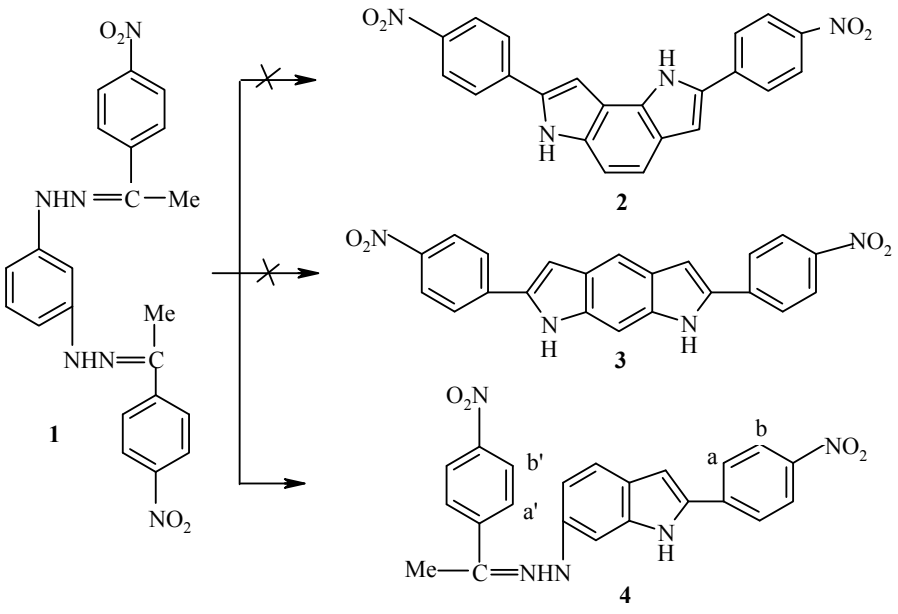
*Chemistry of Heterocyclic Compounds, Vol. 46, No. 6, 2010*

# INDOLE DERIVATIVES. SOME ASPECTS OF THE E. FISCHER REACTION

**Sh. A. Samsoniya[1]*, I. Sh. Chikvaidze[1], D. O. Kadzhrishvili[1], N. N. Barbakadze[1], and N. O. Narimanidze[1]**

**Keywords:** 2-arylindole, hydrazone, indole, pyrroloindole, ultrasonic activation.

In continuing our work on the synthesis and study of novel pyrroloindole systems [1, 2], we found that refluxing a solution of *p*-nitroacetophenone *m*-phenylenedihydrazone (**1**) in a mixture of ethanol and conc. $H_2SO_4$ (5:1) gave not the expected pyrroloindoles **2** and **3** but the monocyclization product **4** with one hydrazone group retained. No additional indole compounds were present in the mixture obtained. An analogous situation is seen with ultrasonic activation (ultrasonic homogenizer GM 3200, UW 3200, SH 213 G, 200 W HF, 20 kHz). In other condensation media including polyphosphoric acid (PPA) this hydrazone is unchanged up to 140ºC. Further heating leads to tarring.




* To whom correspondence should be addressed, e-mail: shota.samsonia@tsu.ge.

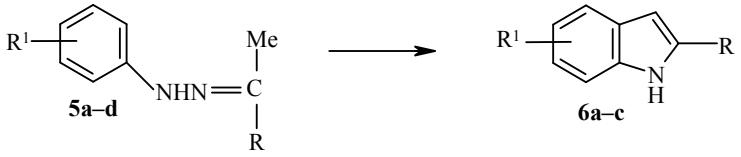
[1]I. Javakhishvili State University, Tbilisi 0179, Georgia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 944-946, June, 2010. Original article submitted April 16, 2009; revision submitted May 3, 2010.

Ethyl pyruvate phenylhydrazone (**5a**) in PPA and its esters indolizes at 70-80ºC but the similar ethyl pyruvate *m*-phenylenedihydrazone at 80-85ºC forms a mixture of the corresponding bicyclization products [1, 2].

*p*-Nitroacetophenone phenylhydrazone (**5b**) cyclizes in PPA at 80ºC over 30-35 min to give a yield up to 70% but in almost quantitative yield of analytically pure product **6b** over 1.5-2 h at 30ºC. The *p*-amino-acetophenone phenylhydrazone (**5c**) behaves in much the same way [3], the amino group being protonated in PPA.




**5**, **6 a–c** $R^1$ = H, **a** R = COOEt, **b** R = $C_6H_4$–$NO_2$-*p*, **c** R = $C_6H_4$–$NH_2$-*p*;
**5d** R = $C_6H_4$–$NO_2$-*p*, $R^1$ = $NO_2$

The *p*-nitroacetophenone *p*-nitrophenylhydrazone (**5d)** does not undergo cyclization either under in the reported conditions or upon ultrasonic activity, being unchanged to 160-180ºC and undergoing tarring above that. Similar properties for this hydrazone have been reported in the literature [4].

It is generally accepted that an acceptor substituent in the hydrazone fragment hinders indolization. However, the effect of R and R' substituents has been little studied. From those reported above and our other observations and also from much literature data it follows that all of the substituents (excepting those sterically hindered) encourage indolization, more of them being acceptors, particularly on the R side [5].

