

Jan Hlaváč and Jan Slouka*

Department of Organic Chemistry, Palacky University, 771 46 Olomouc, Czech Republic
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5-(2-Aminophenyl)-6-azauracil **1** was converted to 7-(6-azauracil-5-yl)isatin **3**, semicarbazone **4** of which was recycled to 2,6-bis(6-azauracil-5-yl)aniline **5**. This one served as a starting compound for preparation of other noncondensed two nuclear heterocycles **7**, **9**, **10** and condensed 1,2,4-triazines **11** and **12** as well.

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Introduction.

A considerable number of polynuclear heterocyclic compounds are noted for the significant biological activity. Some condensed heterocyclic compounds can be placed in this group. Their cancerostatic and virostatic effect is based especially on intercalation into the double helix of DNA or inhibition of topoisomerase [2-7]. Polynuclear condensed heterocyclic compounds, having in their molecules another noncondensed heterocycle, are interesting as well. This is true of some 7-pyridyl- or 7-pyrazolylindoles, the metallic complexes of which could also intercalate into DNA [8] of pyridazinylbenzimidazoles, which are noted for phosphodiesterase inhibition [9,10].

Within the framework of noncondensed and condensed 1,2,4-triazines research, we turned the attention to some compounds of similar structures.

Results and Discussion.

The starting compound for the synthesis of some polynuclear 1,2,4-triazines was 5-(2-aminophenyl)-6-azauracil **1** [11], which was converted by the Sandmeyer method through the 5-(2-oximinoacetyl-amino-phenyl)-6-azauracil **2** to 7-(6-azauracil-5-yl)isatin **3**. Its semicarbazone **4** was recycled to 2,6-bis(6-azauracil-5-yl)aniline **5** by boiling in alkaline medium. This served as the starting compound for the preparation of some other condensed and noncondensed 1,2,4-triazines **6-12**. Two nuclear non-condensed derivatives were obtained by diazotation. The diazonium salt solution **6** was converted into other products. Coupling of **6** with malondinitrile led to the corresponding hydrazone **7**. The relatively long reaction time of this reaction was caused from steric hindrance of the two neighboring 6-azauracil rings. Nucleophilic substitution in a boiling aqueous solution of diazonium salt **6** led to the formation of 2,6-bis(6-azauracil-5-yl)phenol **9**. Reductive cleavage with hypophosphorous acid of the diazonium salt **6** provided to 1,3-bis(6-azauracil-5-yl)benzene **10**. We had the greatest interest in cyclocondensation reactions leading to condensed

1,2,4-triazines. Refluxing **5** for 2 hours in acetic acid gave 2,3-dihydro-6-(6-azauracil-5-yl)-1,2,4-triazino-[5,6-*b*]indol-3-one (**11**) in good yield. The cyclocondensation of 2-hydrazino-1,3-bis(6-azauracil-5-yl)benzene **8** smoothly provided 7-(6-azauracil-5-yl)-2,3,4,6-tetrahydro-1,2,4-triazino[5,6-*c*]cinnolin-3-one **12**. Compound **12** was also obtained from hydrazone **7**. The attempted cyclization of compound **11** did not provide bis(1,2,4-triazino)[*b,e*]benzo[*g,h*]pyrrolizidine system **13**.

Compound **4** was isolated as a mixture of *syn* and *anti* isomers established from the nmr spectrum, where two sets of aromatic hydrogen signals are apparent. The doublet at 7.75 is attributed to the hydrogen at position 4 of the *syn*-isomer and the doublet at 8.18 is attributed to the hydrogen at position 4 of the *anti*-isomer. The ratio of *syn* and *anti* isomers is 1:5. The nmr spectrum of phenol **9** indicates the presence of two isomers. This might occur from the two triazine rings, one freely rotating and the other triazine ring fixed by intramolecular hydrogen bonding (OH •• N).

EXPERIMENTAL

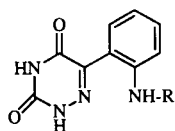
The melting points were determined on a Boetius stage and are not corrected. The infrared spectra were measured in potassium bromide disks and scanned on an ATI Unicam Genesis FTIR instrument. The nmr spectra were measured in solutions in hexadeuteriodimethyl sulfoxide on a Bruker AMX-360 spectrometer (360 MHz); the chemical shifts reported are in ppm. Elemental analyses were performed by using an EA 1108 Elemental Analyzer (Fison Instrument).

6-(2-Oximinoacetylaminophenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (**2**).

