Cyclocondensation Reaction of Heterocyclic Carbonyl Compounds [1]. The Direction of Competitive Cyclocondensation Between Carbonyl Groups of 6-Azauracile and 1,2-Dihydro-quinoxalin-2-one Cycles.

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Received December 29, 2003

In the article the study of cyclocondensation of 3-[2-amino-3-(3,5-dioxo-2,3,4,5-tetrahydro[1,2,4]-triazine-6-yl)phenyl]-2,3-dihydro-quinoxalin-2-one **5** is described and it was found, that the reaction does not proceed by both possible directions, but only cyclization with the carbonyl group of 6-azauracile cycle proceeds. The 6-(3-oxo-3,4-dihydro-quinoxaline-2-yl)-4*H*-2,3-dihydro[1,2,4]triazino[5,6-*b*]indol-3-one **6** was formed in this way. This course of cyclocondensation was confirmed by the fact, that the product **6**, mentioned above, is quite different from isomeric compound **7**, prepared unambiguously by condensation of 7-(6-azauracile-5-yl)isatine **8** with *o*-phenylenediamine.

J. Heterocyclic Chem., **41**, 597 (2004).

Introduction.

Cyclocondensation reactions of amino group with heterocyclic carbonyl are the subject of our study because of the possibility of their use for preparation of various heterocycles. When only one heterocyclic carbonyl group is able to undergo to cyclocondensation, the product of this reaction can be easily predicted, but there is an interesting question of the direction of the cyclocondensation, if the amino group is able to condense with carbonyl groups belonging to two different heterocycles. For example an amino group affinity of about three times greater for the cyclocondensation reaction with the carbonyl group of 2-thio-6-azauracile-cycle than with that of the carbonyl group of 6-azauracile-cycle has been described earlier [2]. During our study of heterocyclic carbonyl group reactivity, we became very interested in comparison of the carbonyl group reactivity in the 6-azauracile-cycle with that of the heterocyclic carbonyl group in ring systems other than [1,2,4] triazine compounds.

Thus we focused on the study of cyclocondensation of 3-[2-amino-3-(3,5-dioxo-2,3,4,5-tetrahydro[1,2,4]triazine-6-yl)phenyl]-2,3-dihydro-quinoxalin-2-one **5**, in which the amino group is between 6-azauracile and 1,2-dihydro-quinoxalin-2-one cycle.

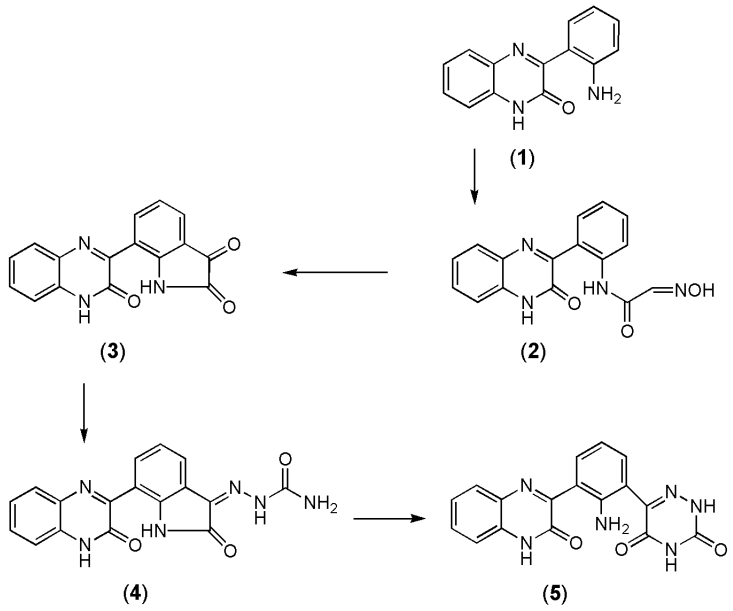

Figure 1.

Results and Discussions.

The starting material for preparation of this compound was 3-(2-aminophenyl)-1,2-dihydro-quinoxalin-2-one **1** [3], which was converted to the corresponding isonitrosoacetanilide **2** by Sandmeyer method. A cyclization of the compound **2** in sulfuric acid afforded 3-(isatine-7-yl)-1,2-dihydro-quinoxalin-2-one **3**. The reaction of the isatine **3** with semicarbazide in acetic acid afforded the corresponding semicarbazone **4**. Compound **4** was recyclized to the 2,6-disubstituted aniline **5** by boiling in alkaline medium.

