Cyclocondensation Reactions of Heterocyclic Carbonyl Compounds VIII[*].

Synthesis of some [1,2,4]triazino[6,5-b]quinoline Derivatives.

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Abstract

2-Phenyl-4-(2-acetylaminobenzylidene)-4,5-dihydrooxazol-5-one **5a**, resp. its analogous 2-methyl derivate **5b** were converted into the 2-benzoylamino-, resp. 2-acetylamino-3-(2-acetylaminophenyl) acrylic acid hydrazides **6a**, resp. **6b**. These hydrazides were cyclized to the 3-phenyl-, resp. 3-methyl-5-(2-acetylaminobenzyl)-1,6-dihydro-[1,2,4]triazine-6-ones **7a**, resp. **7b**. The acidic hydrolysis of acetyl group was followed by the cyclocondensation of derivates **8a**, resp. **8b** into 3-phenyl, resp. 3-methyl-1,5-dihydro-[1,2,4] triazino[6,5-b]quinolines **9a**, resp. **9b**.

Introduction

The cyclocondensation reactions of the oxo derivates of [1,2,4]triazine belong to the most advantageous methods for syntheses of condensed derivates of this heterocycle.

For example the cyclocondensation reactions of the 3-oxo[1,2,4]triazine derivatives were used for syntheses of the [1,2,4]triazino[2.3-a]benzimidazoles[1-4] and [1,2,4]triazino[2.3-a]quinazolines[5].

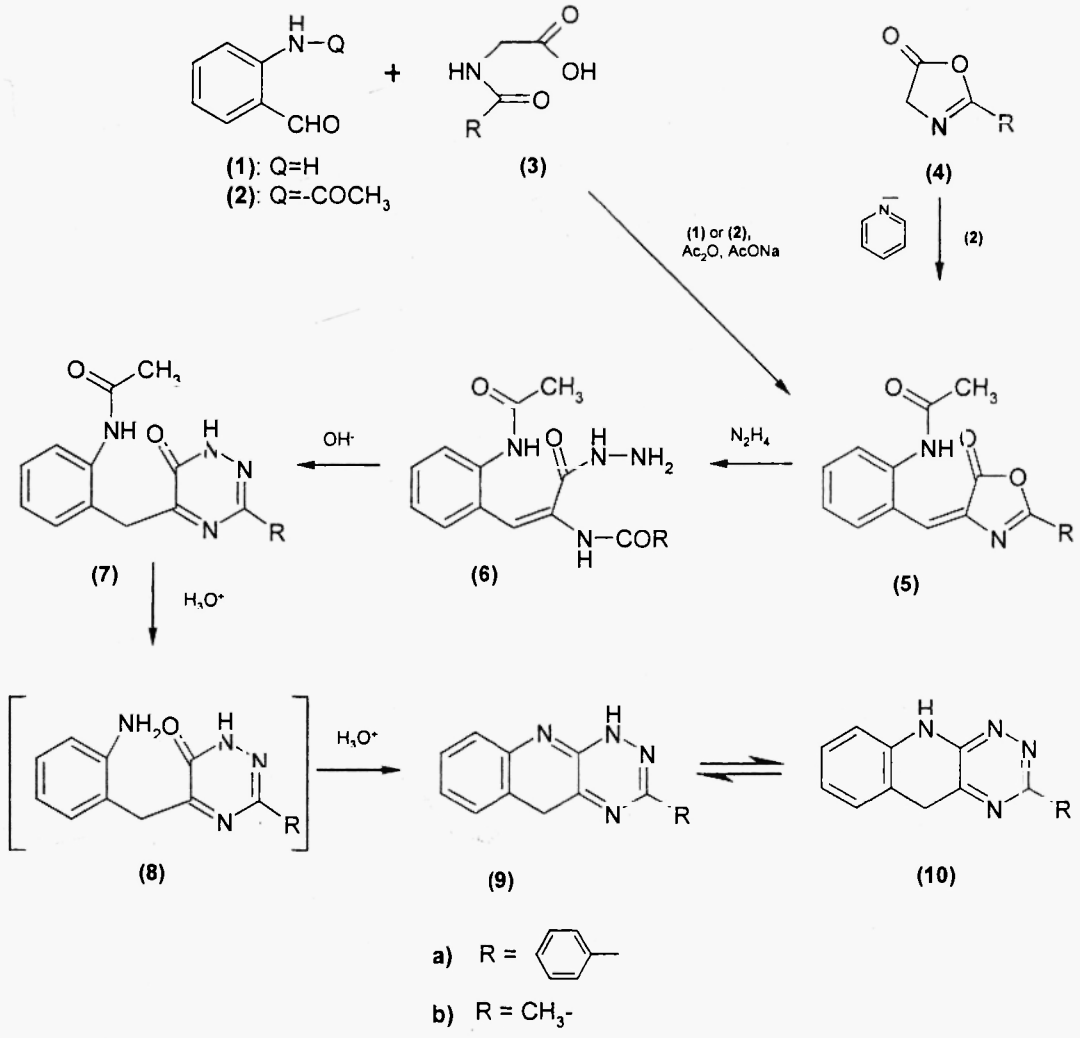
More frequently up to this time the cyclocondensation reactions have been realized with participation of the 5-oxo group of the [1,2,4]triazine ring. A lot of [1,2,4]triazino[5.6-b]indole[6-15], [1,2,4]triazino[5.6-b]quinoline[16,17], [1,2,4]triazino[5.6-c]cinnoline[12,13,18], [1,2,4]triazino[5.6-c]isoquinoline[19,20], [1,2,4]triazino[6.5-f]naphtyridine[21] and [1,2,4]triazino-[5.6-c]isocoumarine[4,v] derivates have been prepared using this method.

