

SYNTHESIS OF SOME *m*-SUBSTITUTED 1-PHENYL-6-AZAURACILS\*

Jan SLOUKA, Vojtech BEKAREK and Jan HLAVAC

*Department of Analytical and Organic Chemistry,  
Palacky University, 771 46 Olomouc, The Czech Republic*

Received August 30, 1994  
Accepted September 7, 1994

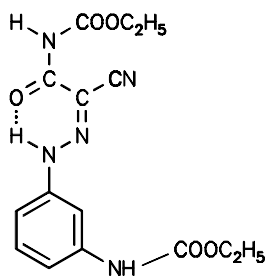
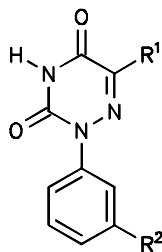
*Dedicated to Professor Milan Kratochvil on the occasion of his 70th birthday.*

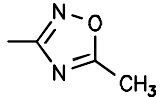
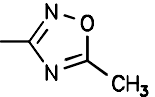
In spite of the fact that anticoccidal effects of many 1-aryl-6-azauracils are known over 20 years<sup>1</sup>, searching of the more effective compounds in this group is still continuing<sup>2,3</sup>. The revival of interest in these compounds have come also with connection of finding out their herbicidal effects<sup>4</sup>.

Many 1-aryl-6-azauracils derivatives were prepared so far, among them the representation of *m*-substituted 1-phenyl derivatives is relatively poor. In this communication we report on the synthesis of the starting material – dicarbamate *I*, which was used for the preparation of some new 1-phenyl-6-azauracil derivatives *II*, containing simple nitrogroup in *m*-position. We focused also on the compounds *III* having two 6-azauracil rings mutually bonded in *m*-position to the benzene ring. These compounds can form hydrogen bonds simultaneously with two bonding centres of fitted substrate and so they can serve as model compounds for the interaction studies. From this type of compounds the dinitrile *IIIa* is known so far<sup>5</sup>.

By diazotiation of ethyl 3-aminophenylcarbamate<sup>6</sup> and subsequent coupling with ethyl cyanoacetylcarbamate the dicarbamate *I* was prepared in good yield. As it exists as (*Z*)-isomer stabilized by intramolecular hydrogen bond<sup>7</sup>, it easily cyclizes to 1-(3-ethoxycarbonylaminophenyl)-6-azauracil-5-carbonitrile (*IIa*). This nitrile, as well as nitriles *IIb*, *IIc* (ref.<sup>5</sup>) served as starting materials for preparation of all other compounds. Thus, by addition of hydrogen sulfide, the nitriles *IIa* and *IIc* were converted to corresponding thioamides *IIe* and *IId*, respectively. Thioamide *IId* was more advantageously obtained directly from nitrile *IIb*, because by the reaction with ammonium sulfide simultaneously proceeds the reduction of the nitro group. 1-(3-Amino-

\* Part XXXVIII in the series On 1-Aryl-6-azauracils; Part XXXVII: Acta Univ. Palacki. Olomuc., Fac. Rerum Nat. 108, 89 (1992).

*I**II**III*

<i>II</i>	R <sup>1</sup>	R <sup>2</sup>	<i>III</i>	R <sup>1</sup>	R <sup>2</sup>
<i>a</i>	CN	NHCOOEt	<i>a</i>	CN	CN
<i>b</i>	CN	NO <sub>2</sub>	<i>b</i>	CN	COOH
<i>c</i>	CN	NH <sub>2</sub>	<i>c</i>	COOH	COOH
<i>d</i>	CSNH <sub>2</sub>	NH <sub>2</sub>	<i>d</i>	H	H
<i>e</i>	CSNH <sub>2</sub>	NHCOOEt	<i>e</i>	C=NOH(NH <sub>2</sub> )	C=NOH(NH <sub>2</sub> )
<i>f</i>	COOH	NO <sub>2</sub>	<i>f</i>		
<i>g</i>	COOH	NH <sub>2</sub>			
<i>h</i>	COOH	NHN=C(CN)CONHCOOEt			

