Synthesis of Some Isomeric Quinoxaline Derivatives with 6-Azauracil Cycle [1]

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By diazotization of 3-(2-aminophenyl)-1,2-dihydroquinoxaline **1c**, its 3-(4-aminophenyl)-isomer **2c**, 3-(2-aminobenzyl)-1,2-dihydroquinoxaline-2-one **3c** and its 3-(4-aminobenzyl)-isomer **4c** and by azo coupling of formed diazonium salts with ethyl cyanoacetylcarbamate, corresponding hydrazones **1d-4d** were prepared. Cyclization of these compounds afforded compounds containing two heterocyclic rings with acidic N-H groups in their molecules: 3-[2-(5-cyano-6-azauracil-1-yl)-phenyl]-1,2-dihydroquinoxaline-2-one **1e**, its 4-isomer **2e**, 3-[2-(5-cyano-6-azauracil-1-yl)-benzyl]-1,2-dihydroquinoxaline-2-one **3e** and its 4-isomer **4e**. The aminoderivative **1c** was prepared by the reaction of *N*-acetylisatine with *o*-phenylenediamine and by hydrolysis of prepared *N*-acetylderivative **1a**. The aminoderivative **2c** was prepared by the condensation of 4-acetylaminophenylglyoxylic acid with *o*-phenylenediamine and by hydrolysis of prepared *N*-acetylderivative **2a**. The aminoderivative **3c** was prepared by the condensation of 2-nitrophenylpyruvic acid with *o*-phenylenediamine and by the reduction of the formed nitroderivative **3b** and finally starting aminoderivative **4c** was obtained by the condensation of *o*-phenylenediamine with 4-aminophenylpyruvic acid.

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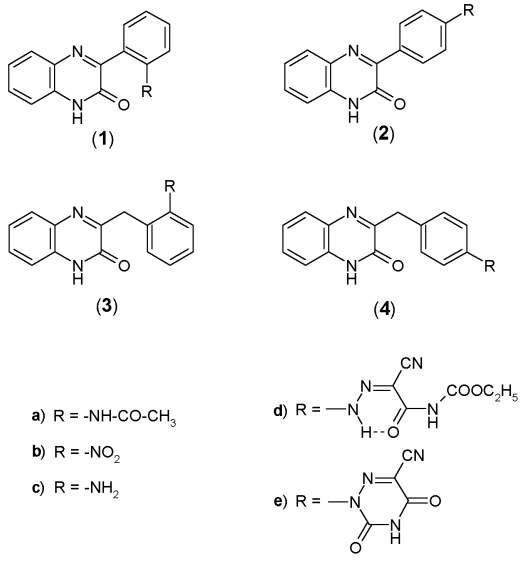
Due to free rotation, non-condensed polynuclear compounds with acidic N-H groups can take up various conformations, which differ in mutual distance of the acidic NH groups. They should be able to interact with biomolecules by means of intermolecular hydrogen bonds on two remote bonding centres and can affect their spatial arrangement.

In the past years we have paid attention to two [2-6] and three-nuclear [6] compounds where the role of heterocycles with acidic N-H groups was played by 6-azauracil cycles.

The subject of this communication is the extension of this area with compounds which, besides the 6-azauracil cycle, contain also the 2-oxo-1,2-dihydro-quinoxaline cycle which have somewhat different N-H groups than 6-azauracil ring. We have focused on the synthesis of compounds where the 2-oxo-1,2-dihydro-quinoxaline cycle is connected in the position 3 with the 6-azauracil cycle by means of either phenyl or benzyl groups (Scheme 1).

