

**FISCHER REACTION OF 1-ACETYL-3-OXO-2,3-DIHYDROINDOLE  
and 1-(*p*-TOLUENESULFONYLOXY)-3-OXO-2,3-DIHYDROINDOLE**

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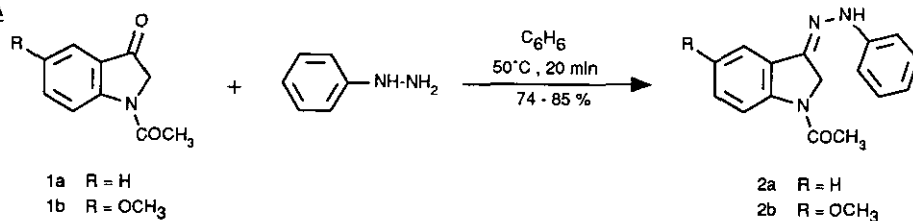
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**Abstract** — 1-(*p*-Toluenesulfonyloxy)-3-oxo-2,3-dihydroindole reacted with phenylhydrazine in acetic acid affording 5-(*p*-toluenesulfonyloxy)indolo[3,2-*b*]indole. By contrast 1-acetyl-3-oxo-2,3-dihydroindole in the same experimental conditions afforded 12-aminoindolo[1,2-*c*]quinazoline.

The Fischer cyclisation<sup>1-3</sup> of phenylhydrazones provides a simple route to indole rings. This reaction has been used to prepare polycycles as thianaphteno[3,2-*b*]indole<sup>4</sup> and benzofuro[3,2-*b*]indole.<sup>5</sup> In connection with our research program<sup>6,7</sup> on the reactivity of 1-acetyl-3-oxo-2,3-dihydroindole (**1a**), the Fischer reaction has been applied to this substrate.

The phenylhydrazones (**2a,b**) were prepared by heating phenylhydrazine with 1-acetyl-3-oxo-5-substituted 2,3-dihydroindoles (**1a,b**) in benzene at 50   C and isolated as solid after cooling (method A).

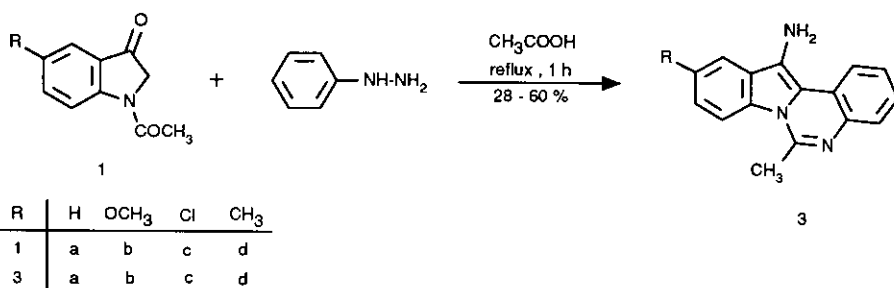
**Method A**



Heating, under acid catalyzed conditions (acetic acid/reflux/1 h),<sup>8,9</sup> of the 5-substituted phenylhydrazones (**2a,b**) afforded after cooling 12-amino-6-methyl-10-substituted indolo[1,2-*c*]quinazolines (**3a,b**) (method B).

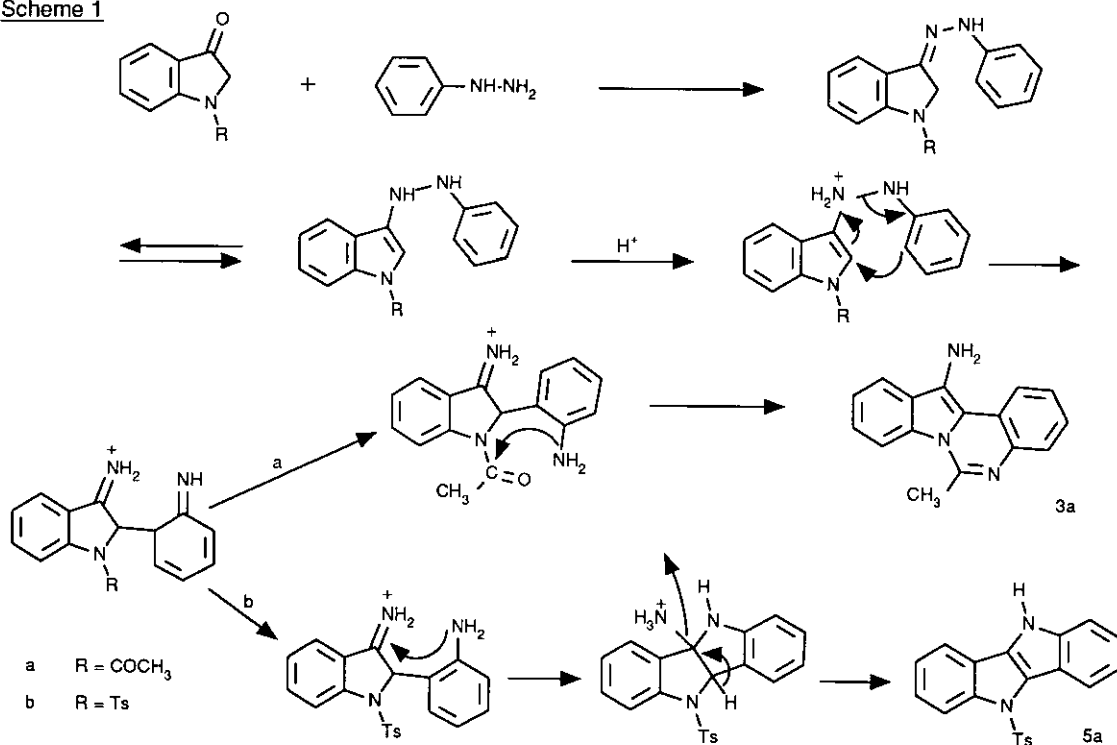
The compounds (**3a-d**) were also directly obtained by heating 1-acetyl-3-oxo-5-substituted 2,3-dihydroindoles (**1a-d**) with phenylhydrazine in acetic acid without isolation of the phenylhydrazones (**2a-d**) (method C).