On the other hand, the reactivity of the oxo group on position 6- of the [1,2,4]triazine skeleton has been studied in a few cases only.

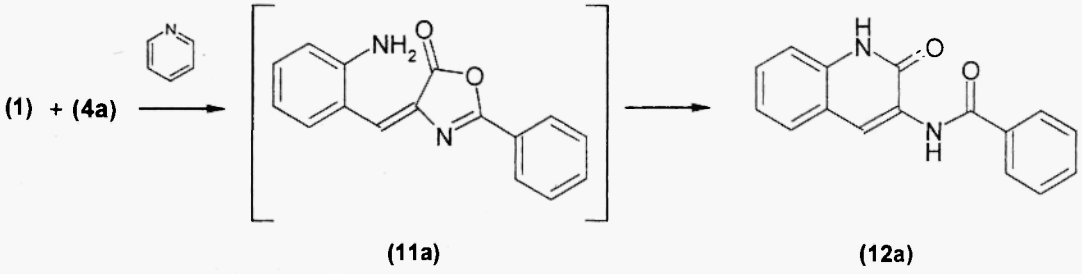
This communication deals with the use of 6-oxo[1,2,4]triazine cyclocondensation reaction of this type for synthesis of some [1,2,4]triazino[6.5-b]quinoline derivatives. The only synthesis of this heterocyclic system known is the cyclization reaction of some 2-hydrazinoquinoline derivatives[22].

[1*] Part VII see ref. (4)

Scheme 1



Scheme 2



Results

The topic of this article is the synthesis leading to 3-substituted-5-(2-aminobenzyl)-1,6-dihydro[1,2,4]triazine-6-ones **8a**, resp. **8b** and the study of their cyclocondensation reactions.

