Cyclocondensation Reactions of Heterocyclic Carbonyl Compounds VI[‡] Cyclocondensation of the isomeric 1-(2-aminophenyl)-6-azauracil-5-carboxylic acid N-methylderivatives.

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Abstract

We prepared two isomeric N-methylderivatives of 1-(2-aminophenyl)-6-azauracil-5-carboxylic acid, that means 1-(2-aminophenyl)-3-methyl-6-azauracil-5-carboxylic acid **3** and 1-(2-N-methylaminophenyl)-6-azauracil-5-carboxylic acid **8** and studied their cyclocondensation reaction. We found that the cyclization reaction proceeds easily in both cases. Acid **3** afforded 3-oxo-4-methyl-3,4-dihydro-1,2,4-triazino[2,3-a]benzimidozol-2-carboxylic acid **5** while acid **8** afforded its 5-methyl-3,5-dihydro isomer **9**. The starting acid **3** was obtained from 1-(2-nitrofenyl)-6-azauracil-5-carbonitrile which arose from the nitroacid **2** while the acid **8** was prepared by coupling 2-(N-methyl-N-acetylamino)-benzendiazonium salt with ethyl cyanoacetylcarbamate which afforded hydrazone **6** which was cyclized to the corresponding 1-aryl-6-azauracil-5-carbonitrile **7**. Then this substance **7** was totally hydrolyzed.

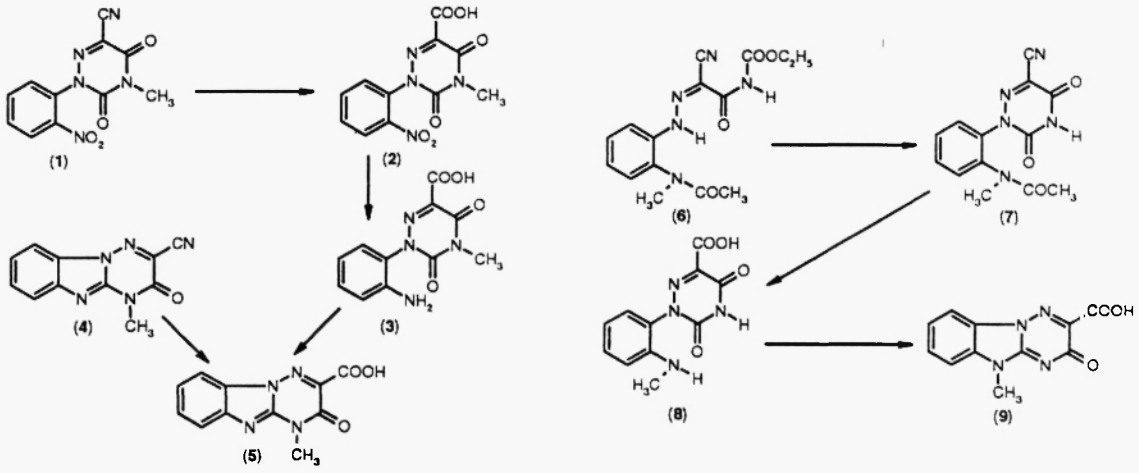
Introduction

In the previous communication **(1)** we were concerned with the study of the cyclocondensation of an amino group with a carbonyl group in position 2 of substituted 3-methyl-6-azauracil. The study of the cyclocondensation of isomeric 1-(2-aminophenyl)-6-azauracil-5-carboxylic acid N-methylderivatives is the object of this communication. In case of 1-(2-aminophenyl)-3-methyl-6-azauracil-5-carboxylic acid **3** no complications during cyclization were expected (according to the previous communication **1**), while in case of isomeric 1-(o-N-methylaminophenyl)-6-azauracil-5-carboxylic acid **8** it was possible to expect complications due to the steric arrangement.

Results

Starting **1**-(2-nitrophenyl)-3-methyl-6-azauracil-5-carboxylic acid **2** was obtained by acidic hydrolysis of corresponding nitrile **1** (**1**). Reduction of the acid **2** to 1-(2-aminophenyl)-3-methyl-6-azauracil-5-carboxylic acid **3** by means of $Fe(OH)_2$ in ethanol proceeded also with good yield. We have found that the cyclocondensation of the acid **3** to 3-oxo-4-methyl-3,4-dihydro-1,2,4-triazino[2,3-a]benzimidazol-2-carboxylic acid **5** proceeds smoothly both by boiling in acetic acid and boiling in anisole under catalysis of p-toluenesulphonic acid. The acid **5** was also prepared by hydrolysis of the appropriate nitrile **4** for comparison **(1)**. The 1-(2-N-methyl-aminophenyl)-6-azauracil-5-carboxylic acid **8**, which is isomeric with **3** was prepared by the following routine: Diazotation of the 2-amino-N-methyl-acetanilide **(2)** and further coupling the diazonium salt with ethyl cyanoacetylcarbamate afforded hydrazone **6** in good yield. This hydrazone was smoothly cyclized to the 1-[2-(N-acetyl-N-methylamino)phenyl]-6-azauracile-5-carbonitrile by boiling in anisole. During hydrolysis of acetyl group we obtained directly 3-oxo-5-methyl-3,5-dihydro-1,2,4-triazino[2,3-a]benzimidazol-2-carboxylic acid **9** without possibility of isolation of compound **8**. This is the evidence of very easy ability of the acid **8** cyclisation.