The cyclocondensation was carried out in boiling acetic acid. Surprisingly we isolated only one product of this reaction, purity of which was declared by NMR and HPLC methods, which means that the cyclization proceeds only one way. Because of theoretically higher sensitivity of carbonyl group in position 5 of the triazine ring in comparison with the carbonyl in the quinoxaline skeleton, it was possible to assume formation of product **6** (Figure 2).

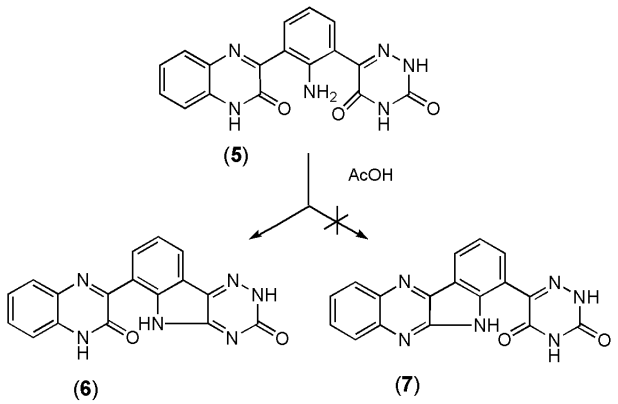

Figure 2

Due to low solubility of the product it was very difficult to recognize, with use of spectral methods, if the product of cyclocondensation is really 6-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-4*H*-2,3-dihydro[1,2,4]triazino[5.6-b]-indol-3-one **6** or an isomeric 4-(3,5-dioxo-2,3,4,5-tetrahydro[1,2,4]triazin-6-yl)-5*H*-indolo[2.3-b]quinoxaline **7** (Figure 3).

Therefore we decided to determine its structure by comparison with product of the condensation of 7-(6-azauracil-5-yl)isatine **8** [4] with *o*-phenylenediamine. The product obtained from this reaction is an isomer with the same elemental analyses and molecular weight but different MS fragmentation, retention time in HPLC analyses, NMR and IR spectra. Because the product could have been **6** or **7** derivative as well, if the reaction had occurred through the opening of the pyrrole ring (known from reaction of isatines and amines [5,6]) with following cyclocondensation of intermediate **5** (Figure 3), we subjected the derivative **5** to cyclization under the same reaction conditions and no reaction was found. It means that reaction of isatine **8** with *o*-phenylendiamine in solution of DMF unambiguously afforded product **7**. The different product of cyclocondensation of compound **5** in acetic acid then possesses the structure **6** (Figure 3).

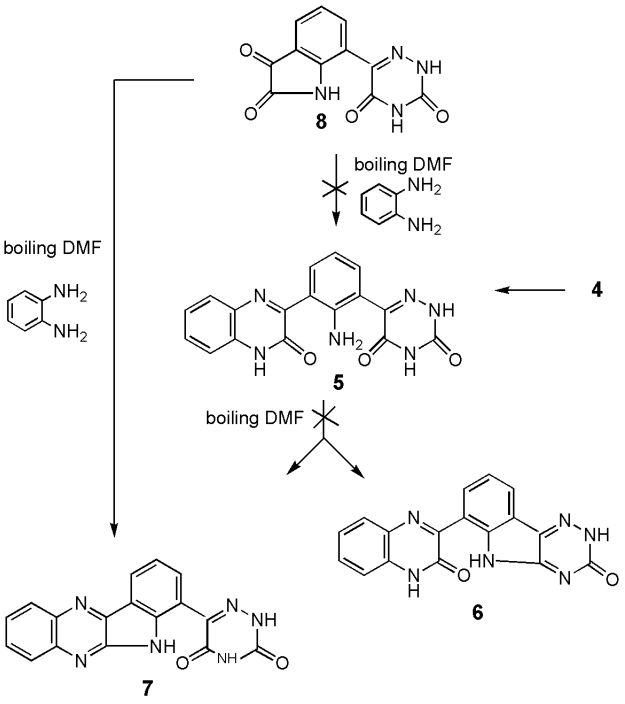

Figure 3

All the prepared compounds are practically insoluble in water and only partially soluble in most organic solvents. They are soluble in hot acetic acid and *N*,*N*-dimethylformamide. These properties aggravated their characterization and study in solution with use of IR and NMR spectroscopy.

