Cyclocondensation Reactions of Heterocyclic Carbonyl Compounds VII[‡] Synthesis of some substituted benzo-[1,2,4]triazino[2,3-a]benzimidazoles.

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Abstract

In this communication we describe synthesis of new heterocyclic condensed compounds that have not been described so far as benzo[e][1,2,4]triazino[2,3-a]benzimidazole and its isomeric benzo[g] condensed system.

The main principle of the synthesis is the cyclocondensation reaction of isomeric derivatives 1-(1-amino-2-naphtyl)-6-azauracil **4** and 1-(2-amino-1-naphthyl)-6-azauracil **13** to the corresponding 3-oxo-3,4-dihydro-benzo[e][1,2,4]triazino[2,3-a]benzimidazol-2-carbonitrile **5** or 3-oxo-3,4-dihydro-benzo[g][1,2,4]triazino[2,3-a]benzimidazol-2-carboxylic acid **14** respectivelly. Isomeric carboxylic acid 6 was obtained by acidic hydrolysis of carbonitrile **5**. Substituted 6-azauracils **4** and **13** were prepared from 1-nitro-2-naphthylamine 1 via hydrazones **2** and 11 that have been cyclized to the substituted 6-azauracils 3 and **12**.

Introduction

Condensed benzo derivatives of [1,2,4]triazino[2,3-a]benzimidazole belonged to never been described compounds. They can be interesting from the view of their possible DNA intercalation. Some derivatives of related [1,2,4]triazino[4,3-a]benzimidazole system act as benzodiazepine receptor ligands (2) and also as A_1 adenosine receptor antagonists (3).

From the group of possible derivatives of the above described compounds, in this communication we focused with the synthesis of benzo[e][1,2,4]triazino[2,3-a]benzimidazole and isomeric benzo[g][1,2,4]triazino[2,3-a]benzimidazole derivatives.

Results

Cyclocondensation of corresponding isomeric aminonaphthyl-6-azauracils was choosen as the most suitable route leading to above described compounds.

The starting compound for both mentioned condensed systems was 1-nitro-2-naphthylamine 1. The usage of this compound was in its diazotisation and coupling with ethyl cyanoacetylcarbamate leading to the corresponding hydrazone **2**. This hydrazone was thermaly cyclized to the 1-(1-nitro-2-naphthyl)-6-azauracil-5-carbonitrile **3** by boiling in xylene solution. The compound was reduced to the aminoderivative **4**. Cyclocondensation of amine **4** to the desired 3-oxo-3,4-dihydro-benzo[e][1,2,4]triazino[2,3-a]benzimidazol-2-carbonitrile **5** was achieved by boiling in acetic acid solution for a few hours. Nitrile **5** was then hydrolyzed to the corresponding acid **6** by boiling in hydrochloric acid/acetic acid solution.