‡ Part V: see ref. 1



Apparatus and methods

The melting points were determined on a Boetius apparatus and are uncorrected. The IR spectra were measured using KBr disc technique and scanned on an ATI Unicam Genesis FTIR instrument. Elemental analyses were performed by 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 and coupling constants are in Hertz.

Experimental

N-methyl-2-(2-nitrofenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-carboxylic acid (**2**)

A mixture of **1** (150 mg, 0.55 mmol) (**1**), HCl (10 ml, 20%) and acetic acid (5ml) was refluxed 5 hours and then taken down on a water bath. The residue was mixed with water (20 ml) and a small amount of $NaHCO_3$. The solution was filtered and the filtrate was acidified with diluted HCl (1:5). The precipitated solid was collected by suction, washed with water and dried in air.

The compound was purified by recrystallisation from water/acetic acid (1:1)
For further details, see tables **1** and **2**.

N-methyl-2-(2-aminofenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-carboxylic acid (**3**)

a) Reduction in ethanol

A warm solution of $Ba(OH)_2 \cdot 8H_2O$ (3.16 g, 10 mmol) in 30 ml of water was mixed with a solution of $FeSO_4 \cdot 7H_2O$ (2.79 g, 10 mmol) in 15 ml of water. The mixture of precipitated $Fe(OH)_2$ and $BaSO_4$ was collected with suction as quickly as possible, washed with ethanol and added portionwise to a warm solution of **2**·H_2O (328 mg, 1 mmol) in ethanol (30 ml). The reaction mixture was refluxed 90 minutes on a water bath and then filtered. The precipitate was thorougly washed with ethanol. Combined filtrates were taken down *in vacuo*. The residue was mixed with water (20 ml) and after a few hours was collected with suction, washed with water and dried in air.

b) Reduction in ammonia

A solution of $FeSO_4 \cdot 7H_2O$ (1.11 g, 4 mmol) in water (8 ml) was added to a warm solution of $Ba(OH)_2 \cdot 8H_2O$ (1.26 g, 4 mmol) in water (13 ml). The mixture of precipitated $Fe(OH)_2$ and $BaSO_4$ was added

portionwise to the solution of the **2**·H_2O (165 mg, 0.5 mmol) and ammonia (25%, 0.3 ml) in water (10 ml). Then the reaction mixture was heated at 60 °C for 5 minutes and on a boiling water bath for 60 minutes with stirring. The hot reaction mixture was filtered and the precipitate was thoroughly washed with 1% ammonia. Combined filtrates were taken down *in vacuo*. The solid was mixed with a small amount of water, ammonia and charcoal and filtered. The filtrate was carefully acidified with diluted HCl (1:5) to pH 5-6. The next day the precipitated solid was collected with suction, washed with water and dried in air.

The compound was purified by recrystallisation from ethanol/water (1:1).
For further details, see tables 1 and **2**.

3-oxo-4-methyl-3,4-dihydro-1,2,4-triazino[2,3-a]benzimidozole-2-carboxylic acid **(5)**

a) Thermic cyclisation in acetic acid

A solution of amine **3**·½H_2O (50 mg, 0.18 mmol) and acetic acid (10 ml) was refluxed 10 hours and then taken down on a water bath. The solid was mixed with a little water and small amount of $NaHCO_3$. A solution was filtered and the filtrate was acidified with diluted HCl (1:5). The precipitated solid was collected with suction, washed with water and dried in air.

b) Hydrolysis in HCl

A mixture of **4** (40 mg, 0.18 mmol) **(1)** and HCl (12 ml, 20%) was refluxed 5 hours and then taken down on a water bath. The solid was mixed with a little water and small amount of $NaHCO_3$. A solution was filtered and the filtrate was acidified with diluted HCl (1:5). The precipitated solid was collected with suction, washed with water and dried in air.

The compound was purified by recrystallisation from acetic acid.
For further details, see tables 1 and **2**.

Ethyl 2-(N-methyl-N-acetyl)phenylhydrazonocyanoacetyl carbamate **(6)**

Hydrochloric acid (37%, 0.5 ml) was added to a solution of 2-amino-N-methylacetanilide (**2**) (100.0 mg, 0.61 mmol) in water (5 ml). A solution of $NaNO_2$ (46.3 mg, 0.67 mmol) in ice-cold water (1.0 ml) was added dropwise at 0-5 °C. After 20 minutes the solution of diazonium salt was added to a pre-cooled solution of ethyl cyanoacetylcarbamate (0.19g, 1.2 mmol) and sodium acetate (1g) in water (60 ml). The reaction mixture was left to stand at 0-5 °C. The next day the precipitated solid was collected by suction, thoroughly washed with water and dried in air.