We used the 2-substituted-4-(2-acetylaminobenzylidene)-4,5-dihydrooxazol-5-ones **5a**, resp. **5b** as a starting material. These azlactones were easily obtained by heating acylglycine **3a**, resp. **3b** and 2-aminobenzaldehyde **1** or 2-acetylaminobenzaldehyde **2** with acetic anhydride in the presence of sodium acetate. The aldole condensation of 2-substituted-4,5-dihydro-oxazol-5-ones **4a**, resp. **4b** with 2-acetylaminobenzaldehyde **2** in pyridine gave the same compounds **5a**, resp. **5b**. The starting 2-phenyl-3,4-dihydro-oxazol-5-one, resp. its corresponding 2-methyl derivative were obtained by the action of dicyclohexylcarbodiimide on benzoylglycine[23], resp. by the action of ethyl chloroformate on acetylglycine in the presence of triethylamine[24]. The identity of compounds **5a**, resp. **5b** prepared by these ways was confirmed by the comparision of ^{1}H NMR spectra, IR spectra, elemental analyses and melting points.

The reaction of azlactones **5a**, resp. **5b** with hydrazine hydrate under mild conditions proceeded to the 2-acylamino-3-(2-acetylaminophenyl)acrylic acid hydrazides **6a**, resp. **6b**. The cyclization reaction of these hydrazides under alkaline conditions proceeded to 3-substituted-5-(2-acetylaminobenzyl)-1,6-dihydro[1,2,4]triazin-6-ones **7a**, resp. **7b**.

We were not able to isolate the aminoderivatives **8a**, resp. **8b** under the performed conditiones of acidic hydrolysis of the acetylaminocompounds **7a**, resp. **7b** because of easy cyclization of them into the 3-substituted-1,5-dihydro[1,2,4]triazino[6,5-b]quinolines **9a**, resp. **9b** that are tautomeric with compounds **10a**, resp. **10b**.

The high reactivity of the 6-oxo group of [1,2,4]triazine skeleton is in agreement with our previous results dealing with the cyclization reactions of some hydrazones leading to the pyrazolo[4,3-e]1,2,4-triazines[25].

The existence of acidic N-H protons on the 3-substituted-1,5-dihydro[1,2,4] triazino[6.5-b]quinoline system causes also the equilibrium between tautomeric forms **9a** and **10a**, resp. **9b** and **10b**.

We also tried to prepare the 3-phenyl-4-(2-aminobenzylidene)-4,5-dihydrooxazol-5-on **11a** analogously by the aldole condensation of 2-phenyl-4,5-dihydrooxazol-5-one **4a** with 2-aminobenzaldehyde **1** in pyridine. It was not possible to isolate the azlactone **11a** because it had recyclized very easily to the isomeric 3-benzoylamino-1,2-dihydro-quinoline-2-one **12a** which Martinez et al.[26] had already synthetised by different way.

We did not engaged in the probleme of the geometric isomery of the compounds **5a**, **5b** and **6a**, **6b** because the course of hydrazinolysis of azlactones **5a**, **5b** and alkaline cyclization of hydrazides **6a**, **6b** does not depend on it.

The tricyclic products of the cyclocondensation may theoretically exist in 1,5-, resp. 5,10- dihydro tautomeric forms. It was not possible to determine between 1,5-dihydro (**9a** resp. **9b**) and 5,10-dihydro tautomeric forms (**10a** resp. **10b**) from the results of NMR spectroscopy. The signal of the methylene group on position 5- however eliminates other possible tautomeric forms.

Apparatus and methods

Melting points were determined on a Boetius block and are uncorrected. Infrared spectra were measured in KBr disks and scanned on an ATI Unicam Genesis FTIR instrument and values are described in cm $^{-1}$. Elemental analyses were performed by using an EA 1108 Elemental Analyzer (Fison Instrument). The ^{1}H NMR spectra were recorded using a Bruker AMX 300 NMR spectrometer. MS spectra were measured on ZAB-EQ (VG Analytical Ltd., England).