## Method C



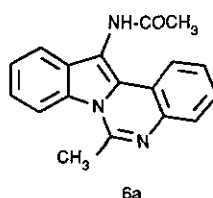
The same compounds (3) have also been prepared from 1-acetyl-3-acetoxy-5-substituted 2,3-dihydroindole and phenylhydrazine by Russian workers.<sup>10</sup> The expected product of the normal Fischer indole cyclisation, 5-acetylindolo[3,2-*b*]indole, was not observed despite the fact that smooth experimental conditions<sup>8,9</sup> were used. Compounds (3a,b) were the result of a normal nucleophilic attack of the amine function on the acetyl group, as reported on Scheme 1.

## Scheme 1

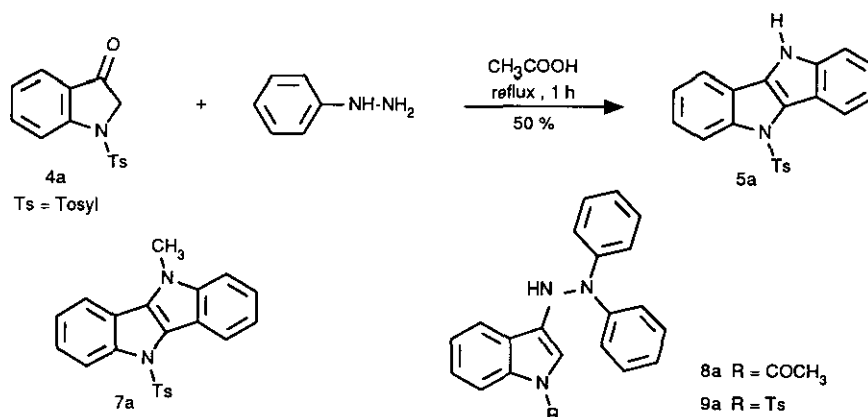


The structure of the 12-amino-6-methylindolo[1,2-c]quinazoline (3a) was in agreement with  $^1\text{H}$  nmr and  $^{13}\text{C}$  nmr in which the 6-methyl group of 3a was observed respectively at 3.1 ppm and 25 ppm; the ir spectrum showed the absence of carbonyl group.

Furthermore the nitrogen atom in 12 position of the compound (3a) was acetylated in acetic anhydride at room temperature affording compound (6a).<sup>11</sup>



In order to establish the role of the acetyl group of compound (1a) in the formation of the compound (3a), 1-(*p*-toluenesulfonyloxy)-3-oxo-2,3-dihydroindole (4a)<sup>12</sup> has been prepared. Compound (4a) and phenylhydrazine were heated in the same conditions than before (acetic acid/reflux/1 h). The normal Fischer indole cyclisation product (5a), the 5-(*p*-toluenesulfonyloxy)indolo[3,2-*b*]indole, was obtained as the result of a [3,3] sigmatropic rearrangement. The examination of spectra (ir and  $^1\text{H}$  nmr) allowed to confirm the structure of 5a. The nitrogen atom in 10 position was methylated (sodium hydride, iodomethane in excess) affording compound (7a).<sup>13</sup>



The reaction of 1,1-diphenylhydrazine with compounds (1a) or (4a) in acetic acid (reflux/1 h) afforded only indolylhydrazines (8a) and (9a)<sup>11</sup> in 68 % and 44 % yield respectively and not indolylhydrazones as 2.