Scheme 1

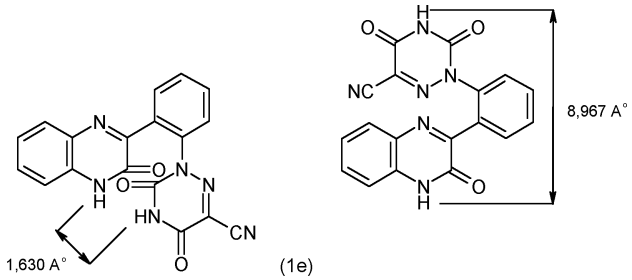


Compounds of this type seem to be very interesting from the view of their possible conformations and the ability to form intermolecular hydrogen bonds with substrates on two bonding centres.

Key intermediates for the synthesis of the mentioned compounds were 1,2-dihydro-quinoxaline-2-ones substituted in the position 3 by 2-aminophenyl **1c**, 4-aminophenyl **2c**, 2-aminobenzyl **3c** or 4-aminobenzyl **4c** group (scheme 1)**.** All of these compounds were further transformed in similar ways. By diazotation of these aminoderivatives and by azo coupling of formed diazonium salts with ethyl cyanoacetylcarbamate in aqueous solution of natrium acetate, the corresponding ethyl arylhydrazono-cyanoacetyl carbamates **1d-4d** were prepared in good yields. By alkaline cyclization of these hydrazones the corresponding substituted 6-azauracils **1e-4e** were easily prepared. Starting aminoderivatives **1c-4c** were prepared in good yields from simple and easily accessible compounds. The compound **1c** was prepared from *N*-acetylisatine by the reaction with *o*-phenylenediamine, according to Schunck and Marchlewski [7] and modified in reference [8], afforded *N*-acetylderivate **1a** which further underwent alkaline hydrolysis. Starting compound for compound **2c** was 4-acetylaminophenylglyoxylic acid, which by the condensation with *o*-phenylenediamine formed *N*-acetylderivative **2a** which further underwent the alkaline hydrolysis. This procedure appeared to be more suitable than the procedure described by Russian authors [9] based on the oxidative arylation of 1,2-dihydroquinoxalin-2-one with aniline. The compound **3c** was prepared by the condensation of *o*-phenylenediamine with 2-nitrophenylpyruvic acid and by the reduction of *o*-nitrobenzylderivative **3b**. The 4-aminobenzylderivative **4c** was prepared by the condensation of *o*-phenylenediamine with 4-aminophenylpyruvic acid.

For all compounds with two heterocyclic rings **1e-4e**, the mutual distance of N-H groups can be continuously changed in a relatively wide range depending on the conformation of

independent cycles. Limiting conformations are planar ones with both minimal and maximal mutual distance of N-H groups. So *e.g.*, the compound **1e** exhibits following limit conformations:



(1e)

(Method of the calculation of distances – see ref. [3])

EXPERIMENTAL

Melting points were determined on a Boetius stage and are not corrected. Infrared spectra were measured in potassium bromide disks and scanned on an ATI Unicam Genesis FTIR instrument. The NMR spectra were measured in DMSO-d_6 solutions on a Bruker AMX-360 spectrometer (360 MHz) with TMS as an internal standard; the reported chemical shifts are in ppm. Elemental analyses were performed by using an EA 1108 Elemental Analyzer (Fison Instrument).

3-(4-Acetylaminophenyl)-1,2-dihydroquinoxaline-2-one (**2a**).

To the solution of *o*-phenylenediamine (216.28 mg; 2.0 mmol) in hot ethanol (3 ml), the solution of *p*-acetylaminophenylglyoxylic acid [10] (414.38 mg; 2.0 mmol) in hot ethanol (8 ml) was added. The reaction mixture was refluxed for 5 minutes. The next day upon cooling, a crystalline compound was collected with suction, washed with water and dried in air to yield (81.5 %) of **2a**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 270-272 °C, ir: 3240 (N-H), 3095 (C-H), 3050 (C-H), 1668 (C=O), 1598 (C=C), 1477 cm^{-1}; ^1H nmr: 2.14 (s, 3H, CH_3), 7.36 (m, 2H, ArH), 7.55 (m, 1H, ArH), 7.74 (d, 2H, J=8.82, ArH), 7.85 (d, 1H, J=8.00, ArH), 8.41 (d, 2H, J=8.82, ArH), 10.23 (s, 1H, NH), 12.56 (s, 1H, NH).