Experimental

2-Phenyl-4-(2-acetylaminobenzylidene)-4,5-dihydrooxazol-5-one (5a)

Method a) The mixture of **1**[27] (1.00 g, 8.2 mmol), **3a** (1.55 g, 8.50 mmol), anhydrous sodium acetate (0.71 g, 8.50 mmol) and acetic anhydride (5.0 ml) was refluxed for 2 hours on boiling water bath. After cooling and 5 hours standing at room temperature the yellow precipitate was filtered off with suction, washed with acetic acid (1.0 ml) and 2 times with ethanol (3.0 ml). The product was recrystallized from ethanol. Yield: 2.20 g (88 %).

Method b) The procedure is the same as in *a)*, instead of **1**[27], acetylaminoderivative **2**[28] (1.32 g, 8.2 mmol) is used. Yield: 2.13 g (85 %).

Method c) Compound **4a**[23] (1.82 g, 11.30 mmol) was dissolved in dry pyridine (7.5 ml) and **2** (1.85 g, 11.30 mmol) was added. The reaction mixture was mixed for 3 hours at room temperature. It was then poured over crushed ice (50 g). After melting of ice the brown crystalline mass was filtered off and washed 3 times with ice water (10.0 ml). It was recrystallized from ethanol. All methods give the same compounds. Their identity was confirmed by the comparision of the IR and ^{1}H NMR spectroscopies, melting point and measuring the mixed melting point. Yield: 2.69 g (78 %), mp 196-199 °C; IR (cm^{-1}):3278, 3067, 2928, 2850, 1793, 1659, 1524, 1448, 1323, 1296, 1170, 983; ^{1}H NMR data (DMSO): 2.18(s, 3H, CH_3); 7.41(s, 1H, =CH); 7.43(m,2H, ArH); 7.56(m, 2H, ArH); 7.69(m, 2H, ArH); 7.77(m, 1H, ArH); 8.19(m, 2H, ArH); 8.83(d, 1H, J=8,0); 10.13(s, 1H, NH); *Anal.* Calcd. for $C_{18}H_{14}N_2O_3$ (305.32); 70.58 %C; 4.61 %H; 9.15 %N. Found: 70.42 %C; 4.94 %H; 9.19 %N.

2-Methyl-4-(2-acetylaminobenzylidene)-4,5-dihydrooxazol-5-one (5b)

Method a) The mixture of **1**[27] (3.25 g, 26.5 mmol), **3b** (3.15 g, 27.0 mmol), anhydrous sodium acetate (2.25 g, 27.0 mmol) and acetic anhydride (12.0 ml) was refluxed for 2 hours on boiling water bath. After cooling to room temperature and 12 hours standing at 5°C was the yellow solid form filtered off with suction and washed 3 times with water (5.0 ml). The product was recrystallized from ethylacetate. Yield: 1.88 g (29 %).

Method b) The procedure is the same as in *a)*, instead of **1**[27], acetylaminoderivative **2**[28] (4.27 g, 26.5 mmol) is used. Yield: 2.27 g (35 %).

Method c) The mixture of **4b**[24] (0.99 g, 10.0 mmol) and **2**[28] (1.61 g, 10.0 mmol) was refluxed for 1,5 hour in dry pyridine (5.0 ml). After cooling to room temperature the reaction mixture was poured over crushed ice (35 g). The solid browny precipitate was filtered off with suction and washed 3 times with ice water (5.0 ml). The compound was recrystallized from ethylacetate.

Yield: 1.37 g (56 %), mp 194-196°C; IR (cm^{-1}): 3275, 3039, 1814, 1664, 1579, 1533, 1463, 1303, 1273, 1168, 903; ^{1}H NMR data (DMSO): 2.12(s, 3H, CH_3); 2.41(s, 3H, CH_3); 7.25(s, 3H, C=H); 7.29(t, 1H, ArH, J=7,2); 7.44-7.56(m, 1H, ArH); 8.57(d, 1H, J=7,2, ArH); 10.04(s,1H, NH); *Anal.* Calcd. for $C_{13}H_{12}N_2O_3$ (244.26); 63.92 %C; 4.95 %H; 11.47 %N. Found: 63.78 %C; 5.03 %H; 10.92 %N.