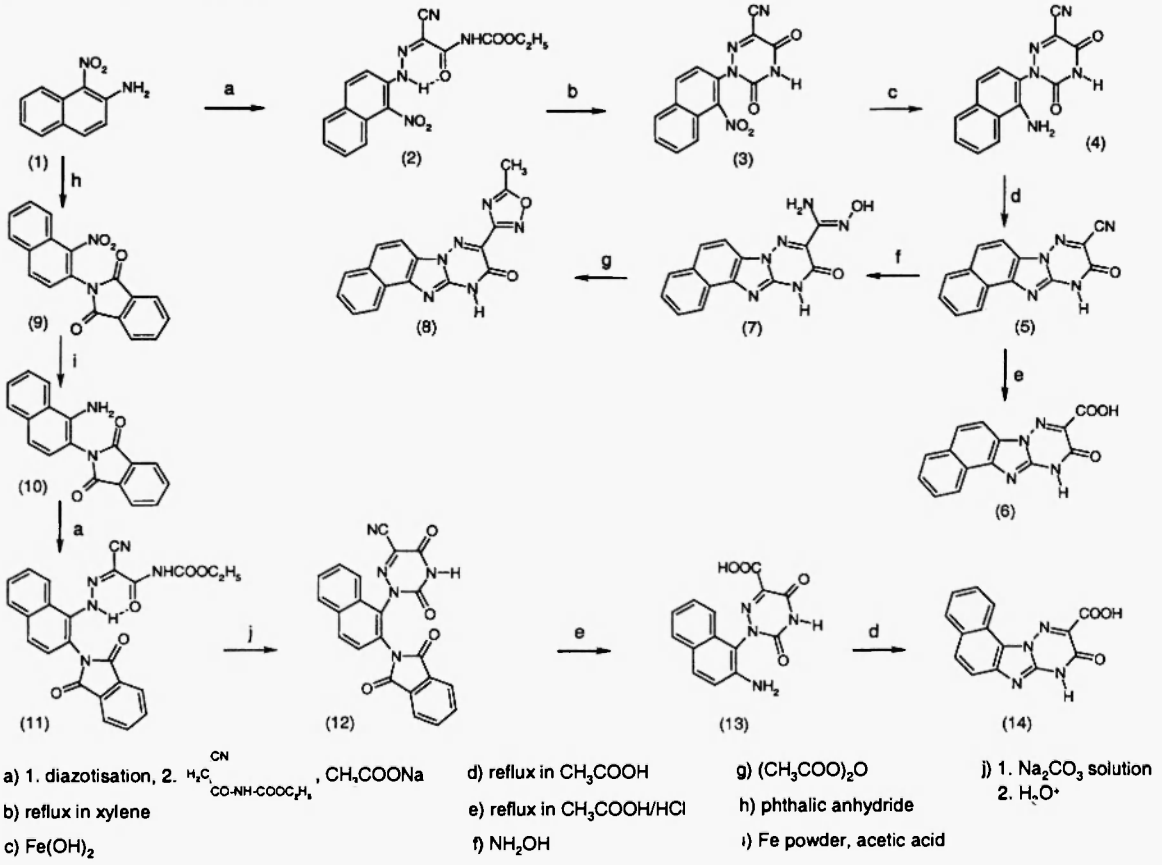
The route leading to the isomeric benzo[g] derivatives was more complicated. In this case, the amino group of amine 1 was protected by phthalylation according to (4) and leading to the derivative **9** that was then reduced to the 2-phthalimido-1-naphthylamine **10** by iron powder according to (5). Diazotisation and further coupling of **10** with ethyl cyanoacetylcarbamate afforded corresponding hydrazone **11** in a good yield. This hydrazone was cyclized to the 1-(2-phthalimido-1-naphthyl)-6-azauracil-5-carbonitrile **12** in sodium carbonate solution at room temperature. The protecting phthalimido group was removed by acidic hydrolysis in boiling HCl. During this process, a nitrile group of derivative **12** was also hydrolysed to the carboxylic group and amino

[‡] Part VI: see ref. (1)

derivative **13** was thus obtained. Cyclocondensation of derivative **13** was achieved again by boiling in acetic acid solution. We obtained 3-oxo-3,4-dihydro-benzo[e][1,2,4]triazino[2,3-a]benzimidazol-2-carboxylic acid **14** that is isomeric with the acid **6**.

Nitrile **5** was also used for preparation of 1,2,4-oxadiazole derivative **8** that was prepared via amidoxime derivative **7** by boiling in acetanhydride/acetic acid solution. Amidoxime **7** was prepared from nitrile **5** by reaction with hydroxylamine.

Compounds **5**, **6**, **7**, **8** and **14** are presented in their 3,4-dihydro tautomeric forms although 3,5-dihydrotautomeric forms are also possible (6).



Apparatus and methods

The melting points were determined on a Boetius stage and are not corrected. The infrared spectra were measured using KBr disc technique and scanned on an ATI Unicam Genesis FTIR instrument. Wavenumbers are reported in cm^{-1}. Elemental analyses were performed using an EA 1108 Elemental Analyser (Fison Instrument). NMR spectra were measured on a Bruker AMX-360 spectrometer (360 MHz) in DMSO-d_6; the chemical shifts δ are reported in ppm with respect to the signal of residual DMSO-d_5 and coupling constants J are in Hz.

