CYCLIZATION REACTIONS OF 2-(6-AZAURACIL-5-YL)BENZOIC ACID AND SOME ITS DERIVATIVES*

Miloslav HEJSEK[a], Jan SLOUKA[a], Vojtěch BEKÁREK[a] and Antonín LYČKA[b]

[a] *Department of Analytical and Organic Chemistry, Palacký University, 771 46 Olomouc*

[b] *Research Institute of Organic Syntheses, 532 18 Pardubice-Rybitví*

Received November, 21, 1990
Accepted May 21, 1991

2-(6-Azauracil-5-yl)benzoic acid (*Ib*) and its 2-thio analogue *Ia* give new heterocyclic compounds, 1,2-dihydro-1,2,4-triazino[5,6-*c*]isocoumarin-3-one (*IVb*) and analogous 3-thione *IVa*, respectively, on treatment with N,N'-dicyclohexylcarbodiimide. A series of substituted 1,2,4-triazino[5,6-*c*]isoquinolines *V*–*XVI* have been prepared from these compounds and from other functional derivatives (*II*, *III*) of the acids *I*.

It is often convenient to synthesize condensed 1,2,4-triazines via condensation reactions of carbonyl groups of compounds with the 6-azauracil cycle. This method was used to synthesize e.g. derivatives of 1,2,4-triazino[2,3-*a*]benzimidazole[1], 1,2,4-triazino[5,6-*b*]indole[2,3], 1,2,4-triazino[5,6-*b*]quinoline[4,5], and derivatives of 1,2,4-triazino[5,6-*c*]cinnoline[6,7]. Derivatives of 1,2,4-triazino[2,3-*a*]quinazoline were obtained by intramolecular condensation of the amidic group of 2-(5-cyano-6-azauracil-1-yl)benzamide with the 2-carbonyl group of 6-azauracil cycle[8]. This cyclization takes place only at enhanced temperatures.

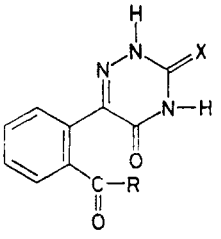
Some time ago we found, on the other hand, that an analogous cyclization of 2-(2-thio-6-azauracil-5-yl)benzamide is so easy that this benzamide was not obtained by amonolysis of methyl 2-(2-thio-6-azauracil-5-yl)benzoate even at mild reaction conditions: the corresponding cyclization product, 3-thioxo-2,3,4,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one, was obtained instead[9]. Similarly it was impossible to trap the respective amide in the reaction of 3-(2-thio-6-azauracil-5-yl)pyridine-2-carboxylic acid with ammonia by action of N,N'-dicyclohexylcarbodiimide: 3-thioxo-2,3,4,6-tetrahydro-1,2,4-triazino[6,5-*f*]-1,7-naphthyridin-6-one was obtained instead[10].

This very smooth course of the cyclizations mentioned initiated a search for other synthetic possibilities in this field. We started from the 2-(2-thio-6-azauracil-5-yl)benzoic acid (*Ia*) prepared in a yield of 64% by a modified method from naphthalene. This 2-thio derivative was oxidized to 2-(6-azauracil-5-yl)benzoic acid (*Ib*).

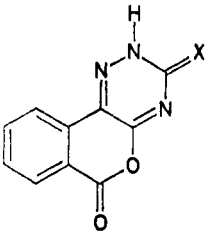
* Part XII in the series on 5-Substitued 6-Azauracils; Part XI: Acta Univ. Palacki. Olomuc., Fac. Rerum Nat. *91*, 203 (1988).

It was interesting to find that also the acids *Ia* and *Ib* themselves are easily cyclized: on treatment with N,N'-dicyclohexylcarbodiimide in boiling dibutyl ether they are lactonized to 2,3-dihydro-1,2,4-triazino[5,6-*c*]isocoumarin-3-thione (*IVa*) and 2,3-dihydro-1,2,4-triazino[5,6-*c*]isocoumarin-3-one (*IVb*), respectively, which represents formation of a new condensed heterocyclic system.

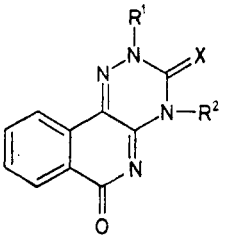
The suggested structure of compounds *IVa* and *IVb* was confirmed by IR and mass spectrometry. The IR spectra show characteristic carbonyl bands of lactam cycles. In the case of compound *IVb* this band is distinctly split into a doublet with maxima at 1 780 and 1 774 cm^{-1}, which is in accordance with previous findings[11].