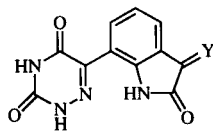
6-(*o*-Aminophenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione **1** (2.05 g, 10 mmoles) was dissolved in a refluxing solution of concentrated hydrochloric acid (1 ml) in water (20 ml). This refluxing mixture was added to the solution of chloral hydrate (1.82 g, 11 mmoles) in water (25 ml). After 1 minute, the solution of hydroxylamine hydrochloride (2.28 g, 32.8 mmoles) in water (10 ml) was added. The mixture was refluxed

for 10 minutes. The next day the solid was filtered and washed with water (1.87 g, 68%). Recrystallization from ethanol afforded orange crystals, mp 243° dec; ir: 3031 (C-H_{arom}), 1696 (C=O), 1650 (C=N); ¹H nmr: δ 7.28 (m, 1H, Ar-H), 7.48 (m, 2H, Ar-H), 7.66 (s, 1H, CH), 7.82 (m, 1H, Ar-H), 9.85 (s, 1H, NH), 12.14 (s, 1H, NH), 12.29 (s, 1H, NH), 12.48 (s, 1H, NH).

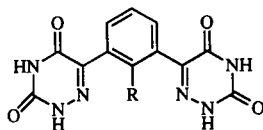
Anal. Calcd. for C₁₁H₉N₅O₄: C, 48.00; H, 3.30; N, 25.45. Found: C, 47.96; H, 3.33; N, 25.00.



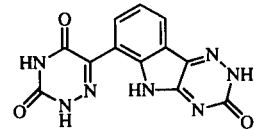
- 1: R = -H
2: R = -CO-CH=N OH



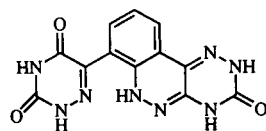
- 3: Y = =O
4: Y = =N-NH-CO-NH₂



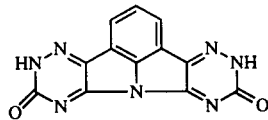
- 5: R = -NH₂
6: R = -N₂⁺
7: R = -NH-N=C(CN)₂
8: R = -NH-NH₂
9: R = -OH
10: R = -H



11



12



13

7-(3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)-2,3-dihydroindole-2,3-dione (3).

Compound 2 (12 g, 43.6 mmol) was slowly added to 89% sulfuric acid (144 ml) at 55-60°. The temperature was maintained for 7 hours. Then the mixture was poured onto ice. The solid was filtered, washed with water and dried at 160° (10.4 g, 92%). Recrystallization from acetic acid afforded a red solid mp >320°; ir: 3332 (NH), 3016 (C-H_{arom}), 1750, 1724, 1699 (C=O), 1605 (C=N); ¹H nmr: δ 7.19 (t, 1H, H₅, J = 8 Hz, Ph), 7.63 (dd, 1H, H₄, J = 1 Hz, J = 7 Hz, Ph), 7.72 (dd, 1H, J = 1 Hz, J = 7 Hz, Ph), 10.91 (s, 1H, N₁-H), 12.22 (br, 1H, N-H), 12.60 (br, 1H, N-H).

Anal. Calcd. for C₁₁H₆N₄O₄: C, 51.17; H, 2.34; N, 21.70. Found: C, 50.99; H, 2.30; N, 21.42.

3-Carbamoylhydrazono-7-(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)-2,3-dihydroindol-2-one (4).

Compound 3 (1.3 g, 5.0 mmol) was dissolved in a refluxing solution of sodium bicarbonate (1.3 g, 12.3 mmol) in water (150 ml). To this solution semicarbazide hydrochloride (0.7 g, 6.3 mmol) was added and the mixture was allowed to stand at

room temperature for two days. The mixture was filtered and the filtrate was acidified with acetic acid to pH 4. After two days the precipitated solid was filtered, washed with water and dried (1.49 g, 95%). Recrystallization from water afforded a yellow solid, mp >320°, ir: 3333 (N-H), 1704 (C=O), 1603 (C=N); ¹H nmr: δ 6.98 (br, 2H, NH₂), 7.16 (m, 1.6 H, H₅, Ph), 7.49 (m, 1.2 H, H₆, Ph), 7.75 (dd, 0.2 H, H₄, J = 1 Hz, J = 8 Hz, Ph), 8.18 (dd, 1H, H₄, J = 1 Hz, J = 8 Hz, Ph).

Anal. Calcd. for C₁₂H₉N₇O₄: C, 45.72; H, 2.87; N, 31.10. Found: C, 45.56; H, 2.63; N, 30.82.