Experimental

Ethyl-1-nitro-2-naphtylhydrazonocyanoacetylcarbamate (**2**)

1-Nitro-2-naphthylamine (7) (940 mg, 5 mmol) was mixed with water (2 ml), sulphuric acid (98%, 1 ml) and acetic acid (98%, 10 ml). After cooling to 0 °C on an ice bath, a solution of sodium nitrite (330 mg, 4.72 mmol) in ice water (6 ml) was slowly added to the reaction mixture. A mixture of amine became a solution during

the addition of the sodium nitrite solution. A solution of diazonium salt was then left to stand for 30 minutes on an ice bath and then was slowly added to the pre-cooled solution prepared in this manner: ethyl cyanoacetyl carbamate (1.05 g, 6.1 mmol) was dissolved in hot water (350 ml) and then cooled down to 5 °C and mixed with sodium acetate (18 g).

After the addition of the whole amount of the diazonium salt solution, the reaction mixture was left to stand overnight at 0-5 °C. The next day, the precipitated solid was collected by suction, washed thoroughly with water and dried in air.

For further details, see tables **1**, **2** and **3**.

2-(1-Nitro-2-naphthyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (3)

A solution of hydrazone **2** (178 mg, 0.5 mmol) in xylene (25 ml) was refluxed for 50 hours. Then, the reaction mixture was taken down *in vacuo*. The residue was mixed with a little benzene an collected by suction.

The solid was then mixed with $NaHCO_3$ (60 mg, 0.7 mmol) and water (15 ml). The mixture was left to stand for a few hours at 40°C and then filtered. The filtrate was slowly acidified with diluted HCl (7%). Precipitated solid was collected by suction, washed with water and dried in air.

This compound was recrystallized from ethanol/water mixture.

For further details, see tables **1**, **2** and **3**.

2-(1-Amino-2-naphthyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**4**)

A solution of $FeSO_4.7H_2O$ (2,225 g, 8 mmol) in water (8 ml) was added to the warm solution of $Ba(OH)_2.8H_2O$ (2,525 g, 8 mmol) in water (18 ml). The mixture of precipitated $Fe(OH)_2$ and $BaSO_4$ was added in small portions to the solution of nitro triazine **3** (309 mg, 1 mmol) and ammonia (25%, 0,4 ml) in water (7 ml). The reaction mixture was then heated for 5 minutes at 60 °C and then on a boiling water bath for 60 minutes with continuous stirring. Hot reaction mixture was then filtered and the precipitate was washed thoroughly with a warm ammonia solution (1%). Combined filtrates were then taken down *in vacuo*. The residue was mixed with little warm water, ammonia and charcoal and resulting solution was filtered. The filtrate was then acidified with acetic acid (98%). The next day the precipitated solid was collected by suction, washed with water and dried in air.

This compound was recrystallized from ethanol/water mixture.

For further details, see tables **1**, **2** and 3.

3-Oxo-3,4-dihydro-benzo[*e*][1,2,4]-triazino[2,3-*a*]benzimidazol-2-carbonitrile (**5**)

A solution of amino triazine 4 (297 mg, 1 mmol) in acetic acid (98%, 18 ml) was refluxed for 10 hours and then taken down on a boiling water bath. The residue was mixed with little water and the precipitate was collected by suction, washed with water and dried in air.

This compound was recrystallized from acetic acid.

For further details, see tables **1**, **2** and 3.

3-Oxo-3,4-dihydro-benzo[*e*][1,2,4]-triazino[2,3-*a*]benzimidazol-2-carboxylic acid (**6**)

A solution of nitrile **5** (135 mg, 0.5 mmol) in acetic acid (98%, 35 ml) and HCl (36%, 13 ml) was refluxed for 5 hours. Approximatelly after 1 hour, the acid started to precipitate from the reaction solution. After 5 hours, the reaction mixture was taken down *in vacuo*. The residue was mixed with little water and collected by suction, washed with water and dried in air.

This compound was recrystallized from acetic acid.

For further details, see tables **1**, **2** and **3**.