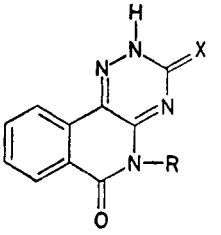
I, R = OH
II, R = OCH_3
III, R = $NHNH_2$



IV



V, $R^1 = R^2 = H$
VI, $R^1 = CH_3$; $R^2 = H$
VII, $R^1 = H$; $R^2 = CH_3$



VIII, R = H
IX, R = CH_3
X, R = C_6H_5
XI, R = NH_2
XII, R = N=CH—C_6H_5

In formulae *I*–*XII*: *a*, X = S *b*, X = O

Both the compounds *IVa* and *IVb* are weak acids dissolving in aqueous alkali hydroxides but not in alkali carbonates. The 1,2,4-triazino[5,6-*c*]isocoumarin system proved to be relatively stable in these compounds. In aqueous alkali hydroxides

the lactone ring is not opened at room temperature even after several hours. Unchanged compounds *IVa* and *IVb* are recovered by acidifying these solutions. The lactone ring is opened only after 30 min boiling in excess alkali hydroxide to give the corresponding acids *Ia* and *Ib*. The lactone ring of compounds *IVa* and *IVb* is also opened by action of ammonia, methylamine, and hydrazine. Only in the hydrazinolysis of compound *IVa* it was possible to trap the intermediate 2-(2-thio-6-azauracil-5-yl)benzhydrazide (*IIIa*). In the reactions with ammonia and with methylamine, however, only the cyclization products of the amides formed could be obtained, i.e. the corresponding derivatives of 1,2,4-triazino[5,6-*c*]isoquinoline *Va* and *Vb* and their 5-methyl derivatives *IXa* and *IXb*, respectively. However, a prolonged reaction of *IVa* with hydrazine produces the cyclization product of hydrazide *IIIa*, i.e. 5-amino derivative *XIa*.

The given series as well as a series of other derivatives of 1,2,4-triazino[5,6-*c*]isoquinoline were also prepared directly from the acids *Ia* and *Ib* or from their methyl esters *IIa* and *IIb*. The esters *IIa* and *IIb* reacted with ammonia to give the respective derivatives of 1,2,4-triazino[5,6-*c*]isoquinoline *Va* and *Vb* directly: it was impossible to trap the intermediate amides. Compound *Va* was prepared in this way earlier[9]. The same result was obtained from the reaction of *Ia* and *Ib* with ammonia in the presence of N,N'-dicyclohexylcarbodiimide.

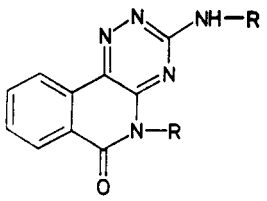
The most characteristic bands in the IR spectra of compounds *Va* and *Vb* are those of carbonyl groups at 1 694 cm^{-1} (*Va*) and at 1 693 and 1 644 cm^{-1} (*Vb*).

With these compounds it is possible to consider both the 2,3,4,6-tetrahydro tautomeric form *V* and 2,3,5,6-tetrahydro tautomeric form *VIII*. With the aim of solving this problem, we synthesized N-methyl derivatives of both these tautomeric forms, i.e. 4-methyl-2,3,4,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinoline-3,6-dione (*VIIb*) and 5-methyl-2,3,5,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinoline-3,6-dione (*IXb*) and the corresponding 3-thio derivative *IXa*. The derivatives *IXa* and *IXb* were obtained both by the reaction of methylesters *IIa*, *IIb* with methylamine and by the reaction of acids *Ia*, *Ib* with methylamine in the presence of N,N'-dicyclohexylcarbodiimide, as well as by the reaction of 1,2,4-triazino[5,6-*c*]isocoumarines *IVa*, *IVb* with methylamine. The 4-methyl derivative *VIIb* was obtained by the methylation of compound *Vb* with methyl iodide in alkaline medium. The structure of this compound *VIIb* follows from the fact that it differs in all its properties from both the other isomeric methyl derivatives *VIb* and *IXb* whose structure was established by their unambiguous synthesis.

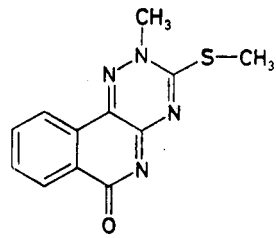
2-Methyl-2,3,4,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinoline-3,6-dione (*VIb*) was obtained by acid hydrolysis of 2-methyl-3-methylmercapto-2,6-dihydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*XVI*) which compound was obtained by methylation of the 3-thio derivative *Va* with two equivalents of methyl iodide in alkaline medium.

Because of the very low solubility of these compounds in aprotic solvents it was impossible to realize the original plan, viz. to establish whether the derivatives of

1,2,4-triazino[5,6-*c*]isoquinoline exist in the 2,3,4,6-tetrahydro tautometric form *V* or in the 2,3,5,6-tetrahydro tautomeric form *VIII*.