phenyl)-6-azauracil-5-carboxylic acid (*Ilg*) was obtained easily by acidic hydrolysis of nitriles *Ila*, *Ilc* as well as thioamides *Ild* and *Ile* and also by reduction of the nitro acid *Ilf*, which was obtained by acidic hydrolysis of nitrile *Iib*. By diazotiation of amino acid *Ilg* with subsequent coupling with ethyl cyanoacetylcarbamate ethyl 3-(5-cyano-6-azauracil-1-yl)phenylhydrazonocynoacetylcarbamate (*Iih*) was prepared, which was cyclized to 1-[3-(5-cyano-6-azauracil-1-yl)phenyl]-6-azauracil-5-carboxylic acid (*Iib*). This acid was hydrolyzed to form dicarboxylic acid *Iic*, which was obtained also by hydrolysis of dinitrile *Iia*. The acid *Iic* was converted by thermic decarboxylation to 1,1'-(*m*-phenylen)-bis-6-azauracil (*Iid*). By addition of hydroxylamine to dinitrile *Iia* the corresponding diamidoxim *Iie* was obtained. Through boiling with acetic anhydride this compound gave 1,3-bis[5-(5-methyl-1,2,4-oxadiazol-3-yl)-6-azauracil-1-yl]benzene *Iif*. The starting dinitrile *Iia* was obtained according to the described procedure<sup>8</sup>.

## EXPERIMENTAL

The melting points were determined by means of a Boetius apparatus and they are not corrected. The IR spectra ( $\text{cm}^{-1}$ ) were measured with an IR-75 apparatus (Zeiss) using the KBr disc technique.

### Ethyl (*Z*)-3-(Ethoxycarbonylamino)phenyl)hydrazonocynoacetylcarbamate (*I*)

A solution of ethyl *m*-aminophenylcarbamate hydrochloride<sup>6</sup> (2.20 g, 10.2 mmol) in a mixture of water (55 ml) and 37% HCl (5 ml) was cooled in an ice bath and the solution of  $\text{NaNO}_2$  (690 mg, 10.0 mmol) in ice water (8 ml) was added with stirring. The solution was left to stand in ice bath with intermittent stirring for 65 min, whereupon it was added portionwise to a stirred mixture obtained by dissolving ethyl cyanoacetylcarbamate (2.10 g, 13.45 mmol) in warm water (500 ml), cooling in ice bath, adding  $\text{CH}_3\text{COONa}$  (35 g) and crushed ice. The reaction mixture was left at 0 – 5 °C with stirring 24 h. The formed yellow solid was then collected by suction, washed with water and dried in air. Yield 3.34 g (96%) of the compound *I*, m.p. 193 – 195 °C (ethanol). For  $\text{C}_{15}\text{H}_{17}\text{N}_5\text{O}_5$  (347.3) calculated: 51.87% C, 4.93% H, 20.17% N; found: 51.91% C, 4.86% H, 20.15% N. IR spectrum: 1 690, 1 703, 1 762 (CO), 2 212 (CN).

### 2-(3-Ethoxycarbonylamino)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (*Iia*)

*Method A.* A mixture of the dicarbamate *I* (1.05 g, 3.02 mmol),  $\text{Na}_2\text{CO}_3$  (1.05 g) and water (50 ml) was heated on boiling water bath until a solution was formed and then for another 20 min. After addition of a small amount of charcoal the reaction mixture was filtered and acidified by acetic acid to pH 3.5. The next day the formed crystalline solid was collected by suction, washed with water and dried. Yield of the compound *Iia* was 738 mg (81%), m.p. 221 – 223 °C (ethanol–water). For  $\text{C}_{13}\text{H}_{11}\text{N}_5\text{O}_4$  (301.3) calculated: 51.83% C, 3.68% H, 23.25% N; found: 51.55% C, 3.67% H, 23.36% N. IR spectrum: 1 676, 1 685, 1 710, 1 740 (CO), 2 230 (CN).

*Method B.* A mixture of the compound *I* (700 mg, 2.02 mmol) and xylene (60 ml) was refluxed for 50 h, concentrated to ca 15 ml and cooled. The formed crystalline solid was collected by suction, washed with benzene and dried. Yield 583 mg (96%) of the compound *Iia*, m.p. 221 – 223 °C (ethanol–water).