Anal. Calcd. For $C_{16}H_{13}N_3O_2$ (279.3): C, 68.81; H, 4.69; N, 15.04. Found: C, 68.70; H, 4.58; N, 15.13.

3-(4-Aminophenyl)-1,2-dihydro-quinoxaline-2-one (**2c**).

The mixture of acetylderivative (**2a**) (12.0g; 10.025 mmol) and the solution of KOH (5.01g; 89.299 mmol) in a mixture of ethanol (25.0 ml) and water (12.5 ml) was heated until a solution formed. The solution was then refluxed for 4 hours. Then, ethanol was evaporated from the reaction mixture by heating on a water bath and the solution was acidified with acetic acid to pH=5. The next day, a yellow crystalline compound was collected with suction, washed with water and dried in air to yield (94.7 %) of **2c**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 197-198 °C (ref. [9] gives mp = 221-223 °C), ir: 3305 (NH_2), 3118, 3100, 3008 (C-H), 1666 (C=O), 1610 (NH_2), 1598 (C=C), 1515 (NO_2), 1473, 1351 (NO_2) cm^{-1}; ^1H nmr: 5.77 (s, 2H, J=5.47, NH_2), 6,67 (d, 2H, J=5.14, ArH), 7.35 (d, 1H, J=7.68, ArH), 7.75 (t, 2H, J=7.70, ArH), 8.33 (d, 2H, J=7.70, ArH), 8.40 (d, 1H, J=5.15, ArH), 12.41 (s, 1H, NH).

Anal. Calcd. For $C_{14}H_{11}N_3O$ (237.26): C, 70.87; H, 4.67; N, 17.71. Found: C, 70.69; H, 4.50; N, 17.49.

3-(2-Nitrobenzyl)-1,2-dihydroquinoxaline-2-one (**3b**).

To the solution of *o*-nitrophenylpyruvic acid [11] (417.6 mg; 1.99 mmol) in ethanol (10 ml) a solution of *o*-phenylenediamine (240.1 mg; 2.24 mmol) in hot ethanol (4 ml) was added. The reaction mixture was refluxed for 5 minutes. Then ethanol was evaporated and water (20 ml) was added to the reaction mixture. The next day, a crystalline compound was collected with suction, washed with water and dried in air to yield (45.7 %) of **3b**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 232-234 °C, ir: 3197, 3114, 1660 (C=O), 1612, 1515 (C=C) cm^{-1}; ^1H nmr: 4.58 (s, 2H, CH_2), 7.24 (t, 1H, J=7.41, ArH), 7.33 (m, 1H, ArH), 7.51 (m, 2H, ArH), 7.62 (m, 2H, ArH), 7.76 (m, 1H, ArH), 8.11 (d, 1H, J=8.11, ArH), 12.51 (s, 1H, NH).

Anal. Calcd. For $C_{15}H_{11}N_3O_3$ (281.27): C, 64.05; H, 3.94; N, 14.94. Found: C, 64.00; H, 3.81; N, 14.98.

3-(2-Aminobenzyl)-1,2-dihydroquinoxaline-2-one (**3c**).