XIII, R = C_6H_5
XIV, R = NH_2
XV, R = N=CH—C_6H_5



XVI

In analogy to the above-mentioned failure of trapping of amide or methylamide, the reaction of acid *Ia* with aniline in the presence of N,N'-dicyclohexylcarbodiimide also fails to give the respective anilide, 3-thioxo-5-phenyl-1,3,5,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*Xa*) being obtained instead. Quite similar are also the reactions of acid *Ia* or methyl ester *IIa* with hydrazine hydrate: the reaction product is 3-thioxo-5-amino-1,3,5,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*XIa*) (which was prepared, as already stated, from compound *IVa*). The 5-amino derivative *XIb* was prepared from the methyl ester *IIb* in similar way. The structure of these 5-amino derivatives *XIa* and *XIb* was confirmed by spectral methods and also by formation of hydrazones *XIIa* and *XIIb* obtained by their reaction with benzaldehyde.

If the reaction of methyl ester *IIa* is carried out with excess aniline at boiling temperature, then the cyclization is accompanied by nucleophilic substitution at 3-position to give 3-anilino-5-phenyl-5,6-dihydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*XIII*). Quite similarly the methyl ester *IIa* reacts with excess hydrazine to give 5-amino-3-hydrazino-5,6-dihydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*XIV*), which compound reacts with benzaldehyde with formation of the corresponding bis-hydrazone *XV*.

EXPERIMENTAL

The IR spectra were measured with a Specord IR-75 (Zeiss, Jena) apparatus in KBr pellets; the wavenumbers are given in cm^{-1}. The ^{13}C and ^{15}N NMR spectra were measured with a JNM-PX 100 (JEOL) apparatus at 25·047 and 10·095 MHz, respectively, in the pulse mode with Fourier transform. The chemical shifts are given in ppm (δ-scale). The solutions to be measured were ca 20% (w/v) or saturated (if little soluble) solutions of the compounds in hexadeuteriodimethyl sulfoxide. The ^{13}C chemical shifts were measured in the standard way with the digital

resolution of 1·22 Hz/point. The experimental conditions of measurements of ^{15}N chemical shifts: spectral width 5 000 Hz; 8 K; 45° pulse; 3 s pulse repetition; proton noise decoupling. The ^{13}C chemical shifts were related to the solvent signal (δ 39·6 ppm). The ^{15}N chemical shifts refer to external nitromethane (25% ^{15}N, δ 0·0 ppm). Negative values denote upfield shifts. The melting temperatures were determined with a Boetius apparatus. The hydrates were analyzed by means of thermal gravimetry (TG, DTA) using a Derivatograph OD 102 (MOM Budapest) apparatus using 130—150 mg samples and a temperature increase of 2·5°C min^{-1}.

2-(3-Thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)benzoic Acid (*Ia*)

A) A mixture of 21·3 g (0·166 mol) naphthalene 6·65 g (0·166 mol) sodium hydroxide, and 330 ml water was heated to boiling with intensive stirring, and a solution of 142·9 g (0·90 mol) potassium permanganate in 1 l water was added thereto during 120 min. After the last addition of permanganate the mixture was boiled for another 30 min, and the excess permanganate was removed by addition of 10 ml methanol, whereupon boiling was continued for another 15 min. After cooling, the MnO_2 formed was removed by filtration, thoroughly washed with boiling water, and resuspended in 200 ml boiling water. After filtration, the combined filtrates were concentrated in vacuum to the final volume of 450 ml. Then the reaction mixture was acidified with concentrated hydrochloric acid to pH 2—1. The solution was treated with thiosecmiarbazide (10·0 g, 0·109 mol), and the mixture was left to stand at room temperature 50 h. The separated yellow solid was collected by suction, thoroughly washed with water, and — without drying — transferred into 150 ml 1·5 M NaOH. The homogeneous mixture was refluxed 5 h. After acidification with dilute hydrochloric acid (1 : 1) to pH 2—1 we obtained 17·41 g (64%) acid *Ia*. Recrystallization from ethanol gave a white crystalline solid, m.p. 300—301°C.

B) Compound *IVa* (0·46 g, 2 mmol) was dissolved in a solution of 0·16 g (4 mmol) NaOH in 20 ml water with stirring, and the mixture was refluxed 30 min. After cooling, it was acidified with dilute hydrochloric acid (1 : 1) to pH 2—1. The white crystalline product with m.p. 299—301°C was obtained in quantitative yield.

C) A mixture of 0·26 g (1 mmol) compound *IIIa* and 15 ml dilute hydrochloric acid (1 : 1) was heated on a boiling water bath with stirring 3 h. After cooling and standing in a refrigerator overnight, the separated white crystalline solid was collected by suction, washed with water, and dried in air. The white crystalline product was obtained in quantitative yield and was purified via its sodium salt and recrystallized from ethanol: m.p. 299—301°C. IR spectrum: 1 713, 1 681, 1 272, 1 170. ^{13}C NMR spectrum: 173·9 (CS); 167·7 (COOH); 153·0, 150·9, 132·7, 132·4 (CH); 131·6, 130·5 (CH); 130·2 129·7 (CH). ^{15}N NMR spectrum: −49·8 (=N—), −192·8 (NH), −201·9 (NH). For $C_{10}H_7N_3O_3S$ (249·9) calculated: 48·20% C, 2·83% H, 16·86% N; found: 47·27% C, 2·84% H, 16·78% N.