3-Oxo-3,4-dihydro-benzo[*e*][1,2,4]-triazino[2,3-*a*]benzimidazol-2-carboamidoxime (**7**)

A solution of nitrile **5** (135 mg, 0.5 mmol) and ammonia (25%, 3 ml) in water (6 ml) was mixed with a solution of $NH_2OH.HCl$ (150 mg, 2.16 mmol) in a little water. Resulting dark red solution was left to stand for 4

days with an intermitent stirring. Then, little charcoal was added and the mixture was filtered. Filtrate was acidified with acetic acid (98%). The precipitated solid was collected by suction, washed with water and dried *in vacuo* over solid KOH.
For further details, see tables **1, 2** and **3**.

2-(5-Methyl-1,2,4-oxadiazol-3-yl)-3,4-dihydro-benzo[e][1,2,4]-triazino[2,3-*a*]benzimidazol-3-one (8)

A solution of amidoxime **7** (151 mg, 0.5 mmol) in acetic acid anhydride (6 ml) and acetic acid (98%, 50 ml) was refluxed for 90 minutes. The color of the mixture changed from red to yellow. Then, little charcoal was added and the mixture was filtered. The filtrate was mixed with water (10 ml) and refluxed for 10 minutes. Then, the solution was taken down *in vacuo* and the residue was mixed with water and collected by suction, washed with water and dried in air.
This compound was recrystallized from acetic acid.
For further details, see tables **1, 2** and **3**.

Ethyl 2-phthalimido-1-naphthylhydrazonocyanoacetylcarbamate (**11**)

2-Phthalimido-1-naphthylamine **10** (5) (144 mg, 0.5 mmol) was mixed with water (1 ml), sulphuric acid (98%, 0.3 ml) and acetic acid (98%, 12 ml). After cooling to 0 °C on an ice bath, a solution of sodium nitrite (40 mg, 0.58 mmol) in ice water (1 ml) was slowly added to the reaction mixture. A solution of diazonium salt was then left to stand for 30 minutes on an ice bath and then was slowly added to the pre-cooled solution prepared in this manner: ethyl cyanoacetyl carbamate (138 g, 0.9 mmol) was dissolved in hot water (110 ml) and then cooled down to 5 °C and mixed with sodium acetate (10 g).

After the addition of the whole amount of the diazonium salt solution, the reaction mixture was left to stand overnight at 0-5 °C. The next day, the precipitated solid was collected by suction, washed thoroughly with water and dried in air.
For further details, see tables **1, 2** and **3**

2-(2-Phthalimido-1-naphthyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**12**)

A solution of hydrazone **11** (455 mg, 1 mmol) and Na_2CO_3 (212 mg, 2 mmol) in water (50 ml) was allowed to stand with intermittent stirring for 10 days. Then, little charcoal was added and the mixture was filtered. Filtrate was slowly acidified with diluted HCl (1:5). Precipitated solid was collected by suction, washed with water and dried in air.
This compound was recrystallized from ethanol/water mixture.
For further details, see tables **1, 2** and **3**.

2-(1-Amino-2-naphthyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic acid (**13**)

A solution of triazine **12** (427 mg, 1 mmol) (in a mixture of HCl (36%, 25 ml) and acetic acid (98%, 25 ml) was refluxed for 6 hours. After addition of little charcoal, the mixture was filtered. The filtrate was taken down *in vacuo*. The residue was mixed with little water, collected by suction, washed with water and dried in air.
This compound was recrystallized from ethanol/water mixture.
For further details, see tables **1, 2** and **3**.

3-Oxo-3,4-dihydro-benzo[*g*][1,2,4]-triazino[2,3-*a*]benzimidazol-2-carboxylic acid (**14**)

A solution of amine (**10**) (158 mg, 0.5 mmol) in acetic acid (98%, 20 ml) was refluxed for 11 hours and then taken down *in vacuo*. The residue was mixed with little water, collected by suction, washed with water and dried in air.
This compound was recrystallized from acetic acid.
For further details, see tables **1, 2** and **3**.