A solution of $FeSO_4 \cdot 7H_2O$ (1.39 g; 5.0 mmol) in water (7 ml) was added to the solution of $Ba(OH)_2 \cdot 8H_2O$ in hot water (15 ml). The mixture of $Fe(OH)_2$ and $BaSO_4$ was quickly collected with suction and washed with hot ethanol. The mixture was added to the solution of 3-(2-nitrobenzyl)-1,2-dihydroquinoxalin-2-one **3b** (140.6 mg; 5.0 mmol) in hot ethanol (30 ml). The reaction mixture was refluxed for 90 minutes on a water bath and then filtered with suction and washed with hot ethanol. The filtrate was evaporated and the solid was mixed with a little water. The compound was collected with suction, washed with water and dried in air to yield (71.6 %) of **3c**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 185-187 °C, ir: 3330 (NH_2), 3154, 2966 (C-H), 1666 (C=O), 1612 (NH_2), 1529 (C=C) cm^{-1}; ^1H nmr: 4.62 (s, 2H, CH_2), 5.21 (s, 2H, NH_2), 7.29 (m, 4H, ArH), 7.50 (t, 2H, J=7.52, ArH), 7.61 (m, 1H, ArH), 7.75 (t, 1H, J=7.51, ArH), 12.47 (s, 1H, NH).

Anal. Calcd. For $C_{15}H_{13}N_3O$ (251.29): C, 71.70; H, 5.21; N, 16.72. Found: C, 71.62; H, 5.29; N, 16.59.

3-(4-Aminobenzyl)-1,2-dihydroquinoxaline-2-one (**4c**).

A solution of *p*-aminophenylpyruvic acid hydrochloride [12] (431.36 mg; 2.0 mmol) in ethanol (40 ml) was added to the solution of *o*-phenylenediamine (216.28 mg; 2.0 mmol) in hot ethanol (8 ml). The reaction mixture was refluxed for 5 minutes and then taken down. The solid was dissolved in water (60 ml) and pH was adjusted to 7 using ammonia solution. The next day, a crystalline compound was collected with suction, washed with water and dried in air to yield (95.6 %) of **4c**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 185-187 °C, ir: 3442, 3330, 3099, 3002, 1666 (C=O), 1612, 1517 cm^{-1}; ^1H nmr: 3.98 (s, 2H, CH_2), 4.93 (s, 2H, NH_2), 6.51 (d, 2H, J=4.43, ArH), 7.02 (d, 2H, J=8.38, ArH), 7.31 (m, 2H, ArH), 7.51 (m, 1H, ArH), 7.76 (m, 1H, ArH), 12.35 (s, 1H, NH).

Anal. Calcd. For $C_{15}H_{13}N_3O$ (251.29): C, 71.70; H, 5.21; N, 16.72. Found: C, 71.62; H, 5.29; N, 16.59.

Ethyl 2-(2-Oxo-1,2-dihydro-quinoxaline-3-yl)-phenylhydrazonocyanoacetylcarbamate (**1d**).

A suspenzion of amino derivative (**1c**) [7,8] (0.48 g; 2.02 mmol) in a mixture of water (35 ml) and HCl (3.0 ml, 37%)

was cooled on an ice bath and treated with a solution of $NaNO_2$ (140.0 mg; 2.0 mmol) in water (4 ml). The suspension dissolved slowly during 35 minutes of stirring. The reaction mixture was filtered from a small amount of indolo[2,3-*b*]quinoxaline and the filtrate was added portionwise to a stirred mixture obtained by dissolving ethyl cyanoacetylcarbamate (0.42 mg; 2.691 mmol) in warm water (110 ml), cooling on an ice bath, adding CH_3COONa (5 g) and crushed ice. The next day, a crystalline compound was collected with suction, washed with water and dried in air to yield (94.1 %) of **1d**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 225-227 °C, ir: 3241 (N-H), 2981 (C-H), 2211 (C≡N), 1776 (C=O), 1743 (C=O), 1652, 1230 (C-O) cm^{-1}; ^1H nmr: 1.29 (t, 3H, J=7.0, CH_3), 4.16 (q, 2H, J=7.0, CH_2), 7.37 (m, 3H, ArH), 7.62 (m, 2H, ArH), 8.00 (d, 1H, J=8.03, ArH), 8.30 (m, 2H, ArH), 10.70 (s, 1H, NH), 12.81 (s, 1H, NH), 12.84 (s, 1H, NH).

Anal. Calcd. For $C_{20}H_{16}N_6O_4 \cdot 1/2H_2O$ (413.39): C, 58.11; H, 4.14; N, 20.33. Found: C, 58.25; H, 4.00; N, 20.01.

