Cyclocondensation Reactions of Heterocyclic Carbonyl Compounds IX‡ Synthesis of some derivatives of 6,7,8-trimethoxy-(1,2,4)triazino[2.3-a]benzimidazole

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Abstract

The diazotation of 2-nitro-3,4,5-trimethoxyaniline and coupling of obtained diazonium salt with ethyl cyanoacetylcarbamate afforded the corresponding hydrazone **1** which was cyclized to 1-(2-nitro-3,4,5-trimethoxyphenyl)-6-azauracil-5-carbonitrile **2**. This derivative was reduced to the corresponding amino derivative **3** which then underwent a cyclocondensation and was transformed into 3-oxo-3,4-dihydro-6,7,8-trimethoxy-(1,2,4)-triazino[2.3-a]benzimidazol **4a** or its 3,5-dihydro tautomer respectively **5a**. The corresponding acid **4b** or **5b** was obtained by the acidic hydrolysis of the cyano group.

Introduction

Derivatives of (1,2,4)-triazino[2.3-a]benzimidazol belong to the group of heterocyclic compounds that are interesting for their biological activity. These compounds create a new class of benzodiazepine receptor ligands[1]. Within the group, selective A_1 adenosine receptor ligands[2] and also aldose reductase inhibitors[3] were found.Due to the fact that the structural changes of compounds with known biological activity belong to the progressive method for the search for new, more efficient compounds[4] we turned in this communication our attention to the synthesis of structurally related compounds derived from isomeric (1,2,4)-triazino[2.3-a]benzimidazol system which is in the scope of our research for a long time[5-7]. At this time we focused with the synthesis of compounds containing 3 vicinal methoxy groups in their molecule which can be also interesting for their biological activity. This arrangement of 3 vicinal methoxygroups can be found in a series of various biologically active compounds like many 3,4,5-trimethoxyphenyl derivatives (e.g. mescaline, peyonine, podophylotoxine, reserpine, combrestatin, trimethoprim, colchicine) or heterocyclic compounds substituted with three vicinal methoxy groups like muscle relaxant Nuromax[8] and some other derivatives of isochinoline with with three vicinal methoxylic groups[9] or 6,7,8-trimethoxychinazoline antihypertensive trimazosine[10]. Significant group is also created by compounds containing 5,6,7-trimethoxyindole group like duocarmine A[11-15] and SA[16,17] that are DNA minor groove binding agents and attract great attention at this time[18,19]. The great attention is at the moment also paid to the various analogues of combrestatine that are inhibitors of tubuline polymerization[20].

Results

The starting material for the synthesis of compounds mentioned above was 2-nitro-3,4,5-trimethoxyaniline which was obtained in the way described in literature[21,22].

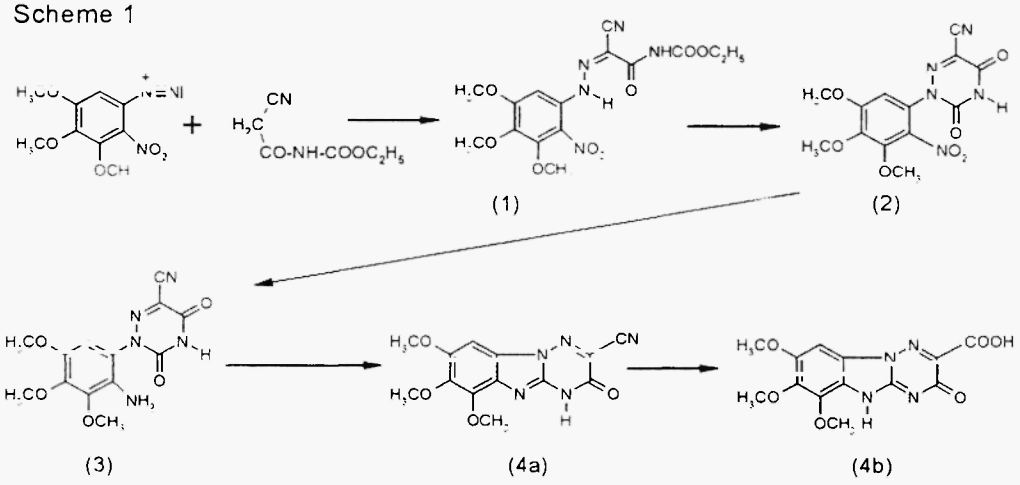
Diazotation of that amine and coupling of obtained diazonium salt with ethyl cyanoacetylcarbamate in a water solution of natrium acetate afforded corresponding hydrazone **1** in a good yield. Alkaline cyclization afforded 1-(2-nitro-3,4,5-trimethoxyphenyl)-6-azauracil-5-carbonitril **2** smoothly. The attempt to prepare this compound by nitration of 1-(3,4,5-trimethoxyphenyl)-6-azauracil-5-carbonitrile[23] failed. In the next step, the nitro group of that compound was reduced to the corresponding aminoderivative **3**. For that purpose, the reduction with $Fe(OH)_2$ in ammonia solution appeared to be the best. Cyclocondensation of amino compound to the corresponding 3-oxo-6,7,8-trimethoxy-3,4-dihydro-(1,2,4)triazino[2.3-a]benzimidazol-2-carbonitrile **4a** was

‡ Part VIII: see T. Gucky J. Slouka and I. Wiedermannova Heterocycl. Commun., in press

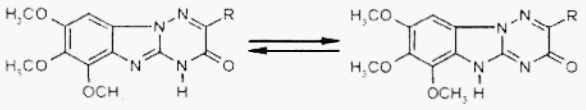
achieved by boiling of its solution in acetic acid and proceeded in the same way like other cyclocondensations of that type[6-8]. By boiling in a water solution of hydrochloric acid, nitrile **3a** was hydrolyzed to the corresponding acid **4b** (Scheme 1).