Table 1
Characteristic data of compounds

Compound	M.p. (°C) Yield (%)	Formula M.W.	Elemental analysis (Calculated/Found) % C	 % H	 % N
2	182-185 (dec.) 76.9	$C_{16}H_{13}N_5O_5$ 355.3	54.08 53.86	3.66 3.38	19.71 19.57
3	263-265 69.4	$C_{14}H_7N_5O_4$ 309.2	54.38 54.67	2.28 2.35	22.65 22.21
4	230-233 (dec.) 79.1	$C_{14}H_9N_5O_2.H_2O$ 297.3	56.57 56.43	3.73 3.91	23.56 23.35
5	> 360 84.6	$C_{14}H_7N_5O.½H_2O$ 270.2	62.22 62.26	2.98 2.63	25.91 25.47
6	295-297 (dec.) 92.4	$C_{14}H_8N_4O_3$ 280.3	60.00 60.32	2.88 2.51	19.99 19.72
7	285 (dec.) 95.1	$C_{14}H_{10}N_6O_2.$ ½H_2O 303.3	55.45 55.19	3.66 3.45	27.71 27.42
8	343-345 (dec.) 71.2	$C_{16}H_{10}N_6O_2.$ H_2O 336.3	57.14 57.39	3.60 3.37	24.99 24.66
11	132 (dec.) 81.9	$C_{24}H_{17}N_5O_5$ 455.4	63.30 63.56	3.76 4.00	15.38 14.86
12	155-157 63.7	$C_{22}H_{11}N_5O_4.$ H_2O 427.4	61.83 62.08	3.07 3.27	16.39 16.03
13	243-245 (dec.) 57.4	$C_{14}H_{10}N_4O_4.$ H_2O 316.3	53.17 53.52	3.82 3.67	17.71 17.35
14	262 (dec.) 79.7	$C_{14}H_8N_4O_3$ 280.3	60.00 59.76	2.88 2.67	19.99 19.57

Table 2
^{1}H-NMR spectra of compounds

Compound	^{1}H-NMR spectrum
2	1.33(t, 3H, J=7.1, CH_3); 4.26(q, 2H, J=7.1, CH_2); 7.68(t, 1H, J=7.1, H_6); 7.80(t, 1H, J=7.3, H_7); 7.96(d, 1H, J=8.6, H_5); 8.14(d, 1H, J=8.1, H_8); 8.34(s, 2H, H_3+H_4); 10.32 (s, 1H, NH)
3	7.33(d, 1H, J=8.7, H_3); 7.83(dq, 2H, J=8.6, J=1.8, H_6+H_7); 8.17-8.20(m, 2H, H_4+H_8); 8.34(d, 1H, J=8.2, H_5); 13.25 (br, 1H, NH)
4	6.21(s, 2H, NH_2); 7.17(d, 1H, J=8.7, H_4); 7.27(d, 1H, J=8.7, H_3); 7.52(t, 1H, J=6.9, H_7); 7.58(t, 1H, J=6.9, H_6); 7.85(d, 1H, J=7.6, H_8); 8.25(d, 1H, J=8.2, H_5); 12.99(s, 1H, NH)
5	7.71(t, 1H, J=7.2, H_8); 7.80(t, 1H, J=7.2, H_7); 8.02(q, 2H, J=8.8, H_{11}+H_{10}); 8.19 (d, 1H, J=8.3, H_9); 8.41(d, 1H, J=8.2, H_6)
6	7.72(t, 1H, J=7.7, H_8); 7.82(t, 1H, J=7.7, H_7); 8.08(q, 2H, J=8.5, H_{11}+H_{10}); 8.22 (d, 1H, J=8.1, H_9); 8.46(d, 1H, J=8.1, H_6)
7	6.13(s, 2H, NH_2); 7.66(q, 1H, J=8.2, H_7); 7.76(q, 1H, J=8.2, H_8); 8.00(m, 2H, H_6+H_9); 8.11(s, 1H, ½NH_2); 8.17(t, 1H, J=8.0, H_{11}); 8.42(d, 1H, J=8.3, H_{10}); 8.95(s, 1H, ½NH_2); 10.05(br, 1H, OH)
8	2.78(s, 3H, CH_3); 7.68 (t, 1H, J=7.0, H_8); 7.79(t, 1H, J=7.0, H_7); 8.01(m, 2H, H_6+ H_9); 8.19(d, 1H, J=8.3, H_{11}); 8.44(dd, 1H, J=8.1, J=2.8, H_{10})