2,6-Bis(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)aniline (5).

Compound 4 (3 g, 9.5 mmol) was refluxed in a 1M solution of sodium hydroxide (50 ml) for 3 hours. After cooling, the mixture was filtered and acidified with acetic acid. The powder was filtered after several hours, washed with water and dried at 100° (2.62 g, 87%). Recrystallization from ethanol afforded a red solid, mp >320°, ir: 3075 (C-H_{arom}), 1737, 1714 (C=O); ¹H nmr: δ 5.45 (br, 2H, NH₂), 6.63 (t, 1H, H₅, J = 8 Hz, Ph), 7.22 (d, 2H, H₄, H₆, J = 8 Hz, Ph), 11.7-12.6 (m, br, 4H, NH).

Anal. Calcd. for C₁₂H₉N₇O₄: C, 45.72; H, 2.87; N, 31.10. Found: C, 45.83; H, 2.66; N, 30.73.

2,6-Bis(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)phenylhydrazonomalonitrile (7).

Compound 5 (1.03 g, 3.3 mmol) was dissolved in a solution of sodium hydroxide (2 g) in water (20 ml) and the sodium nitrite (0.37 g, 5.4 mmol) was added. The solution was cooled to 0-5° and then it was added dropwise to the solution of hydrochloric acid (10 ml) in water (50 ml) cooled to the same temperature and the solution was stirred for several hours. Then it was added to mixture of sodium acetate (20 g, 0.24 mol) and malondinitrile (0.42 g, 6.4 mmol) in water (100 ml) cooled in an ice bath. The pH was brought to 7 by adding sodium carbonate. After two weeks the mixture was acidified with hydrochloric acid and the resulting solid was filtered, washed with water and dried (1.1 g, 85%). Recrystallization from ethanol afforded a brown solid, mp 302° dec ir: 2226, 2218 (CN), 1739, 1718 (C=O); ¹H nmr: δ 7.4-7.7 (m, 3H, H₃, H₄, H₅, Ph), 12.24 (s, 2H, N₂-H), 12.56 (s, 2H, N₄-H).

Anal. Calcd. for C₁₅H₈N₁₀O₄: C, 45.93; H, 2.06; N, 35.70. Found: C, 45.90; H, 1.93; N, 35.33.

2,6-Bis(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)phenol (9).

Compound 5 (1.06 g, 3.4 mmol) was dissolved in a solution of potassium hydroxide (1 g, 17.9 mmol) in water (20 ml) and the sodium nitrite (0.31 g, 4.5 mmol) was added. The mixture was cooled to 0-5° and then it was added dropwise to a cool solution of 10% sulfuric acid (55 ml). The mixture was stirred for two hours at this temperature. The solution was filtered and the filtrate was refluxed for one hour. After cooling, the solid was filtered, washed with water and dried (0.8 g, 74%). Recrystallization from water afforded a slightly yellow solid, mp <320°; ir: 3334 (N-H), 3251 (O-H), 1710, 1678 (C=O); ¹H nmr: δ 6.97 (t, 1H, H₄, J = 8 Hz, Ph), 6.98 (t, 1H, H₄, J = 8 Hz, Ph), 7.40 (d, 2H, H₃, H₅, J = 8 Hz, Ph), 7.41 (d, 2H, H₃, H₅, J = 8 Hz, Ph).

Anal. Calcd. for C₁₂H₈N₆O₅: C, 45.57; H, 2.55; N, 26.58. Found: C, 45.20; H, 2.62; N, 26.10.

1,3-Bis(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)benzene (10).

Compound **5** (1.1 g, 3.5 mmol) was dissolved in a solution of sodium hydroxide (2 g, 50.0 mmol) in water (20 ml) and the sodium nitrite (0.38 g, 5.5 mmol) was added. The mixture was cooled to 0–5°, then added dropwise to the solution of hydrochloric acid (10 ml) in water (50 ml). The mixture was stirred for two hours and hypophosphorous acid (17 ml) was added. After three weeks the solid was filtered, washed with water and dried (0.62 g, 59%). Recrystallization from ethanol afforded red crystals, mp >320°; ir: 3242 (N–H), 3075 (C–H_{arom}), 1690 (C=O), 745, 699 (C–H_{arom}); ¹H nmr: δ 7.55 (t, 1H, H₅, J = 8 Hz, Ph), 8.00 (dd, 2H, H₃, H₅, J = 1 Hz, J = 8 Hz, Ph), 8.42 (s, 1H, H₁, Ph), 12.17 (s, 2H, N–H₂), 12.59 (s, 2H, N–H₄).