| Compound | R                | Molecular Formula                                               | Method | Yield %  | mp °C | ms (m/z) M <sup>+</sup> +1 | ir (ν cm <sup>-1</sup> ) (KBr) | <sup>1</sup> H nmr δ                                                                                                                                           |
|----------|------------------|-----------------------------------------------------------------|--------|----------|-------|----------------------------|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2a       | H                | C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O                | A      | 74       | 189   |                            | 3250(NH)<br>1640(C=O)          | b <sub>2</sub> .2(s, 3H, COCH <sub>3</sub> );<br>4.7(s, 2H, CH <sub>2</sub> );<br>7.0(m, 9H, arom H);<br>9.3(s, 1H, NH).                                       |
| 2b       | OCH <sub>3</sub> | C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>   | A      | 85       | 180   |                            | 3200(NH)<br>1650(C=O)          | b <sub>2</sub> .2(s, 3H, COCH <sub>3</sub> );<br>3.7(s, 3H, OCH <sub>3</sub> );<br>4.7(s, 2H, CH <sub>2</sub> );<br>7.0-8.2(m, 8H, arom H);<br>9.2(s, 1H, NH). |
| 3a       | H                | C <sub>16</sub> H <sub>13</sub> N <sub>3</sub>                  | B<br>C | 84<br>60 | 205   | 248                        | 3300-3200(NH <sub>2</sub> )    | a <sub>3</sub> .1(s, 3H, CH <sub>3</sub> );<br>7.3-8.4(m, 8H, arom H);<br>9.8(s, 2H, NH <sub>2</sub> ).                                                        |
| 3b       | OCH <sub>3</sub> | C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O                | B<br>C | 60<br>32 | 140   | 278                        | 3300-3200(NH <sub>2</sub> )    | a <sub>3</sub> .0(s, 3H, CH <sub>3</sub> );<br>3.9(s, 3H, OCH <sub>3</sub> );<br>6.9-8.5(m, 7H, arom H);<br>9.8(s, 2H, NH <sub>2</sub> ).                      |
| 3c       | Cl               | C <sub>16</sub> H <sub>12</sub> N <sub>3</sub> Cl               | C      | 36       | 220   |                            | 3300-3200(NH <sub>2</sub> )    | a <sub>2</sub> .9(s, 3H, CH <sub>3</sub> );<br>7.2-8.5(m, 7H, arom H);<br>9.8(s, 2H, NH <sub>2</sub> ).                                                        |
| 3d       | CH <sub>3</sub>  | C <sub>17</sub> H <sub>15</sub> N <sub>3</sub>                  | C      | 28       | >250  |                            | 3300-3200(NH <sub>2</sub> )    | b <sub>2</sub> .2(s, 3H, CH <sub>3</sub> );<br>3.1(s, 3H, COCH <sub>3</sub> );<br>7.0-8.5(m, 7H, arom H);<br>9.8(s, 2H, NH <sub>2</sub> ).                     |
| 5a       | H                | C <sub>21</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> S | C      | 50       | 180   | 361                        | 3400(NH)                       | a <sub>2</sub> .2(s, 3H, CH <sub>3</sub> );<br>6.8-8.6(m, 12H, arom H);<br>8.2(s, 1H, NH).                                                                     |

a CDCl<sub>3</sub>; b DMSO-d<sub>6</sub>.

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- 10 G. N. Kurilo, S. Y. Ryabova, and A. N. Grinev, Khim. Geterotsikl. Soedin., 1979, 832 (Chem. Abstr., 1979, **91**, 175292c).
- 11 12-Acetylamino-6-methylindolo[1,2-c]quinazoline (6a).<sup>10</sup> Yield 36 % ; mp > 250 °C ; ms (m/z) 288 ; ir (KBr) : 3250 (NH), 1650 (CO), cm<sup>-1</sup> ; <sup>1</sup>H nmr (DMSO-d<sub>6</sub>) δ : 2.25 (s, 3H, COCH<sub>3</sub>), 3.12 (s, 3H, CH<sub>3</sub>), 7.3-8.5 (m, 8H, arom H), 9.88 (s, 1H, NH). 1,1-Diphenyl-2-[(1-acetylindole)-3-yl]hydrazine (9a). Yield 44% ; mp 205 °C ; <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ : 2.37 (s, 3H, CH<sub>3</sub>), 7.00-7.69 (m, 10H, arom H), 7.59 (s, 1H, =CH), 8.35 (d, J=8.5Hz, 2H, arom H), 8.61 (d, J=8.5 Hz, 2H, arom H).
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- 13 10-Methyl-5-(p-toluenesulfonyloxy)indolo[3,2-b]indole (7a). Compound (4a) (0.50 g, 1.1 mmol) was added to a suspension of sodium hydride (100%) (0.29 g, 1.2 mmol) in tetrahydrofuran (20 ml) under nitrogen at 0 °C. The mixture was stirred for 1 h at 0 °C, then 1 h at room temperature. Iodomethane (0.47 g, 3.3 mmol) was added and the mixture stirred for 20 h at room temperature and then evaporated on vacuo. Water (20 ml) was added to the residue which was extracted with dichloromethane (2 x 20 ml). After drying over magnesium sulfate and evaporation, the residue is chromatographed over silica gel (230/400 mesh) using dichloromethane as eluant ; yield 0.146 g (33 %) ; mp 215 °C ; <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ : 2.25 (s, 3H, CH<sub>3</sub>), 4.05 (s, 3H, NCH<sub>3</sub>), 6.9 - 8.6 (m, 12 H, arom H).

Received, 28th January, 1991