Beside here described 3,4-dihydro tautomeric forms **4a** and **4b**, it is also possible to consider 3,5-dihydro tautomeric form **5a** or **5b** for these compounds (Scheme 2). This tautomeric equilibrium is very fast as it can be concluded from 1H-NMR spectra where only one broad NH signal can be found at ambient temperature.

Scheme 1



Scheme 2



a) R=CN
b) R=COOH

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 in cm^{-1}. Elemental analyses were performed by using an EA 1108 Elemental Analyser (Fison Instrument). NMR spectra were measured on a Bruker AMX-360 (360 MHz) and Varian Unity+ 300 (300 MHz) spectrometers in DMSO-d_6 solutions; the chemical shifts δ are reported in ppm.

Experimental

Ethyl 2-nitro-3,4,5-trimethoxyphenylhydrazonocyanoacetylcarbamate **(1)**

2-nitro-3,4,5-trimethoxyaniline[21,22] (228 mg, 1 mmol) was dissolved in a mixture of water (15 ml) and hydrochloric acid (37%, 5.5 ml) and cooled to 0 °C on an ice bath. A solution of sodium nitrite (70 mg, 1.02 mmol) in ice water (1 ml) was then added drop wise to the solution of amine. 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 cyanoacetylcarbamate (200 mg, 1.16 mmol) was dissolved in hot water (75 ml) and then cooled down to 5 °C and mixed with sodium acetate (7 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 and **2**.

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

A solution of hydrazone 1 (202 mg, 0.5 mmol) and Na_2CO_3 (120 mg, 1.16 mmol) in water (15 ml) was left to stand at room temperature with intermittent stirring for 12 days. Then, the reaction mixture was filtered with charcoal and the filtrate was slowly acidified with diluted HCl (1:5) to pH 1-2. The precipitated solid was collected with suction, washed with water and dried on air.

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

2-(2-Amino-3,4,5-trimethoxyphenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-carbonitrile **(3)**

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 **2** (349 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 an 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 the 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.

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

6,7,8-Trimethoxy-3-oxo-3,4-dihydro-[1,2,4]-triazino[2.3-*a*]benzimidazol-2-carbonitrile **(4a)**

A solution of amino triazine **3** (319 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.

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

6,7,8-Trimethoxy-3-oxo-3,4-dihydro-[1,2,4]-triazino[2.3-*a*]benzimidazol-2-carboxylic acid **(4b)**

A solution of carbonitrile **3** (160 mg, 0.5 mmol) in a mixture of acetic acid (98%, 10 ml) and hydrochloric acid (36%, 10 ml) was refluxed for 3 hours and then taken down *in vacuo*. The residue was mixed with little water and collected with suction, washed with water and dried in air.

The compound was purified by recrystallisation from acetic acid/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	89-92 88.4	$C_{15}H_{17}N_5O_8.½H_2O$ 404.3	44.55 44.44	4.45 4.35	17.32 16.99	1774	2216
2	194-197 66.6	$C_{13}H_{11}N_5O_7$ 349.3	44.70 44.52	3.15 3.45	20.06 19.87	1753 1729	2240
3	255-256 67.8	$C_{13}H_{13}N_5O_5$ 319.3	48.90 48.07	4.07 3.90	21.94 21.69	1716	2242
4a	267 (dec.) 87.9	$C_{13}H_{11}N_5O_4.H_2O$ 319.3	48.90 49.02	4.07 4.37	21.94 21.45	1667	2240
4b	246-247 (dec.) 83.4	$C_{13}H_{12}N_4O_6.H_2O$ 338.3	46.16 46.02	4.17 4.39	16.56 16.27	1748 1702	

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

Compound	^{1}H-NMR spectrum
1	1.30(t. 3H, J=7.2, CH_3); 3.84(s, 3H, OCH_3); 3.96(d, 6H, 2xOCH_3); 4.23(q, 2H, J=7.2, CH_2); 7.28(s, 1H, H_6); 9.68(s, 1H, NH)
2	3.94(s, 3H, OCH_3); 3.95(s, 3H, OCH_3); 4.00(s, 3H, OCH_3); 7.23(s, 1H, H_6)
3	3.70(s, 3H, OCH_3); 3.79(s, 3H, OCH_3); 3.83(s, 3H, OCH_3); 4.98(s, 2H, NH_2); 6.72(s, 1H, H_6); 12.95(s, 1H, NH)
4a	3.84(s, 3H, OCH_3); 3.94(s, 3H, OCH_3); 4.05(s, 3H, OCH_3); 7.33(s, 1H, H_9)
4b	3.86(s, 3H, OCH_3); 3.97(s, 3H, OCH_3); 4.07(s, 3H. OCH_3); 7.28(s, 1H, H_9), 12.37(br, 1H, NH)

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