EXPERIMENTAL

Melting points were determined on a Boetius stage. Infrared spectra (KBr disks) were taken with an ATI Unicam Genesis FTIR instrument. NMR spectra of solutions in DMSO-d_6 (TMS as internal standard) were measured on a Bruker Avance 300 spectrometer (300 MHz). Mass spectrometric experiments were performed using an LCQ ion trap mass spectrometer (Finnigan MAT, San Jose, CA, USA). Elemental analyses were obtained with an EA 1108 Elemental Analyzer (Fison Instrument). The purity of compounds was confirmed by HPLC analyzer Beckmann System Gold (USA) with Merck Lichrospher RP-select B 250x3 mm, 5µm column on reversed phase C-18, gradient H_2O/methanol.

3-[2-(2-Oximinoacetylamino)phenyl]-1,2-dihydro-quinoxalin-2-one (**2**).

To the solution of 3-(2-aminophenyl)-1,2-dihydro-quinoxalin-2-one (**1**) [3] (15.00 g, 63 mmoles) in a boiling mixture of water (2400 ml) and 37% HCl (45 ml) was added chloralhydrate (12.00 g, 72,6 mmoles) in water (20 ml). After 1 minute a solution of hydroxylamine hydrochloride (16.20 g, 234.8 mmoles) in water (20 ml) was added and the reaction mixture was refluxed for 25 minutes. The next day the solid was collected by filtration, washed with water and dried to yield 13.40 g (69%), mp 260-262°; ir: NH 3282, Ar-H 3003, CO 1669 cm^{-1}; ^1H nmr: δ 7.26 (t, 1H, Ar-H, J= 7.5 Hz), 7.38 (m, 2H, Ar-H), 7.55 (m, 3H, Ar-H, C-H), 7.91 (d, 1H, Ar-H, J= 7 Hz), 8.14 (m, 2H, Ar-H), 11.29 (s, 1H, NH), 12.29 (s, 1H, NH), 12.68 (b, 1H, =NOH); ms: m/z 309 $[M+H]^+$.

Anal. Calcd. for $C_{16}H_{12}N_4O_3$ (308.30): C, 62.34; H, 3.92; N, 18.17. Found: C, 61.94; H, 3.88; N, 17.77.

3-(2,3-Dioxo-2,3-dihydro-indole-7-yl)-2,3-dihydro-quinoxalin-2-one (**3**).

Compound (**2**) (13.39 g, 43.4 mmoles) was added to 89% sulfuric acid (145 ml). The mixture was stirred at 55-60° for 7 hours. Then the mixture was poured onto crushed ice. The next day, the resulting solid was collected by filtration, properly washed with water and dried at 150° to yield 7.00 g (55%). Recrystallization from *N*,*N*-dimethylformamide afforded orange crystals, mp >360°; ir: NH 3320, CO 1743, 1656 cm^{-1}; ^1H nmr: δ 7.20 (t, 1H, Ar-H, J= 7.5 Hz), 7.38 (m, 2H, Ar-H), 7.63 (m, 2H, Ar-H), 7.93 (d, 1H, Ar-H, J= 7.5 Hz), 8.18 (d, 1H, Ar-H, J= 7.5 Hz), 10.89 (b, 1H, NH), 12.58 (b, 1H, NH); ms: m/z 292 $[M+H]^+$.

Anal. Calcd. for $C_{16}H_9N_3O_3$ (291.27): C, 65.98; H, 3.11; N, 14.43. Found: C, 65.70; H, 2.98; N, 13.97.

3-(2-Oxo-3-carbamoylhydrazono-2,3-dihydro-indol-7-yl)-2,3-dihydro-quinoxaline-2-one (**4**).

To the boiling solution of compound (**3**) (500.0 mg, 1.7 mmoles) in acetic acid

(300 ml) semicarbazide hydrochloride (300.0 mg, 2.7 mmoles) was added. The reaction mixture was refluxed for 5 hours. Then the solvent was evaporated to dryness, the solid was then mixed with water (100 ml), collected by filtration and dried to yield 320.0 mg (53.5%), mp >360°; ir: NH 3497, 3230, Ar-H 3009, CO 1740, 1698, 1664 cm^{-1}; ^1H nmr: δ 7.20 (m, 3H, Ar-H, NH_2), 7.35 (m, 2H, Ar-H), 7.57 (t, 1H, Ar-H, J= 7.7 Hz), 7.76 (d, 1H, Ar-H, J= 7.5), 7.95 (m, 2H, Ar-H), 10.91 (b, 1H, NH), 11.75 (b, 1H, NH), 12.54 (b, 1H, NH). ms: m/z 349 $[M+H]^+$.

Anal. Calcd. for $C_{17}H_{12}N_6O_3$ (348.32): C, 58.62; H, 3.47; N, 24.13. Found: C, 57.98; H, 3.40; N, 23.89.