2-Benzoylamino-3-(2-acetylaminophenyl)acrylic acid hydrazide (6a)

To the mixed suspension of **5a** (2.65 g, 8.7 mmol) in methanol (5.0 ml), 80% hydrazin hydrate (0.60 ml, 9,60 mmol) was slowly added. After 10 minutes the white crystalline mass was filtered off with suction and washed 5 times with water (2 ml). Yield: 2.79 g (95 %), mp: 201-202°C; IR (cm^{-1}): 3352, 3252, 3199, 3028, 2928, 2851, 1671, 1644, 1514, 1474, 1441, 1295, 1269; ^{1}H NMR data (DMSO): 2.13(s, 3H, CH_3); 4.44(s , 2H, NH_2); 7.09(t, 1H, J=7,33, ArH); 7.19(s, 1H, CH); 7.29(t, 1H, J=7.67, ArH); 7.51-7.60(m, 5H, ArH); 7.96(d, 2H, J=7.48, ArH); 9.53(s, 1H, NH); 9.58(s, 1H, NH); 9.87(s, 1H, NH); *Anal.* Calcd. for $C_{18}H_{18}N_4O_3$ (338.38); 63.89 %C; 5.36 %H; 16.56 %N. Found: 64.068%C; 5.24 %H; 16.10 %N.

2-Acetylamino-3-(2-acetylaminophenyl)acrylic acid hydrazide (6b)

To the stirred suspension of **5b** (1.51 g, 7.5 mmol) in methanol (6.0 ml), 80% hydrazin hydrate (0.55 ml, 8.80 mmol) was slowly added. After ten minutes the white crystalline mass was filtered off with suction and washed 3 times with ethanol (2.0 ml). Yield: 1.55 g (75 %), mp162-165°C; IR (cm^{-1}): 3315, 3245, 3060, 2984, 1674, 1523, 1373, 1308; *Anal.* Calcd. for $C_{13}H_{16}N_4O_3$ (276.31); 56.51 %C; 5.84 %H; 20.28 %N. Found: 56.25 %C; 5.55 %H; 20.07 %N.

3-Phenyl-5-(2-acetylaminobenzyl)-1,6-dihydro-1,2,4-triazine-6-one (7a)

The compound **6a** (0.48 g, 1.4 mmol) was refluxed for 5 minutes in 4% sodium hydroxide water solution (8.0 ml). After cooling to room temperature the reaction mixture was acidified with conc.hydrochloric acid to pH=2. The white precipitate was filtered off and washed 2 times with 1ml of water. It was recrystallized from ethanol. Yield of hemihydrate: 0.28 g (72 %), mp 212-214°C; IR (cm^{-1}): 3325, 3039, 2929, 2864, 1694, 1654, 1629, 1584, 1543, 1453, 1303, 1248, 1093; ^1H NMR data (DMSO): 2.04(s, 3H, CH_3); 4.23 (s, 2H, CH_2); 7.20(t, 1H, J=7.5, ArH); 7.28(m, 1H, ArH); 7.40(d, 1H, J=6.5, ArH); 7.49(m, 4H, ArH); 7.56(d, 1H, J=7.5, ArH); 7.98(m, 2H, ArH); 9.51(s, 1H, NH); 13.61(s, 1H, NH); *Anal.* Calcd. for $C_{18}H_{16}N_4O_2.I/2\ H_2O$ (338.37): 65.64 %C; 5.20 %H; 17.01 %N. Found: 65.37 %C; 4.95 %H; 16.72 %N.