2-(3-Aminophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-carbothioamide (*IId*)

A solution of *IId* (ref.<sup>5</sup>, 500 mg, 1.93 mmol) in 5% aqueous ammonia (20 ml) was saturated for 50 min with hydrogen sulfide, allowed to stand in a stoppered flask at room temperature for 6 days and then evaporated to dryness on the boiling water bath. The residue was treated with 5% aqueous ammonia (30 ml) and after several hours the mixture was filtered and sulfur on filter was repeatedly washed with 2% aqueous ammonia. Combined filtrates were evaporated, the residue was treated with water (3 ml) and acidified with acetic acid to pH 5. After several hours the crystalline solid was collected by suction, washed with water and dried on air. The yield of the compound *IId* monohydrate was 411 mg (76%), m.p. (dec.) 272 – 275 °C (ethanol–water). For C<sub>10</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub>S (281.2) calculated: 42.71% C, 3.94% H, 24.90% N; found: 42.98% C, 3.86% H, 24.71% N. IR spectrum: 1 596 (CO).

2-(3-Ethoxycarbonylamino-phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-carbothioamide (*IIf*)

A solution of the compound *IIf* (305 mg, 1.01 mmol), water (9 ml) and 25% aqueous ammonia (0.5 ml) was saturated with hydrogen sulfide, the mixture was left to stand 4 days in a stoppered flask and then acidified with acetic acid. The next day the formed crystalline solid was collected by suction, washed with water and dried in air. Yield of the compound *IIf* dihydrate was 314 mg (84%), m.p. 206 – 208 °C (ethanol–water). For C<sub>13</sub>H<sub>17</sub>N<sub>5</sub>O<sub>6</sub>S (371.3) calculated: 42.05% C, 5.50% H, 18.86% N; found: 41.81% C, 5.20% H, 18.57% N. IR spectrum: 1 600, 1 710, 1 740 (CO).

2-(3-Nitrophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-carboxylic Acid (*IIf*)

A mixture of the nitrile<sup>5</sup> *IIf* (1.10 g, 4.24 mmol), 37% HCl (32 ml) and water (25 ml) was refluxed for 3 h and cooled. The next day the separated crystalline solid was collected by suction, washed with water and dried in air. The yield of the compound *IIf* monohydrate was 1.035 g (82%). Above the temperature 110 °C the compound loses crystalline water and then melts at 191 – 193 °C. For C<sub>10</sub>H<sub>8</sub>N<sub>4</sub>O<sub>7</sub> (296.2) calculated: 40.55% C, 2.72% H, 18.92% N; found: 40.47% C, 2.77% H, 18.89% N. IR spectrum: 1 610, 1 710 (CO); 1 350, 1 536 (NO<sub>2</sub>).

2-(3-Aminophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic Acid (*IIf*)

*Method A:* A mixture of *IIf* (500 mg, 1.66 mmol), 37% HCl (60 ml) and water (75 ml) was refluxed 5 h and then evaporated to dryness. The residue was treated with water (5 ml) and (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> (75 mg) and the next day crystalline solid was collected by suction, washed with little amount of water and dried in air. The yield of the *IIf* monohydrate was 312.5 mg (71%), m.p. (dec.) 186 – 188 °C (water). The hydrolysis of thioamide *IIf* occurs by the same procedure and the hydrolysis of nitrile *IIf* (ref.<sup>5</sup>) with shorter reaction time (3 h) proceeds as well. For C<sub>10</sub>H<sub>10</sub>N<sub>4</sub>O<sub>5</sub> (266.2) calculated: 45.11% C, 3.79% H, 21.05% N; found: 44.98% C, 3.95% H, 20.90% N. IR spectrum: 1 595, 1 612, 1 690, 1 725 (CO).

*Method B:* A solution of *IIf* (700 mg, 2.36 mmol) in mixture of 25% aqueous ammonia (7 ml) and water (15 ml) was 40 min saturated with hydrogen sulfide. The mixture was left to stand 4 days in stoppered flask and then evaporated on boiling water bath. The residue was treated with mixture of 37% HCl (1 ml) and water (20 ml). Reaction mixture was warmed to about 60 °C, filtered, sulfur on filter was washed with warm water and combined filtrates were evaporated to dryness. The residue was treated with water (4 ml) and pH was adjusted to 3 – 4 by addition of CH<sub>3</sub>COONa. The next day crystalline solid was collected by suction, washed with water and dried on air. The yield of *IIf* monohydrate was 587 mg (93%), m.p. (dec.) 186 – 188 °C (water).