2-(3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)benzoic Acid (*Ib*)

A) During 2·5 h a warm solution (35—40°C) of 25·3 g (160 mmol) potassium permanganate in 350 ml water was added drop by drop to a solution of 20 g (80 mmol) compound *I a* and 9 g (160 mmol) potassium hydroxide in 350 ml water, whereupon 10 ml methanol was added and the mixture was left to stand 1 h. The separated manganese(IV) oxide was collected by suction, washed with 3 × 50 ml boiling water, and resuspended in 60 ml boiling water, shortly boiled, and again collected by suction. The combined filtrates were also boiled for a short time, and acidified with concentrated hydrochloric acid to pH 1. The white crystalline product, m.p. 298—301°C, was obtained in the yield of 17·5 g (93·5%).

B) Compound *IVb* (0·43 g, 2 mmol) was dissolved in a boiling solution of 0·16 g (4 mmol) sodium hydroxide in 20 ml water, and the solution was refluxed 30 min. After cooling, it was acidified with dilute hydrochloric acid (1 : 1) to pH 2—1. The white crystalline product, m.p. 298—301°C was obtained in a quantitative yield. IR spectrum: 1 729, 1 718, 1 695, 1 271. For $C_{10}H_7N_3O_4$ (233·2) calculated: 51·51% C, 3·03% H, 18·02% N; found: 51·40% C, 2·90% H, 17·91% N.

Methyl 2-(3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)benzoate (*IIb*)

Compound *Ib* (15 g, 16·32 mmol) was dissolved in 200 ml boiling solution of 3% HCl in methanol. The mixture was refluxed 3 h, concentrated to a half volume, and — with cooling — diluted with water to the final volume of 400 ml. The solution was neutralized with 9·3 g (84·9 mmol) sodium carbonate and acidified with 30 ml acetic acid, whereupon it was left to stand in a refrigerator 1 day. The separated white crystalline solid was collected by suction, washed with water, and dried in air. Yield 13·53 g (85%) compound *IIb*, m.p. 201—202°C (methanol). IR spectrum: 1 711, 1 648, 1 291, 1 272. For $C_{11}H_9N_3O_4$ (247·2) calculated: 53·44% C, 3·67% H, 17·00% N; found: 53·35% C, 3·58% H, 16·91% N.

2-(3-Thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)benzhydrazide (*IIIa*)

Compound *IVa* (1 g, 4·3 mmol) was dissolved in 20 ml 80% hydrazine hydrate (329 mmol), and the solution was left to stand at room temperature 12 h. Then the reaction mixture was diluted by addition of 25 ml water, filtered, and acidified with dilute hydrochloric acid (1 : 1) to pH 3. The yellow crystalline solid precipitated after 1 day standing in a refrigerator was collected by suction, washed with water and with ethanol, and dried in air. Yield 1·05 g (92%), m.p. 267—269°C. IR spectrum: 1 715, 1 695, 1 571, 1 249, 1 174. For $C_{10}H_9N_5O_2S$ (263·2) calculated: 45·63% C, 3·45% H, 26·61% N; found: 45·78% C, 3·36% H, 26·79% N.

1,2-Dihydro-1,2,4-triazino[5,6-*c*]isocoumarin-3-thione (*IVa*)

Compund *Ia* (1·25 g, 5 mmol) was added to a solution of 1·25 g, (6 mmol) N,N′-dicyclohexylcarbodiimide in 50 ml dibutyl ether. After 10 min boiling the formed yellow crystalline solid was hot filtered and digested with 2 × 30 ml dibutyl ether. Yield 1·15 g (99%), m.p. 229—231°C. IR spectrum: 1 766, 1 375, 1 252, 1 191, 1 089, 1 006. For $C_{10}H_5N_3O_2S$ (131·1) calculated: 51·96% C, 2·18% H, 18·18% N; found: 52·10% C, 2·00% H, 18·18% N.

1,2-Dihydro-1,2,4-triazino[5,6-*c*]isocoumarin-3-one (*IVb*)

Compound *Ib* (2·0 g, 9 mmol) was added to a solution of 2·1 g (10·1 mmol) N,N′-dicyclohexylcarbodiimide in 80 ml dibutyl ether. After 10 min boiling, the separated light brown crystalline solid was hot filtered and digested with 2 × 50 ml dibutyl ether. Yield 1·82 g (99%) compound *IVb*, m.p. 284—286°C. IR spectrum: 1 780, 1 774, 1 681, 1 613, 1 479, 1 244, 1 194, 968, 782. For $C_{10}H_5N_3O_3$ (215·2) calculated 55·82% C, 2·34% H, 19·53% N; found: 55·78% C, 2·57% H, 19·32% N.