3-Methyl-5-(2-acetylaminobenzyl)-1,6-dihydro-1,2,4-triazine-6-one (7b)

The compound **6b** (0.70 g, 2.5 mmol) was refluxed for 5 minutes in 4% sodium hydroxide water solution (3.0 ml). After cooling to room temperature the reaction mixture was acidified with conc.hydrochloric acid to pH 2. The white precipitate was filtered off and washed 3 times with water (1.0 ml). The compound was recrystallized from ethanol. Yield of dihydrate: 0.54 g (73 %), mp 211-214°C; IR (cm^{-1}): 3440, 3230, 3050, 2904, 1694, 1644, 1584, 1533, 1423, 1308, 1153, 978; ^1H NMR data (DMSO): 1.92(s, 3H, CH_3); 2.03(s, 3H, CH3); 2.08(s, 2H, CH_2); 7.13-7.27(m, 2H, ArH); 7.46(d, 1H, J=7.2, ArH); 7.54(d, 1H, J=7.2, ArH); 9.38(s, 1H, NH); 10.78(s, 1H, NH); *Anal.* Calcd. for $C_{13}H_{14}N_4O_2.2H_2O$ (294.33): 53.05 %C; 6.16 %H; 19.04 %N. Found: 53.22 %C; 6.38 %H; 18.99 %N

3-Phenyl-1,5-dihydro[1.2.4]triazino[6,5-b]quinoline (9a) resp. 5,10-dihydrotautomer (10a)

The compound **7a** (0.250 g, 0.78 mmol) was refluxed for 30 minutes in 15% hydrochlorid acid water solution (5.0 ml). After cooling to room temperature the solution was evaporated *in vacuo*. The precipitate was suspended in water (5.0 ml), filtered off with suction and washed two times with water (2.0 ml). The compound was recrystallized from benzene. Yield: 0.210 g (88 %), mp 251-253°C; IR (cm^{-1}): 3070, 1634, 1553, 1488, 1393, 1323, 1233, 1048, 1023; ^1H NMR data ($CDCl_3$): 4.29(s, 2H, CH_2), 7.19-8.32(m, 9H, ArH); MS, *m/z* (rel.int.): 263(M^+), (100); *Anal.* Calcd. for $C_{16}H_{12}N_4$ (262,32): 73.83 %C; 4.65 %H; 21.52 %N. Found: 73.56 %C; 4.88 %H; 21.32 %N

3-Methyl-1,5-dihydro[1.2.4]triazino[6,5-b]quinoline (9b) resp. 5,10-dihydrotautomer (10b)

The compound **7b** (0.250 g, 0.85 mmol) was refluxed for 30 minutes in 15% hydrochlorid acid water solution (5.0 ml). After cooling to room temperature the solution was evaporated *in vacuo*. The precipitate was suspended in water (5.0 ml), filtered off with suction and washed two times with water (2.0 ml). The compound was recrystallized from benzene. Yield: 0.170 g (76 %), mp 222-225°C; IR (cm^{-1}): 3053, 1618, 1553, 1521, 1386, 1209, 1027; ^1H NMR data ($CDCl_3$): 2.08(s, 3H, CH_3), 4.14(s, 2H, CH_2), 7.38-8.56(m, 5H, ArH); MS, *m/z*

(rel.int.): 199(M^+) (100); *Anal.* Calcd. for $C_{11}H_{10}N_4$ (198,24) : 66.65 %C; 5.08 %H; 28.26 %N. Found: 66.37 %C; 5.38 %H; 27.98 %N

3-Benzoylamino-1,2-dihydro-quinoline-2-one (12a)

The mixture of compound **1**[27] (1.38 g, 11.30 mmol) and **4a**[23] (1.82 g, 11.30 mmol) was mixed in dry pyridine (5.0 ml) for 1,5 hour at room temperature. The solvent was then vacuum evaporated and the oily residue was triturated with water (10.0 ml). The white precipitate was filtered off with suction and washed with ice water (5.0 ml). It was not recrystallized. Yield: 2.00 g (67 %), mp 205-207°C, mp (ref.[23]): 205-207°C; IR (cm^{-1}): 3370, 3160, 2864, 1649, 1579, 1543, 1473, 1443, 1398, 1278, 903; ^1H NMR data ($CDCl_3$): 7.32(d, 2H, J=6,6, ArH); 7.49(t, 1H, J=9.0, ArH); 7.55-7.63(m, 3H, ArH); 7.69(m, 1H, ArH); 8.02(m, 2H, ArH); 9.04(s, 1H, CH); 9.31(s, 1H, NH); 10.56(s, 1H, NH); *Anal.* Calcd. for $C_{16}H_{12}N_2O_2 \cdot H_2O$ (264,29): 68.07 %C, 5.00 %H, 9.92 %N. Found: 68.05 %C, 5.34 %H, 10.11%N.