11	1.26(t, 3H, J=7.1, CH_3); 4.14(q, 2H, J=7.1, CH_2); 7.68(d, 1H, J=8.7, H_8); 7.75(m, 2H, H_6+H_7); 7.97(m, 4H, $H_{3'}$+$H_{4'}$+$H_{5'}$+$H_{6'}$); 8.13(dd, 2H, J=8.2, H_3+H_4); 8.24(d, 1H, J=8.6, H_5); 9.25(s, 1H, NH); 12.42(br, 1H, NH)
12	7.42(d, 1H, J=6.7, H_8); 7.59-7.65(m, 3H, $H_{3'}$+H_4 +$H_{5'}$); 7.72(t, 1H, J=8.2, H_7); 7.78(d, 1H, J=8.1, $H_{6'}$); 7.94-7.97(m, 2H, H_3+H_4); 8.07(d, 1H, J=8.9, H_5); 8.33(t, 1H, J=7.9, H_6); 13.22(br, 1H, NH)
13	5.96(s, 2H, NH_2); 7.10(d, 1H, J=8.9, H_3); 7.22(t, 1H, J=6.5, H_6); 7.37(m, 2H, H_4+H_7); 7.77(d, 2H, H_5+H_8)
14	7.69(t, 1H, J=8.9, H_{10}); 7.81(d, 1H, J=8.8, H_6); 7.88(t, 1H, J=7.8, H_9); 8.14(d, 1H, J=8.8, H_7); 8.22(d, 1H, J=8.2, H_8); 8.96(d, 1H, J=8.4, H_{11})

Table 3
IR spectra of compounds

Compound	Wavenumbers (cm^{-1})
2	3420, 3255, 3120, 2984, 2219, 1788, 1714, 1624, 1605, 1527, 1486, 1432, 1366, 1294, 1260, 1191, 1154, 1132, 1023, 955, 924, 868, 825, 778, 751, 693, 508
3	3448, 3047, 2845, 2246, 1753, 1716, 1627, 1603, 1531, 1420, 1357, 1322, 1268, 1254, 1201, 1088, 1010, 969, 866, 827, 774, 747, 661, 628, 579, 538, 515, 452
4	3448, 3386, 3062, 2244, 1714, 1636, 1417, 1317, 1187, 1028, 803, 774, 743, 628, 553
5	3065, 2776, 2244, 1660, 1613, 1594, 1510, 1450, 1406, 1319, 1272, 1147, 1100, 944, 878, 806, 779, 558, 452, 418
6	3435, 3041, 1758, 1648, 1577, 1453, 1410, 1395, 1328, 1274, 1124, 1093, 945, 880, 814, 780, 707, 678, 523
7	3304, 1684, 1643, 1612, 1584, 1496, 1392, 1309, 1271, 1180, 1134, 1023, 961, 880, 804, 740, 678, 635, 561, 540, 522, 449
8	3435, 3055, 2929, 1694, 1612, 1592, 1534, 1455, 1412, 1179, 1096, 1036, 989, 906, 881, 807, 753, 677, 542
11	3420, 3375, 3351, 2988, 2214, 1777, 1760, 1734, 1707, 1623, 1602, 1518, 1485, 1428, 1370, 1304, 1261, 1194, 1152, 1021, 958, 922, 827, 773, 690, 572, 509
12	3183, 3062, 2858, 2840, 2250, 1747, 1720, 1698, 1604, 1556, 1533, 1508, 1425, 1361, 1342, 1321, 1274, 1261, 1199, 865, 827, 788, 777, 746, 661, 626
13	3532, 3056, 1752, 1735, 1619, 1604, 1529, 1509, 1434, 1411, 1357, 1342, 1321, 1153, 865, 821, 761, 580
14	3195, 3034, 2824, 1714, 1621, 1519, 1477, 1413, 1393, 1353, 1305, 1269, 1210, 1144, 1114, 856, 806, 786, 750, 728, 688, 626, 578, 522, 463

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