In our opinion a detailed study of this question can clarify certain aspects of the E. Fischer reaction unresolved at this time.

The structures of the synthesized compounds were confirmed by spectroscopic methods.

IR spectra were taken on a Thermo Nicolet AVATAR-370 instrument using vaseline oil and $^1$H NMR spectra on a Varian Mercury-300 (300 MHz) using acetone-$d_6$ and with TMS as internal standard. Mass spectra were obtained on a Finnigan MAT-95 spectrometer.

***p*-Nitroacetophenone *m*-Phenylenedihydrazone (1)**. A solution of *p*-nitroacetophenone (29.7 g, 180 mmol) in 2-propanol (300 ml) was added to a solution of *m*-phenylenedihydrazine (18.81 g, 90 mmol), prepared by method [6]) in water (500 ml) and stirred for 1 h. The precipitate was filtered off, washed with 2-propanol (2×10 ml), water to neutral pH, and dried. The product was recrystallized from ethanol. Yield of product **1** 27.22 g (70%). $R_f$ 0.3 (benzene–ether, 3:1); mp 253-254ºC. IR spectrum, ν, $cm^{-1}$: 3345 (NH), 1650 (>C=N), 1530, 1370 ($NO_2$). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 9.16 (2H, s, NH); 8.26, 8.11 (8H, two d, AB system, *J* = 9.2, Ar); 7.44 (1H, d, *J* = 1.8, H-2); 7.16 (1H, t, *J* = 8.2, H-5); 6.85 (2H, dd, *J* = 1.8 and *J* = 8.2, H-4,6); 2.37 (6H, s, $CH_3$). Found, %: C 61.32; H 4.84; N 19.61. $C_{22}H_{20}N_6O_4$. Calculated, %: C 61.11; H 4.63; N 19.44.

***p*-Nitroacetophenone 2-(*p*-Nitrophenyl)indol-6-ylhydrazone (4)**. Conc. $H_2SO_4$ (3 ml) was added to a solution of dihydrazone **1** (1.3 g, 3 mmol) in absolute ethanol (15 ml) and refluxed for 3 h. The product was cooled, poured into crushed ice (150 g), and then filtered, washed with water to neutral reaction, and dried. Yield of product **4** 1.03 g (83%). Purification was carried out on a silica gel column with benzene–ether (3:1) as eluent. $R_f$ 0.54 (benzene–acetone, 3:1). Mp 210-212ºC. IR spectrum, ν, $cm^{-1}$: 3355, 3335 (NH), 1630 (>C=N); 1560, 1345 ($NO_2$). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 9.61 (1H, s, NH); 9.21 (1H, s, NH); 8.29, 8.20, 7.73 (8H, three d, two AB systems, *J* = 9.2 and *J* = 8.8, Ar); 8.22 (1H, d, *J* = 1.8, H-7); 8.12 (1H, d, *J* = 2.2, H-3); 7.67 (1H, d, *J* = 8.1, H-4); 7.57 (1H, dd, *J* = 1.8 and *J* = 8.1, H-5); 2.43 (3H, s, $CH_3$). Found: *m/z* 415.1283 $[M]^+$. $C_{22}H_{17}N_5O_4$. Calculated: M 415.4058.

This project was carried out with the financial support of the Georgian National Science Foundation (Grant No. GNSF/ST07/4-181). Any opinions expressed in this publication are those of the authors. We express thanks to the German Department of Academic Collaboration (DAAD) for collaboration and the program of exchange between the I. Javakhishvili State University, Tbilisi and the Saarland University in Germany.

**REFERENCES**

1. Sh. A. Samsoniya, I. Sh. Chikvaidze, D. O. Kadzhrishvili, and N. L. Targamadze, *Khim. Geterotsikl. Soedin.*, 679 (2010). [*Chem. Heterocycl. Comp.*, **46**, 536 (2010)].
2. Sh. A. Samsoniya, N. L. Targamadze, and N. N. Suvorov, in: V. G. Kartsev (editor), *Selected Methods for the Synthesis and Modification of Heterocycles* [in Russian], Vol. 3, IBS Press, Moscow (2004), p. 555.
3. I. Sh. Chikvaidze, E. A. Mumladze, Sh. A. Samsoniya, and N. N. Suvorov, *Khim.-Farm. Zh.*, **28**, No. 10, 47 (1994).
4. N. M. Przheval'skii, N. S. Skvortsova, and I. V. Magedov, *Khim. Geterotsikl. Soedin.*, 189 (2003). [*Chem. Heterocycl. Comp.*, **39**, 161 (2003)].
5. Sh. A. Samsoniya, I. Sh. Chikvaidze, and T. G. Narindoshvili, in: V. G. Kartsev (editor), *Selected Methods for the Synthesis and Modification of Heterocycles* [in Russian], Vol. 3, IBS Press, Moscow (2004), p. 306.
6. Sh. A. Samsoniya, N. L. Targamadze, L. G. Tret'yakova, T. K. Efimova, K. F. Turchin, I. M. Gverdtsiteli, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 938 (1977). [*Chem. Heterocycl. Comp.*, **13**, 757 (1977)].