3-[2-Amino-3-(3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazine-6-yl)phenyl]-2,3-dihydro-quinoxalin-2-one (**5**).

Compound (**4**) (100.0 mg, 0.29 mmoles) was refluxed in 10% solution of sodium bicarbonate (20 ml) for 4.5 hours. After cooling, the mixture was filtered then acidified with acetic acid. The resulting powder was collected by filtration after several hours, washed with water and dried at 100° to yield 83.0 mg (83%). Recrystallization from cellosolve afforded yellow crystals, mp >360°; ir: NH 3382, 3251, Ar-H 3041, CO 1730, 1705, 1648 cm^{-1}; ^1H nmr: δ 6.32 (s, 2H, NH_2), 6.65 (t, 1H, Ar-H, J= 8 Hz), 7.23 (d, 1H, Ar-H, J= 6 Hz), 7.32 (m, 2H, Ar-H), 7.53 (t, 1H, Ar-H, J= 8 Hz), 7.78 (d, 1H, Ar-H, J= 8 Hz), 7.95 (d, 1H, Ar-H, J= 6 Hz), 11.96 (s, 1H, NH), 12.35 (s, 1H, NH), 12.50 (s, 1H, NH); ms: m/z 349 $[M+H]^+$.

Anal. Calcd. for $C_{17}H_{12}N_6O_3$ (348.32): C, 58.62; H, 3.47; N, 24.13. Found: C, 59.01; H, 3.42; N, 24.22.

6-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-4*H*-2,3-dihydro-[1,2,4]triazino[5,6-*b*]indol-3-one (**6**).

Compound (**5**) (100.0 mg, 0.29 mmoles) was refluxed in acetic acid (15 ml) for 5 hours. Then the solvent was evaporated with heating to one third of volume and cooled. The yellow crystalline solid was collected by filtration, washed with water and dried to yield 80.0 mg (95%), mp >360°; ir: NH 3285, Ar-H 3007, CO 1686, 1658 cm^{-1}; ^1H nmr: δ 7.37 (m, 3H, Ar-H), 7.60 (t, 1H, Ar-H, J= 7 Hz), 8.00 (m, 2H, Ar-H), 8.18 (d, 1H, Ar-H, J= 7 Hz), 11.85 (b, 1H, NH), 12.70 (b, 1H, NH), 13.05 (b, 1H, NH); ms: m/z 331 $[M+H]^+$. Fragments obtained by collision-induced dissociation of the quasimolecular ions had massed: 313 (11), 303 (100), 286 (25), 275 (56), 260 (12), 248 (51), 245(26).

Anal. Calcd. for $C_{17}H_{10}N_6O_2$ (330.31): C, 61.82; H, 3.05; N, 25.44. Found: C, 61.65; H, 3.01; N, 24.98.

4-(3,5-Dioxo-2,3,4,5-tetrahydro[1,2,4]triazin-6-yl)-5*H*-indolo[2,3-*b*]quinoxaline (**7**).

To the mixture of compound (**8**) (200.0 mg, 0.78 mmoles) [4] in *N*,*N*-dimethylformamide (10 ml) *o*-phenylendiamine (84.0 mg, 0.78 mmoles) was added and the reaction mixture was refluxed for 30 minutes. After cooling, the yellow crystalline solid was collected by filtration, washed with ethanol, water and dried to yield 150.0 mg (58.5%), mp >360°; ir: NH 3296, 2982, CO 1716, 1684 cm^{-1}; 1H nmr: δ 7.45 (t, 1H, Ar-H, J= 8 Hz), 7.79 (m, 2H, Ar-H), 7.94 (d, 1H, Ar-H, J= 7 Hz), 8.10 (d, 1H, Ar-H, J= 7 Hz), 8.29 (d, 1H, Ar-H, J= 8 Hz), 8.45 (d, 1H, Ar-H, J= 7 Hz), 11.85 (s, 1H, NH), 12.27 (b, 1H, NH), 12,49 (b, 1H, NH); ms: m/z 331$[M+H]^+$. Fragments obtained by collision-induced dissociation of the quasimolecular ions had masses: 303 (2), 292 (3), 260 (100), 245 (3), 232(10).

Anal. Calcd. for $C_{17}H_{10}N_6O_2$ (330.31): C, 61.82; H, 3.05; N, 25.44. Found: C, 61.75; H, 3.04; N, 25.05.

Acknowledgements.

Financial support for this work by the Ministry of Education, Youth and Sport of Czech Republic, grant No 15 31 0008 and 15 31 00013, is gratefully acknowledged.

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