Ethyl (Z)-(3,5-Dioxo-6-carboxy-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl)phenylhydrazono-cyanoacetylcarbamate (*IIIh*)

A solution of *IIg* · H<sub>2</sub>O (545 mg, 2.05 mmol) in mixture of 37% HCl (1.8 ml) and water (16 ml) was cooled in ice bath and diazotized with a solution of NaNO<sub>2</sub> (138 mg, 2.00 mmol) in ice water (4 ml). The solution was left to stand in ice bath with stirring 35 min and then it was added portionwise to a stirred mixture obtained by dissolving ethyl cyanoacetylcarbamate (430 mg, 2.75 mmol) in warm water (85 ml), adding CH<sub>3</sub>COONa (4.0 g) and cooling in ice bath. The reaction mixture was left to stand at 0 – 5 °C with occasional stirring 24 h, acidified to pH 1 and yellow solid was then collected by suction, washed with water, and dried on air. Yield of *IIIh* monohydrate was 764 mg (88%), m.p. 263 – 265 °C (ethanol–water). For C<sub>16</sub>H<sub>15</sub>N<sub>7</sub>O<sub>7</sub> (433.4) calculated: 44.35% C, 3.49% H, 22.63% N; found: 44.08% C, 3.52% H, 22.35% N. IR spectrum: 1 610, 1 690, 1 766 (CO), 2 213 (CN).

1,3-Bis(3,5-dioxo-6-cyano-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl)benzene (*IIIa*)

A mixture of ethyl (3,5-dioxo-6-cyano-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl)phenylhydrazono-cyanoacetylcarbamate<sup>5</sup> (200 mg, 0.505 mmol) and pyridine (15 ml) was refluxed for 24 h and then evaporated to dryness. The residue was treated with water (3 ml) and acidified with 37% HCl to pH 1. After several hours the crystalline solid was collected by suction, washed with water and dried in air. Yield of the *IIIa* monohydrate was 163 mg (88%), after recrystallization from water, m.p. and IR spectrum were identical with the data of this compound prepared before<sup>5</sup>.

2-[3-(3,5-Dioxo-6-cyano-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-carboxylic acid (*IIIb*)

A mixture of *IIIh* · H<sub>2</sub>O (440 mg, 1.02 mmol), Na<sub>2</sub>CO<sub>3</sub> (600 mg) and water (20 ml) was heated on boiling water bath for 25 min. After addition of charcoal the reaction mixture was filtered, concentrated to about 5 ml and acidified to pH 1. After several hours the crystalline solid was collected by suction, washed with water and dried on air. The yield of *IIIb* monohydrate was 318 mg (81%), m.p. 272 – 274 °C (water). For C<sub>14</sub>H<sub>9</sub>N<sub>7</sub>O<sub>7</sub> (387.3) calculated: 43.42% C, 2.34% H, 25.32% N; found: 43.20% C, 2.26% H, 25.22% N. IR spectrum: 1 600, 1 700 (CO), 2 238 (CN). By drying of the monohydrate at 120 °C it was found the weight decrease corresponding to loss of one molecule of water.

1,3-Bis(3,5-dioxo-6-carboxy-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl)benzene (*IIIc*)

A mixture of *IIIb* · H<sub>2</sub>O (200 mg, 0.52 mmol), 37% HCl (20 ml) and water (20 ml) was refluxed for 3 h and cooled. The next day was the solid collected by suction, washed with water and dried on air. The yield of *IIIc* dihydrate was 193 mg (88%), m.p. (dec.) 252 – 254 °C (water). For C<sub>14</sub>H<sub>12</sub>N<sub>6</sub>O<sub>10</sub> (424.3) calculated: 39.63% C, 2.85% H, 19.81% N; found: 39.60% C, 2.71% H, 19.74% N. IR spectrum: 1 700, 1 730 (CO). The same procedure was used for preparation of the compound *IIIc* from the dinitrile *IIIa*.