3-Thioxo-2,3,4,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*Va*)

A) Compound *Ia* (650 mg, 2·6 mmol) was dissolved in a mixture of 1·0 ml 25% ammonium hydroxide (13·5 mmol) and 10 ml ethanol, and the solution was treated with 650 mg (3 mmol)

N,N'-dicyclohexylcarbodiimide, whereafter it was refluxed 30 min and cooled. The precipitated N,N'-dicyclohexylurea was removed by filtration, and the filtrate was acidified with dilute hydrochloric acid (1 : 1) to pH 4. The yellow-orange crystalline precipitate formed was collected by suction, washed with water, and dried at 110°C. Yield 500 mg (83%) raw product which was purified by repeated digestion with ethanol to give 450 mg (73%) compound *Va*, m.p. 321—325°C (decomp.).

B) Compound *IVa* (100 mg, 4·3 mmol) was dissolved in 5 ml 25% ammonium hydroxide (67·5 mmol), and the solution was left to stand at room temperature 48 h. The mixture was filtered, and the filtrate was acidified with dilute hydrochloric acid (1 : 1) to pH 4, which gave 60 mg (67%) yellow-orange crystalline solid, m.p. 320—325°C (after repeated (2×) digestion with ethanol). IR spectrum: 1 694, 1 594, 1 575, 1 310, 1 170. For $C_{10}H_6N_4OS$ (230·2) calculated: 52·18% C, 2·63% H, 24·34% N; found: 51·97% C, 2·52% H, 24·18% N.

2,3,4,6-Tetrahydro-1,2,4-triazino[5,6-*c*]isoquinoline-3,6-dione (*Vb*)

A) A mixture of 500 mg (2·01 mmol) compound *IIb* and 15 ml 25% ammonium hydroxide (200 mmol) was left to stand at room temperature 15 days, whereafter the mixture was diluted with 30 ml water and acidified with dilute hydrochloric acid (1 : 1) to pH 4. The light yellow crystalline solid obtained was collected by suction, washed with water, and dried at 110°C. Yield 270 mg (62%), m.p. 360°C (decomp.) after repeated (3×) digestion with ethanol.

B) Compound *Va* (1·5 g, 6·51 mmol) was dissolved in a solution of 750 mg (13·4 mmol) potassium hydroxide in 40 ml water, and a warm (50—60°C) solution of 2·1 g (13·3 mmol) potassium permanganate in 30 ml water was added thereto dropwise with stirring during 45 min. Then, 1 ml methanol was added and the mixture was stirred for another 15 min. The separated MnO_2 was collected by suction, washed with 3× 10 ml boiling water, resuspended in 25 ml boiling water, boiled for a short time, and collected by suction again. The combined filtrates were boiled for a short time and acidified with concentrated hydrochloric acid to pH 4—3. Yield 1·2 g (86%) light yellow crystalline product, m.p. 360°C (decomp.) after repeated (3×) digestion with ethanol.

C) Compound *IVb* (500 mg, 2·32 mmol) was dissolved in 20 ml 25% ammonium hydroxide (266 mmol) and the solution was left to stand at room temperature 48 h, whereafter it was diluted with 20 ml water and acidified with dilute hydrochloric acid (1 : 1) to pH 3. The separated solid was collected by suction, washed with boiling water and with boiling ethanol, and dried at 110°C. Yield 330 mg (68%) white crystals, m.p. 360°C (decomp.). IR spectrum: 1 693, 1 644; 1 596, 1 318, 982, 791. For $C_{10}H_6N_4O_2$ (214·2) calculated: 56·07% C, 2·82% H, 26·15% N, found: 55·92% C, 2·89% H, 26·29% N.

2-Methyl-2,3,4,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinoline-3,6-dione (*VIb*)

A mixture of 270 mg (1 mmol) dimethyl derivative *XVI* and 10 ml 5% hydrochloric acid was refluxed 30 min and cooled to give a white crystalline solid which was collected by suction, washed with cold and boiling water and with boiling ethanol, and dried. Yield 210 mg (94%) compound *VIb*, m.p. 341—343°C (after repeated (3×) digestion with ethanol). IR spectrum: 1 688, 1 521, 1 433, 1 277, 1 168, 1 122, 1 053. For $C_{11}H_8N_4O_2$ (228·2) calculated: 57·89% C, 3·53% H, 24·55% N; found: 57·71% C, 3·47% H, 24·69% N.

4-Methyl-2,3,4,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinoline-3,6-dione (*VIIb*)

Compound *Vb* (450 mg, 2·1 mmol) was dissolved in a solution of 450 mg (4·27 mmol) potassium

hydroxide in 15 ml water, and 0·12 ml (2·2 mmol) methyl iodide was added to the solution. After 5 h stirring, the mixture was acidified with 5% hydrochloric acid, and the separated yellowish crystalline product *VIIb* was collected by suction, washed with water, with boiling ethanol, and dried. Yield 470 mg (99%) compound *VIIb*, m.p. 345—348°C (ethanol; decomp.). IR spectrum: 1 693, 1 654, 1 585, 1 531, 1 273, 782. For $C_{11}H_8N_4O_2$ (228·2) calculated: 57·89% C, 3·53% H, 24·55% N; found: 57·67% C, 3·47% H, 24·43% N.