References

(1) Slouka J., *Coll. Czech. Chem. Commun.* **42**, 894 (1977).
(2) Bílek P., Slouka J., *Heterocycl. Commun.* **4**, 325 (1998).
(3) Bílek P., Slouka J., *Heterocycl. Commun.* **5**, 231 (1999).
(4) Bílek P., Slouka J., *Heterocycl. Commun.* **8**, 123 (2002).
(5) Slouka J., Bekárek V., *J. Prakt. Chem.* **316**, 943 (1974).
(6) Doleschall G., Lempert K., *Acta Chim. (Budapest)* **64**, 369 (1970).
(7) Ioffe I.S., Tomchin A.B., *Zh. Obsch. Khim.* **40**, 859 (1970).
(8) Tomchin A.B., Ioffe I.S., *Zh. Org. Khim.* **8**, 1287 (1972).
(9) Tomchin A.B., *Zh. Org. Khim.* **26**, 860 (1990).
(10) Hlaváč J., Slouka J., *Acta Univ. Palacki. Olomuc. Fac. Rer. Nat.* **112**, 97 (1993).
(11) Hlaváč J., Slouka J., *Acta Univ. Palacki. Olomuc. Fac. Rer. Nat.* **117**, 65 (1994).
(12) Hlaváč J., Slouka J., *Coll. Czech. Chem. Commun.* **61**, 941 (1996).
(13) Hlaváč J., Slouka J., *J. Heterocyclic Chem.* **34**, 917 (1997).
(14) Hlaváč J., Slouka J., Hradil P., Lemr K., *J. Heterocyclic Chem.* **37**, 115 (2000).
(15) Hlaváč J., Slouka J., *Acta Univ. Palacki. Olomuc. Fac. Rer. Nat.* **34**, 27 (1995).
(16) Hajpal I., Berenyi E., *J. Heter. Chem.* **19**, 313 (1982).
(17) Slouka J., Bekárek V., Nálepa K., Lycka A., *Coll. Czech. Chem. Commun.* **49**, 2628 (1984).
(18) Slouka J., *Coll. Czech. Chem. Commun.*, **44**, 2438 (1979).
(19) Hejsek M., Slouka J., *Pharamazie* **39**, 186 (1984).
(20) Hejsek M., Slouka J., Bekárek V., Lycka A., *Coll. Czech. Chem. Commun.* **57**, 123 (1992).
(21) Hejsek M., Slouka J., *Pharmazie* **41**, 284 (1986).
(22) Kidwai M., Kohli S., Goel A..K., Dubey M.P., *Ind. J. Chem. Sect. B* **37**, 1063 (1998).
(23) Strukow A.P., *Zh. Obsch. Khim.* **29**, 2359 (1959).
(24) Kumar P., Mukerjee A.K., *Ind. J. Chem. Sect. B* **19**, 704 (1980).
(25) Nálepa K., Slouka J. *Pharmazie* **39**, 504 (1984)
(26) Martinez A.P., Skinner W.A., Lee W.W., Goodman L., Baker B.R., *J. Org. Chem.* **26**, 860 (1961).
(27) Smith L.I., Opie J.W.: *Organic Syntheses Collective Volume* **3**, 56.
(28) Friedlander P., Goehring C.F., *Ber. Dtsch. Chem. Ges.* **17**, 460 (1884).

Received on June 2, 2003.