Ethyl 4-(2-Oxo-1,2-dihydro-quinoxaline-3-yl)-phenylhydrazonocyanoacetylcarbamate (**2d**).

This compound was prepared analogically to **1d** from amino derivative **2c** by using amino derivative **2c** (0.48 g, 2.02 mmol), HCl (3 ml, 37%), water (45 ml) in the yield (63.3 %) of **2d**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 218-220 °C, ir: 2985 (C-H), 2215 (C≡N), 1776 (C=O), 1704 (C=O), 1666, 1604, 1191 (C-O) cm^{-1}; ^1H nmr: 1.32 (t, 3H, J=7.06, CH_3), 4.25 (d, 2H, J=7.10, CH_2), 7.36 (m, 2H, ArH), 7.57 (m, 1H, ArH), 7.86 (d, 3H, J=8.85, ArH), 8.47 (d, 2H, J=8.90, ArH), 10.68 (s, 1H, NH), 12.31 (s, 1H, NH), 12.59 (s, 1H, NH).

Anal. Calcd. For $C_{20}H_{16}N_6O_4$ (404.38): C, 59.40; H, 3.99; N, 20.78. Found: C, 59.25; H, 3.79; N, 20.59.

Ethyl 2-(2-Oxo-1,2-dihydro-quinoxaline-3-ylmethyl)-phenylhydrazonocyanoacetylcarbamate (**3d**).

This compound was prepared in analogically **1d** from amino derivative **3c** by using amino derivative **3c** (0.5076 g, 2.02 mmol), HCl (3 ml, 37%), water (60 ml) in the yield (69.3 %) of **3d**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 197-198 °C, ir: 3062 (C-H), 2985, 2211 (C≡N), 1772 (C=O), 1720 (C=O), 1658, 1612 cm^{-1}; ^1H nmr: 1.28 (t, 3H, J=7.09, CH_3), 4.21 (d, 2H, J=7.09, CH_2), 4.26(s, 2H, CH_2), 7.23(t, 1H, J=7.39, ArH), 3.36(m, 3H, ArH), 7.47(d, 1H, J= 7.39, ArH), 7.56 (m, 1H, ArH), 7.94 (d, 1H, J=7.88, ArH), 8.02 (d, 1H, J=7.92, ArH), 10.69 (s, 1H, NH), 12.04 (s, 1H, NH), 12.79 (s, 1H, NH).

Anal. Calcd. For $C_{21}H_{18}N_6O_4$ (418.41): C, 60.28; H, 4.34; N, 20.09. Found: C, 60.11; H, 4.29; N, 19.85.

Ethyl 4-(2-Oxo-1,2-dihydro-quinoxaline-3-ylmethyl)-phenylhydrazonocyanoacetylcarbamate (**4d**).

This compound was prepared analogically to **3d** from amino derivative **4c** in the yield (63.3 %) of **4d**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 175-176 °C, ir: 3226 (N-H), 3189, 3056 (C-H), 2983 (C-H), 2904, 2213 (C≡N), 1768 (C=O), 1666, 1610 (C=C), 1200 (C-O) cm^{-1}; ^1H nmr: 1.30 (t, 3H, J=7.06, CH_3), 4.21 (m, 4H, CH_2), 7.31 (t, 2H, J=7.67, ArH), 7.41 (t, 2H, J=8.50, ArH), 7.53 (t, 1H, J=7,14, ArH), 7.68 (d, 2H, J=8.51, ArH), 7,76 (t, 1H, J=7.45, ArH), 10.53 (s, 1H, NH), 12.44 (s, 1H, NH), 12.66 (s, 1H, NH).

Anal. Calcd. For $C_{21}H_{18}N_6O_4$ (418.41): C, 60.28; H, 4.34; N, 20.09. Found: C, 60.35; H, 4.40; N, 20.32.