5-Methyl-3-thioxo-2,3,5,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*IXa*)

A) Compound *IIa* (2 g, 7·6 mmol) was dissolved in 25 ml 35% aqueous methylamine (307 mmol) with stirring, and the reaction mixture was left to stand at room temperature 10 days. Thereafter the solution was diluted with 35 ml water and acidified with diluted hydrochloric acid (1 : 1) to pH 4. The separated yellow crystalline solid was collected by suction, washed with water, and dried at 110°C. Yield 1·33 g (72%), m.p. 265—267°C (ethanol).

B) Compound *Ia* (650 mg, 2·6 mmol) was dissolved in a mixture of 0·5 ml 35% aqueous methylamine (6 mmol) and 15 ml ethanol, whereafter 650 mg (3·2 mmol) N,N′-dicyclohexylcarbodiimide was added, and the reaction mixture was refluxed 30 min. After cooling and diluting with 15 ml water, the precipitated N,N′-dicyclohexylurea was collected by suction. The mother liquor was acidified with dilute hydrochloric acid (1 : 1) to pH 3. The separated solid was collected to give 520 mg (82%) yellow crystals, m.p. 265—267°C (ethanol).

C) Compound *IVa* (100 mg, 0·43 mmol) was dissolved in 4 ml 35% aqueous methylamine (48 mmol), and the solution was left to stand at room temperature 48 h. Then it was filtered, and the filtrate was acidified with dilute hydrochloric acid (1 : 1) to pH 3, which gave 70 mg (66%) yellow crystalline product, m.p. 265—267°C (ethanol). IR spectrum: 1 692, 1 600, 1 529, 1 170. For $C_{11}H_8N_4OS$ (244·2) calculated: 54·10% C, 3·30% H, 22·94% N; found: 54·01% C, 3·27% H, 22·73% N.

5-Methyl-2,3,5,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinoline-3,6-dione (*IXb*)

A) Compound *IIb* (1 g, 4 mmol) was dissolved in 15 ml 35% aqueous methylamine (185 mmol) with stirring, and the solution was left to stand at room temperature 10 days. Thereafter it was diluted with 25 ml water and acidified with dilute hydrochloric acid (1 : 1) to pH 3. The separated white crystalline solid was collected by suction, washed with boiling water, with boiling ethanol, and dried at 110°C. Yield 0·53 g (58%), m.p. 348—350°C.

B) Compound *IVb* (400 mg, 1·85 mmol) was dissolved in 12 ml 35% aqueous methylamine (147 mmol), and the solution was left to stand at room temperature 100 h. Then the reaction mixture was diluted with water to a volume of 50 ml, filtered, and acidified with dilute hydrochloric acid (1 : 1) to pH 3. The separated white crystalline solid was collected by suction, washed with boiling water and with boiling ethanol, and dried at 110°C. Yield 290 mg (68%) compound *IXb*, m.p. 347—350°C. IR spectrum: 1 687, 1 666, 1 589, 1 568, 1 311, 1 114, 955. For $C_{11}H_8N_4O_2$ (228·2) calculated: 57·89% C, 3·53% H, 24·55% N; found: 57·67% C, 3·52% H, 24·67% N.

3-Thioxo-5-phenyl-2,3,5,6-tetrahydro-1,2,4-triazino-[5,6-*c*]isoquinolin-6-one (*Xa*)

Compound *Ia* (550 mg, 2·2 mmol) was dissolved in 25 ml 75% ethanol at the boiling temperature, and the solution was treated successively with 0·46 g (2·23 mmol) N,N′-dicyclohexylcarbodiimide and with 0·2 ml (2·2 mmol) aniline. The reaction mixture was refluxed 3 h, cooled, and treated

with a solution of 0·1 g sodium hydroxide in 15 ml water. The undissolved N,N′-dicyclohexylurea was removed by filtration, and the filtrate was acidified with dilute hydrochloric acid (1 : 1) to pH 3. The separated yellow crystalline solid was collected by suction and dried. Yield 260 mg (71%), m.p. 320–322°C (acetic acid). IR spectrum: 1 703, 1 601, 1 544, 1 266, 1 160. For $C_{16}H_{10}N_4OS$ (306·3) calculated: 62·74% C, 3·29% H, 18·29% N; found: 62·60% C, 3·46% H, 18·19% N.

