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NOVEL APPROACH TO SYNTHESIS OF THE TETRACYCLIC CONDENSED SYSTEM FURO[2',3';3,4]-CYCLOPENTA[1,2-*c*]ISOQUINOLIN-8(6H)-ONE

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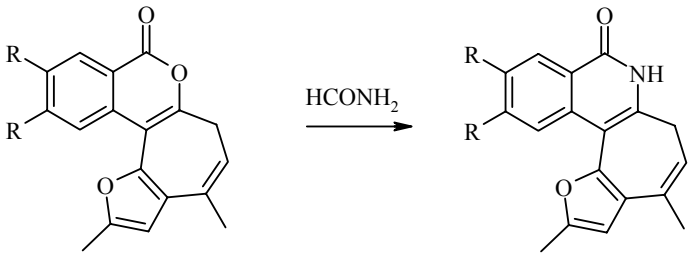
Isoquinolone derivatives and hydrogenated analogs of isoquinolone are very abundant in nature and comprise a broad class of isoquinoline alkaloids [1, 2]. Furthermore, among synthesized compounds of this type, substances have been found that have various kinds of biological activity [3, 4]. It is for precisely this reason that there has been steady interest both in synthesis of new substances including an isoquinolone moiety in their structures and in development of new approaches to formation of such a moiety.

We reported earlier about synthesis of a novel tetracyclic isoquinolone system of type **1**, based on successive reactions of recyclization and intramolecular cyclization of the benzylamide of 2-carboxyphenyl-bis(5-methyl-2-furyl)methane [5]. In this paper, we report on synthesis of the indicated heterocyclic system from readily available tetracyclic derivatives of isocoumarin **2** [6].

Going directly from isocoumarins to isoquinolones by replacing the oxygen atom by a nitrogen atom is a rather well known reaction [7]. Nevertheless, methods described in the literature [8-10] have not given the desired result for the systems used in our study. We have found that boiling isocoumarins **2a,b** for 45 min in formamide leads to the corresponding isoquinolone derivatives **1a,b** in high yields.



1a,b **2a,b**

1, **2 a** R = H, **b** R = OMe

We have determined the optimal ratios of the reactants: 45 ml formamide per 0.01 mol isochromone. Decreasing the amount of formamide leads to an increase in the reaction time and a decrease in the product yield, since the reaction rate is limited by the solubility of the starting isochromone in formamide. An increase in the amount of formamide compared with the optimal value does not have a substantial effect on the yield and the reaction time.

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2,4-Dimethylfuro[2',3':3,4]cyclohepta[1,2-*c*]isoquinolin-8(6H)-one (1a). A mixture of compound **2a** (2.78 g, 0.01 mol) and formamide (45 ml) was boiled under reflux for 45 min (monitored by TLC). The solution obtained was poured into water (300 ml). The precipitate formed was filtered out and recrystallized from a 1,4-dioxane–ethanol mixture. Yield 2.36 g (85%); decomp >310°C (C_2H_5OH–1,4-dioxane). ^{1}H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.98 (3H, s, CH_3); 2.46 (3H, s, CH_3); 2.92 (2H, d, *J* = 4.1, CH_2); 5.36 (1H, t, *J* = 6.7, =CH); 6.45 (1H, s, H_{Fur}); 7.45-7.54 (1H, m, H_{Ar}); 7.72-7.81 (1H, m, H_{Ar}); 8.23-8.29 (1H, m, H_{Ar}); 8.34-8.40 (1H, m, H_{Ar}); 11.61 (1H, s, NH). Found, %: C 77.80; H 5.52. $C_{18}H_{15}NO_2$. Calculated, %: C 77.96; H 5.45.

10,11-Dimethoxy-2,4-dimethylfuro[2',3':3,4]cyclohepta[1,2-*c*]isoquinolin-8(6H)-one (1b) was obtained as for compound **1a**. Yield 80.5%; decomp >310°C (C_2H_5OH–1,4-dioxane). ^{1}H NMR spectrum (250 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.98 (3H, s, CH_3); 2.45 (3H, s, CH_3); 2.89 (2H, d, *J* = 4.1, CH_2); 3.87 (3H, s, OCH_3; 3.91 (3H, s, OCH_3); 5.34 (1H, d, *J* = 6.7, =CH); 6.45 (1H, s, H_{Fur}); 7.64 (1H, s, H_{Ar}); 7.87 (1H, s, H_{Ar}); 11.49 (1H, s, NH). Found, %: C 71.17; H 5.60. $C_{20}H_{19}NO_4$. Calculated, %: C 71.20; H 5.68.

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REFERENCES

1. M. Shamma and J. L. Moniot, *Isoquinoline Alkaloids Research, 1972-1977*, Plenum Press, New York/London (1978), p. 57
2. A. A. Semenov, *The Chemistry of Natural Compounds* [in Russian], Nauka/Siberian Printing Company of the Russian Academy of Sciences, Novosibirsk (2000).
3. T. Okomoto, Y. Torii, and Y. Isogai, *Chem. Pharm. Bull.*, **16**, 1860 (1968).
4. J. H. Hutchinson, J. J. Cook, K. M. Brashear, M. J. Breslin, J. D. Glass, R. J. Gould, W. Halczenko, M. A. Holahan, R. J. Lynch, G. R. Sitko, M. T. Stranieri, and G. D. Hartman, *J. Med. Chem.*, **39**, 4583 (1996).
5. V. T. Abaev, A. A. Osipova, and A. V. Butin, *Khim. Geterotsikl. Soedin.*, 849 (2001).
6. A. V. Gutnov, V. T. Abaev, A. V. Butin, and A. S. Dmitriev, *J. Org. Chem.*, **66**, 8685 (2001).
7. V. A. Glushkov and Yu. V. Shklyaev, *Khim. Geterotsikl. Soedin.*, 723 (2001).
8. E. P. Souza and P. S. Fernandes, *Ind. J. Chem.*, **29B**, 961 (1990).
9. S. Ferrer, D. P. Naughton, H. Parveen, and M. D. Threadgill, *J. Chem. Soc., Perkin Trans. 1*, 335 (2002).
10. T. Sakamoto, M. Annaka, Y. Kondo, and H. Yamanaka, *Chem. Pharm. Bull.*, **34**, 2754 (1986).