2-[2-(2-Oxo-1,2-dihydroquinoxaline-3-yl)-phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-carbonitril (**1e**).

A mixture of hydrazone **1d** (0.413 g; 1.0 mmol), Na_2CO_3 (120.0 mg) and water (10 ml) was heated on a boiling water bath until a solution was formed and then for an additional 15 minutes. The solution was then allowed to cool down and acidified with 37% HCl to pH=1. After several hours, the crystalline solid was collected by suction, washed with a little water and dried in air to yield (74.6 %) of **1e**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 178-179 °C, ir: 3448 (N-H), 3220, 3048 (C-H), 2244 (C≡N), 1707 (C=O), 1660 cm^{-1}; ^1H nmr: 7.39 (m, 2H, ArH), 7.70 (m, 5H, ArH), 8.05 (m, 1H, ArH), 12.74 (s, 1H, NH), 12.82 (s, 1H, NH).

Anal. Calcd. For $C_{18}H_{10}N_6O_3$ (358.32): C, 60.34; H, 2.81; N, 23.45. Found: C, 60.29; H, 2.80; N, 23.15.

2-[4-(2-Oxo-1,2-dihydroquinoxaline-3-yl)-phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-carbonitril (**2e**).

This compound was prepared by an analogous procedure as that of **1e** from hydrazone **2d**, by using hydrazone **2d** (0.413g; 1.0 mmol), Na_2CO_3 (120.0 mg), water (15 ml, in a yield (80.6 %) of **2e**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 303-305 °C, ir: 3035 (C-H), 2933, 2244 (C≡N), 1712 (C=O), 1660, 1612 cm^{-1}; ^1H nmr: 7.40 (d, 2H, J=7.75, ArH), 7.60 (m, 3H, ArH), 7.91 (d, 1H, J=7.80, ArH), 8.48 (m, 2H, ArH), 12.68 (s, 1H, NH), 12.71 (s, 1H, NH).

Anal. Calcd. For $C_{18}H_{10}N_6O_3$ (358.32): C, 60.34; H, 2.81; N, 23.45. Found: C, 60.29; H, 2.74; N, 23.52.

2-[2-(2-Oxo-1,2-dihydroquinoxaline-3-ylmethyl)-phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-carbonitril (**3e**).

This compound was prepared by an analogous procedure as that of **1e** from hydrazone **3d** in the yield (78.3 %) of **3e**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 165-166 °C, ir: 3068, 3009 (C-H), 1750 (C=O), 1655, 1600, 1549 cm^{-1}; ^1H nmr: 4.15 (s, 2H, CH_2), 7.31 (m, 2H, ArH), 7.45 (m, 2H, ArH), 7.55 (t, 3H, J=7.20, ArH), 7.64 (d, 1H, J=6.60, ArH),12.47 (s, 1H, NH), 13.08 (s, 1H NH).

Anal. Calcd. For $C_{19}H_{12}N_6O_3$ (372.34): C, 61.29; H, 3.25; N, 22.57. Found: C, 61.18; H, 3.17; N, 22.30.

2-[4-(2-Oxo-1,2-dihydroquinoxaline-3-ylmethyl)-phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-carbonitril (**4e**).

This compound was prepared analogically to **1e** from hydrazone **4d** in the yield (76.0 %) of **4e**. Recrystallization from ethanol and water (1:1 v/v) afforded the yellow solid, mp = 190-191 °C, ir: 3100, 3079, 3024 (C-H), 1736 (C=O), 1666, 1600 cm^{-1}; ^1H nmr: 4.34 (s, 2H, CH_2), 7.40 (m, 4H, ArH), 7.68 (m, 4H, ArH), 12.55 (s, 1H, NH), 13.18 (s, 1H NH).

Anal. Calcd. For $C_{19}H_{12}N_6O_3$ (372.34): C, 61.29; H, 3.25; N, 22.57. Found: C, 61.00; H, 3.30; N, 22.19.

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