Anal. Calcd. for C₁₂H₈N₆O₄: C, 48.01; H, 2.69; N, 27.99. Found: C, 47.89; H, 2.55; N, 27.67.

6-(3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)-2,3-dihydro-1,2,4-triazino[5,6-*b*]indol-3-one (11).

Compound **5** (1.9 g, 6.0 mmol) was refluxed in acetic acid (100 ml) for two hours. After cooling the solid was filtered, washed with water and dried (1.65 g, 93%). Recrystallization from acetic acid afforded a yellow solid, mp >320°; ir: 3336 (N–H), 1724, 1697 (C=O), 1634 (C=N); ¹H nmr: δ 7.37 (t, H₈, J = 8 Hz, Ph), 7.68 (dd, H₇, J = 1 Hz, J = 8 Hz, Ph), 8.01 (dd, H₉, J = 1 Hz, J = 8 Hz, Ph), 11.79 (s, 1H, NH), 12.25 (s, 1H, NH), 12.62 (s, 1H, NH), 13.17 (s, 1H, NH).

Anal. Calcd. for C₁₂H₇N₇O₃: C, 48.49; H, 2.37; N, 32.99. Found: C, 48.15; H, 2.11; N, 32.60.

7-(3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazino-6-yl)-2,3,4,6-tetrahydro-1,2,4-triazino[5,6-*c*]cinnolin-3-one (12).

a) Compound **5** (1.7 g, 5.4 mmol) was dissolved in a solution of sodium hydroxide (1 g, 25 mmol) in water (50 ml). Sodium nitrite (0.43 g, 6.2 mmol) was added. The solution was cooled in an ice bath, it added dropwise to the mixture of hydrochloric acid (10 ml) and acetic acid (10 ml) in water (50 ml)

cooled to 0–5°. The mixture was stirred for several hours at this temperature and then the sodium sulphite heptahydrate (50 g, 198.3 mmol) was added. The solution was allowed to stand in the refrigerator for two days. The mixture was heated to 80° for one hour, acidified with hydrochloric acid to pH 1 and refluxed for 6 hours. After cooling, the solid was filtered, washed with water and dried (1.2 g, 71%).

b) Compound **7** (0.5 g, 1.3 mmol) in mixture of concentrated hydrochloric acid (40 ml), acetic acid (30 ml) and water (25 ml) was refluxed for 10 hours. The solid was filtered, washed with water and dried (0.34 g, 85%). Recrystallization from acetic acid afforded a yellow solid, mp >320°; ir: 3021 (C–H_{arom}), 1770, 1703, 1723 (C=O); ¹H nmr: δ: 7.29 (t, 1H, H₉, J = 8 Hz, Ph), 7.98 (d, 1H, H₈, J = 8 Hz, Ph), 8.05 (d, 1H, J = 8 Hz, Ph), 11.50–13.00 (m, br, 4H, NH).

REFERENCES AND NOTES

- [1] Paper 4 in this series. For the previous paper see: J. Hlaváč and J. Slouka, *Collect. Czech. Chem. Commun.*, **61**, 941 (1996).
- [2] B. C. Baguley, *Anti-Cancer Drug Design*, **6**, 1 (1991).
- [3] R. P. Hertzberg and R. K. Johnson, *Annu. Rep. Med. Chem.*, **28**, 167 (1993).
- [4] R. K. Johnson and R. P. Hertzberg, *Annu. Rep. Med. Chem.*, **25**, 129 (1990).
- [5] M. Binaschi, F. Zunino and G. Capranico, *Stem Cells*, **13**, 369 (1995).
- [6] E. De Clercq, *J. Antimicrob. Chemother.*, **32**, Suppl. A, 121 (1993).
- [7] G. Capranico and F. Zunino, *Curr. Pharm. Des.*, **1**, 1 (1995).
- [8] D. St. C. Black, G. B. Deacon and G. L. Edwards, *Aust. J. Chem.*, **44**, 1771 (1991).
- [9] R. Jonas, M. Klockow, I. Lues, H. Prücher, H. J. Schliep and H. Wurziger, *Eur. J. Med. Chem.*, **27**, 129 (1992).
- [10] R. Jonas, H. Prücher and H. Wurziger, *Eur. J. Med. Chem.*, **28**, 141 (1993).
- [11] G. Doleschall and K. Lempert, *Acta. Chim. (Budapest)*, **64**, 369 (1970).
- [12] T. Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919).