.

2-(*p*-Methylbenzyl)-3(2*H*)-cinnolinone (**V**ic****).

This compound was prepared in 89% yield by the oxidative-rearrangement of **V**c**** according to the procedure used for **V**ia****. The yellow crystals were purified by flash chromatography, mp 105-106°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.93; H, 5.61; N, 11.07.

2-Isopropyl-3(2*H*)-cinnolinone (**V**id****).

This compound was prepared in 39% yield by the oxidative-rearrangement of **V**d**** according to the procedure used for **V**ia****. The yellow crystals were purified by flash chromatography, mp 78.5-79.5°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.00; H, 6.43; N, 15.00.

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