5-Amino-3-thioxo-2,3,4,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*XIa*)

A) Methyl ester *IIa* (500 mg, 1·9 mmol) was dissolved in 10 ml 50% aqueous hydrazine hydrate (156 mmol), and the solution was left to stand at room temperature 3 days. Then the reaction mixture was diluted with 25 ml water and filtered. The filtrate was acidified with dilute hydrochloric acid (1 : 1) to pH 4, and the separated yellow solid was collected by suction, washed with water and with hot ethanol, and dried in air. Yield 310 mg (67%) compound *XIa*, m.p. 280–282°C (acetic acid).

B) Methyl ester *IIa* (500 mg, 1·9 mmol) was dissolved in 10 ml 80% hydrazine hydrate (165 mmol), and the solution was left to stand at room temperature 15 h. Then it was diluted with 30 ml water, filtered, and the filtrate was acidified with dilute hydrochloric acid (1 : 1) to pH 4–3. The yellow crystalline product was processed as above sub *A*). Yield 360 mg (78%) product *XIa*, m.p. 280–282°C (acetic acid).

C) Compound *Ia* (650 mg, 2·6 mmol) was dissolved in a mixture of 20 ml 50% ethanol and 0·25 ml 80% hydrazine hydrate (6·25 mmol) whereafter 0·6 g (2·9 mmol) N,N′-dicyclohexylcarbodiimide was added, and the mixture was refluxed 3 h. After cooling, the N,N′-dicyclohexylurea formed was removed by filtration, and the filtrate was acidified with dilute hydrochloric acid (1 : 1) to pH 4–3. The separated yellow crystalline solid was collected by suction, washed with water and with hot alcohol, and dried in air. Yield 450 mg (70%), m.p. 280–282°C (acetic acid).

D) Compound *IVa* (1 g, 4·3 mmol) was dissolved in 20 ml 80% hydrazine hydrate (329 mmol), and the solution was left to stand at room temperature 48 h. Then it was diluted with 25 ml water and filtered. The filtrate was acidified with dilute hydrochloric acid (1 : 1) to pH 4–3, and the separated yellow crystalline solid was collected by suction. Yield 760 mg (72%), m.p. 280–282°C (acetic acid). IR spectrum: 1 691, 1 608, 1 550, 1 273, 1 170, 1 144. For $C_{10}H_7N_5OS$ (245·2) calculated: 48·98% C, 2·88% H, 28·56% N; found: 48·92% C, 2·71% H, 28·67% N.

5-Amino-2,3,5,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinoline-3,6-dione (*XIb*)

A) Methyl ester *IIb* (500 mg, 2·02 mmol) was dissolved in 10 ml 80% hydrazine hydrate (165 mmol), and the solution was left to stand at room temperature 6 days. Then it was diluted with 30 ml water and filtered. The filtrate was acidified with dilute hydrochloric acid (1 : 1) to pH 4, and the light yellow precipitate was collected by suction, washed with boiling water and with boiling ethanol, and dried in air at room temperature. Yield 290 mg (63%), m.p. 337–340°C (acetic acid) (decomp.).

B) Compound *IVb* (1 g, 4·6 mmol) was dissolved in 25 ml 80% hydrazine hydrate (412 mmol), and the solution was left to stand at room temperature 53 h. Then it was diluted with 26 ml water and filtered. The filtrate was acidified with dilute hydrochloric acid (1 : 1) to pH 4–3. The separated light yellow crystalline solid was collected by suction, washed with hot water and with hot ethanol, and dried in air at room temperature. Yield 730 mg (69%) compound *XIb*, m.p.

338—340°C (decomp.) (acetic acid). IR spectrum: 1 702, 1 691, 1 597, 1 570, 1 432, 1 268, 1 004, 793. For $C_{10}H_7N_5O_2$ (229·2) calculated: 52·40% C, 3·08% H, 30·65% N; found: 52·26% C, 3·18% H, 30·75% N.

5-Benzylideneamino-3-thioxo-2,3,5,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*XIIa*)

Compound *XIa* (250 mg, 1 mmol) was dissolved in 30 ml boiling acetic acid, and, after addition of 0·15 ml (1·5 mmol) benzaldehyde, the solution was refluxed 10 min. The yellow crystalline solid precipitated on cooling was collected by suction, washed with ethanol and with ether, and dried in air at room temperature. Yield 330 mg (99%) compound *XIIa*, m.p. 301—303°C. IR spectrum: 1 696, 1 595, 1 522, 1 261, 1 182, 1 133. For $C_{17}H_{11}N_5OS$ (333·3) calculated: 61·26% C, 3·33% H, 21·01% N; found: 60·98% C, 3·16% H, 20·82% N.