1,3-Bis(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl)benzene (*IIId*)

The acid *IIIc* · 2 H<sub>2</sub>O (110 mg, 0.26 mmol) was heated at 240 – 260 °C until decarboxylation had ceased. The residue was recrystallized from water with use of charcoal and the filtrate was concentrated to a small volume. The next day the crystalline solid was collected by suction, washed with water and dried on air. Yield of *IIId* dihydrate was 71 mg (82%), m.p. 163 – 165 °C. For

$C_{12}H_{12}N_6O_6$  (336.3) calculated: 42.86% C, 3.60% H, 24.99% N; found: 42.61% C, 3.35% H, 24.72% N. IR spectrum: 1 707 (CO).

1,3-Bis[3,5-dioxo-6-(*N*-hydroxyamidino)-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl]benzene (*IIIe*)

To a solution of the nitrile<sup>5</sup> *IIIa* · H<sub>2</sub>O (190 mg, 0.52 mmol) in 8% aqueous ammonia (15 ml) was added hydroxylamine hydrochloride (280 mg) and the solution was allowed to stand in stoppered flask at room temperature for 10 days. After evaporating under reduced pressure the residue was mixed with a small volume of water and several drops of acetic acid. Next day the crystals were collected by suction, washed with water and air-dried at room temperature. The yield of *IIIe* dihydrate was 177 mg (76%). The compound decomposed above 300 °C and did not melt up to 350 °C. For  $C_{14}H_{16}N_{10}O_8$  (452.4) calculated: 37.17% C, 3.56% H, 30.97% N; found: 37.47% C, 3.40% H, 30.95% N. IR spectrum: 1 705 (CO).

1,3-Bis[3,5-dioxo-6-(5-methyl-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl]benzene (*IIIf*)

To a boiling solution of *IIIe* · 2 H<sub>2</sub>O (120 mg, 0.27 mmol) in acetic acid (7 ml) was added acetanhydride (20 ml) and reaction mixture was refluxed 4 h and then treated with water (20 ml). The next day after addition of a small amount of charcoal the solution was filtered and evaporated to dryness. The residue was mixed with water (3 ml) and the crystals were after several hours collected by suction and dried at 140 °C. Yield 94 mg of the compound *IIIf* (76%), m.p. 343 – 345 °C (water). For  $C_{18}H_{12}N_{10}O_6$  (464.4) calculated: 46.56% C, 2.61% H, 30.23% N; found: 46.41% C, 2.73% H, 30.04% N. IR spectrum: 1 703 (CO).

## REFERENCES

1. Pfizer Ch. and Co., Inc.: Brit. 1 206 698; Chem. Abstr. 74, 53856 (1971).
2. Fukami H., Hashimoto M., Niwata S., Imose S., Kanaguchi H., Takahashi H., Takahashi T.: Eur. Pat. Appl. EP 576 251; Chem. Abstr. 120, 270461 (1994).
3. Cooper Ch. B., Mc Farland J. W., Blair K. T., Fontaine E. H., Jones Ch. S., Muzz M. L.: Bioorg. Med. Chem. Lett. 4, 835 (1994).
4. Lyga J. W., Halling B. P., Witkowski D. A., Patera R. M., Seeley J. A., Plummer M. J., Hotzman F. W. in: *Synthesis and Chemistry of Agrochemicals II* (D. R. Baker, J. G. Fenyes and W. K. Moberg, Eds), ACS Symposium Series 443, p. 170. ACS, Washington D.C. 1991.
5. Slouka J.: Collect. Czech. Chem. Commun. 55, 2967 (1990).
6. Slouka J., Nalepa K.: Z. Chem. 26, 134 (1986).
7. Bekarek V., Slouka J.: Collect. Czech. Chem. Commun. 39, 566 (1974).
8. Slouka J.: Monatsh. Chem. 99, 1808 (1968).

Translated by autor (J. H.).

## Errata:

Slouka J.: Collect. Czech. Chem. Commun. 55, 2967 (1990)  
p. 2973, line 31:  
For "and" read " , 160 ml water and".