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

2-(N-methyl-N-acetylphenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile **(7)**

A solution of **6** (100.0 mg, 0.3 mmol) in dry anisole (10 ml) was refluxed 48 hours and then taken down *in vacuo*. The solid was mixed with water (10 ml) and a small amount of $NaHCO_3$. The mixture was filtered and the filtrate was acidified with diluted HCl (1:8) to pH 6-7. Precipitated solid was collected with suction, washed with water and dried in air.

The compound was purified by recrystallisation from ethanol.
For further details, see tables 1 and **2**.

3-oxo-5-methyl-3,5-dihydro-1,2,4-triazino[2,3-a]benzimidazol-2-carboxylic acid **(9)**

A solution of triazine **7** (120 mg, 0.42 mmol) in diluted HCl (10ml, 1:1) was refluxed 3 hours and then taken down on a water bath. The residue was mixed with little water and the precipitated solid was collected with suction, washed with water and dried in air.
The compound was purified by recrystallisation from ethanol/water (1:1).

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

Table 1
Characteristic data of compounds

Compound	M.p. (°C) Yield (%)	Formula M.w.	Elemental analysis (Calculated/Found) % C	% H	% N	ν(C=O) cm^{-1}	ν(CN) cm^{-1}
1	see ref. (1)	$C_{11}H_7N_5O_4$ 273.1					
2	98-100	$C_{11}H_8N_4O_6.H_2O$ 310.2	42.59 42.59	3.25 3.21	18.06 17.97	1754, 1722 1669	
3	233-235 (d.) 81.4[a], 72.3[b]	$C_{11}H_{10}N_4O_4.½H_2O$ 271.2	48.70 48.52	4.06 3.75	20.66 20.40	1720 1681	
4	see ref. (1)	$C_{11}H_7N_5O$ 225.2					
5	223-225 (d.) 78.2[c], 71.2[d]	$C_{11}H_8N_4O_3.1½H_2O$ 271.2	48.52 48.54	4.05 3.64	20.58 20.21	1736, 1709 1684	
6	167-169 94.2	$C_{15}H_{17}N_5O_4$ 331.3	54.38 54.69	5.14 4.85	21.15 20.97	1779	2206
7	314-315 (d.) 81.3	$C_{13}H_{11}N_5O_3$ 285.3	54.74 55.01	3.89 4.01	24.55 24.35	1744 1715	2246
9	229-230 (d.) 74.2	$C_{11}H_7N_5O$ 225.2	52.18 51.91	3.58 3.59	22.13 21.93	1754	

Note: [a] reduction in ethanol [b] reduction in ammonia [c] cyclisation in acetic acid [d] hydrolysis in HCl

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

Compound	^{1}H-NMR spectrum
2	3.27(s, 3H, CH_3); 7.79(d, 1H, J=7.9, H_6); 7.85(t, 1H, J=7.9, H_4); 8.02(t, 1H, J=7.8, H_5); 8.27(d, 1H, J=8.1, H_3)
3	3.24(s, 3H, CH_3); 5.45(br, 2H, NH_2); 6.60(dt, 1H, J=7.7, J=1.3, H_5); 6.78(dd, 1H, J=8.1, J=1.3, H_3); 7.13(dd, 1H, J=7.8, J=1.5, H_6); 7.17(dt, 1H, J=7.5, J=1.6, H_4)
5	3.60(s, 3H, CH_3); 7.39(dt, 1H, J=7.4, J=1.1, H_7); 7.45(dt, 1H, J=7.4, J=1.2, H_8); 7.71(d, 1H, J=7.5, H_6); 7.82(d, 1H, J=8, H_9)
6	1.31(t, 3H, J=7.1, CH_3); 1.79(s, 3H, CH_3); 3.11(s, 3H, CH_3); 4.23(q, 2H, J=7.1, CH_2); 7.31(t, 1H, J=7.3, H_4); 7.42(d, 1H, J=7.3, H_6); 7.51 (t, 1H, J=8.6, H_5); 8.08 (d, 1H, J=8.2, H_3); 10.61(s, 1H, NH); 11.17(s, 1H, NH)
7	1.76(s, 3H, CH_3); 3.01(s, 3H, CH_3); 7.58-7.70(br, 4H, ar. H); 13.16(s, 1H, NH)
9	3.76(s, 3H, CH_3); 7.53(t, 1H, J=7.8, H_7); 7.62(t, 1H, J=7.7, H_8); 7.83(d, 1H, J=8.1, H_6); 7.94(d, 1H, J=8.0, H_9)

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References
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