5-Benzylideneamino-2,3,5,6-tetrahydro-1,2,4-triazino[5,6-*c*]isoquinoline-3,6-dione (*XIIb*)

Compound *XIb* (230 mg, 1 mmol) was dissolved in 60 ml boiling acetic acid, and 0·15 ml (1·5 mmol) benzaldehyde was added thereto, whereafter the mixture was refluxed 10 min. After cooling, the yellow crystalline solid was collected by suction, washed with boiling ethanol and with ether, and dried in air at room temperature. Yield 310 mg (99%) compound *XIIb*, m.p. 345—347°C. For $C_{17}H_{11}N_5O_2$ (317·3) calculated: 64·35% C, 3·49% H, 22·07% N; found: 64·16% C, 3·51% H, 22·09% N.

3-Anilino-5-phenyl-5,6-dihydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*XIII*)

A mixture of 500 mg (1·9 mmol) compound *IIa* and 4 ml (44 mmol) aniline was refluxed 5 h. After cooling to room temperature, 40 ml 15% hydrochloric acid was added, and the mixture was left to stand at room temperature 5 h. The separated yellow crystalline solid was collected by suction, thoroughly washed with water and with boiling ethanol, and dried at 110°C. Yield 430 mg (63%) compound *XIII*, m.p. 344—345°C. IR spectrum: 1 685, 1 681, 1 604, 1 527, 1 278. For $C_{22}H_{15}N_5O$ (365·4) calculated: 72·31% C, 4·14% H, 19·17% N; found: 72·18% C, 4·01% H, 19·09% N.

5-Amino-3-hydrazino-5,6-dihydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*XIV*)

Compound *IIa* (500 mg, 1·9 mmol) was dissolved in 10 ml 80% hydrazine hydrate (165 mmol), and the solution was left to stand at room temperature 6 days. Then it was dissolved with 30 ml water and acidified with dilute hydrochloric acid (1 : 1) to pH 4. The separated yellow crystalline solid was collected by suction, washed with boiling water and with boiling ethanol, and dried in air at room temperature. Yield 300 mg (66%) compound *XIV*, m.p. 278—280°C (acetic acid). IR spectrum: 1 666, 1 602, 1 551, 1 270, 1 170, 1 142. For $C_{10}H_9N_7O$ (243·2) calculated: 49·37% C, 3·73% H, 40·31% N; found: 49·22% C, 3·58% H, 40·11% N.

5-Benzylideneamino-3-benzylidenehydrazino-5,6-dihydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*XV*)

A solution of 250 mg (1 mmol) compound *XIV* in 50 ml boiling acetic acid was treated with 0·3 ml (3 mmol) benzaldehyde and refluxed 10 min. The yellow precipitate obtained on cooling was collected by suction and washed with boiling ethanol and with ether. Yield 420 mg (99%) compound *XV*, m.p. 320—322°C. IR spectrum: 1 709, 1 611, 1 541, 1 258, 1 181, 1 137. For

$C_{24}H_{17}N_7O$ (419·4) calculated: 68·72% C, 4·08% H, 23·38% N; found: 68·57% C, 4·21% H, 23·17% N.

2-Methyl-3-methylmercapto-2,6-dihydro-1,2,4-triazino[5,6-*c*]isoquinolin-6-one (*XVI*)

Compound *Va* (2·3 mg, 10 mmol) was dissolved in a solution of 500 mg (22 mmol) sodium in 30 ml methanol, 2 ml (37 mmol) methyl iodide was added thereto, and the mixture was refluxed 30 min. The methanol was distilled off, and the solid evaporation residue was triturated with 30 ml water and collected by suction. The white crystalline substance was digested several times with boiling water and with ethanol. Yield 2·22 (85%) semihydrate, m.p. 158—160°C (after three digestions with ethanol). IR spectrum: 1 695, 1 611, 1 528, 1 280. For $C_{12}H_{10}N_4OS$ calculated: 53·92% C, 4·14% H, 20·96% N; found: 54·11% C, 4·21% H, 21·09% N.

REFERENCES

1. Slouka J.: Collect. Czech. Chem. Commun. *42*, 894 (1977).
2. Ioffe I. S., Tomchin A. B.: Zh. Obshch. Khim. *40*, 859 (1970).
3. Tomchin A. B., Ioffe I. S.: Zh. Org. Khim. *8*, 1287 (1972).
4. Hajpál I., Berényi E.: J. Heterocycl. Chem. *19*, 313 (1982).
5. Slouka J., Bekárek V., Nálepa J., Lyčka A.: Collect. Czech. Chem. Commun. *49*, 2628 (1984).
6. Slouka J.: Collect. Czech. Chem. Commun. *44*, 2438 (1979).
7. Slouka J., Hejsek M.: Acta Univ Palacki. Olomuc., Fac. Rerum. Nat. *85*, 85 (1986).
8. Slouka J., Bekárek V.: J. Prakt. Chem. *316*, 943 (1974).
9. Hejsek M., Slouka J.: Pharmazie *39*, 186 (1984).
10. Hejsek M., Slouka J.: Pharmazie *41*, 284 (1986).
11. Jones R. N., Angell C. L., Ito T., Smith J. D.: Can. J. Chem. *37*, 2007 (1959).

Translated by J. Panchartek.