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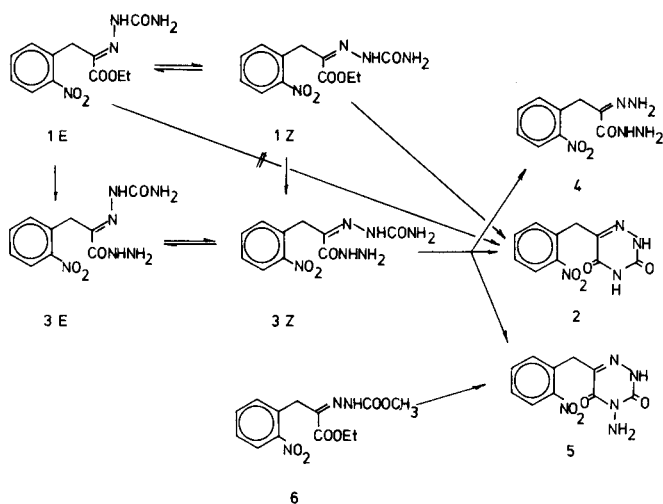
6-(2-Nitrobenzyl)-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazines were prepared as intermediates for investigations aimed at the synthesis of *as*-triazino[5,6-*b*]quinolines. The substances were obtained by new methods based on the elucidation of stereochemical conditions.

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6-Substituted-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazines has been prepared by the alkaline cyclization of α -oxo-carboxylic acid semicarbazones (1).

Starting from the semicarbazone of ethyl 2-nitrophenylpyruvate (1) cyclization was not observed either under acidic or alkaline conditions. A partial transformation occurred heating 1 in solvents or in melt, however this transformation only took place until an equilibrium was reached. The mixture could be separated by fractional crystallization. The new compound obtained gave an elemental analysis which was identical with that of the starting ester (1), but its physical properties were different. Thus, 1 and the new substance were supposed to be stereoisomers.

Scheme 1



The stereochemistry of compounds containing the C=N bond are known in the literature (2,3,4). Just and Kim (5) synthesized the *E* and *Z* isomers of methyl pyruvate-semicarbazone and established that the last compound could be cyclized to 6-azathymine by sodium methoxide in methanol at room temperature.

On the basis of comparing the spectroscopical values to literature data it was concluded that the compound prepared originally had a configuration *E* while the isomerized substance was *Z*. This isomerization was reversible: when 1-*Z* was heated under identical conditions, an equilibrium mixture was obtained. In contrast to 1-*E*, 1-*Z*

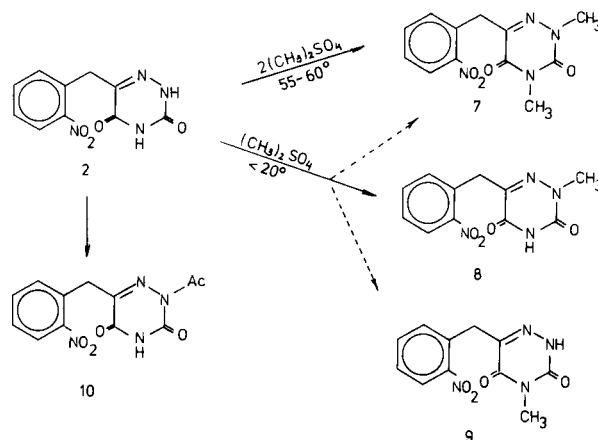
could be cyclized in a good yield by sodium ethoxide in ethanol at room temperature.

We succeeded in finding a new method for preparation of the triazine 2. The appropriate acid hydrazid was formed from 1-*E* during a short reaction period. On increasing the time of the reaction, three compounds could be isolated from the mixture. The same result was obtained when the reaction was carried out with 1-*Z*. It was supposed that similarly to 1, 3 could also exist in two stereoisomeric forms. It was tried to bring 1-*Z* into reaction with hydrazine hydrate in ethanol, however the least soluble known 3-*E* precipitated from the mixture in this case.

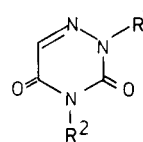
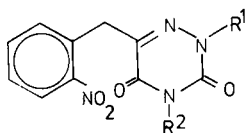
By chromatographic follow-up we arrested the reaction starting from 1-*Z* at a point where a significant amount of 3-*Z* could be found in the double equilibrium system. After cautious evaporation the mixture of 3-*E* and 3-*Z* was obtained. In the nmr spectrum of the mixture a singlet also appeared at 11.9 ppm together with the bands characteristic of 3-*E*. This singlet indicated the NH-group participating of the intramolecular hydrogen bond, an observation rendering our hypothesis probable. (The experiments of separation were unsuccessful.)

In our opinion cyclization in fact occurred from 3-*Z* in two directions to 2 and 5 in addition to a side reaction (4) when hydrazine hydrate provided the required alkaline conditions.

SCHEME 11



Table



	R ₁	R ₂	(C=O) cm ⁻¹		pK _a
2	H	H	1730	1705	8.15 12
8	CH ₃	H	1720	1705	7.75
9	H	CH ₃	1730	1680	9.75
				1668	
7	CH ₃	CH ₃	1715	1665	
5	H	NH ₂	1730	1665	9.30
10	CH ₃ CO	H	1735	1715	

	R ₁	R ₂	(C=O) cm ⁻¹		pK _a
	H	H	1730	1703	7.00 12.9
	CH ₃	H	1720	1700	6.99
	H	CH ₃	1734	1687	9.52
				1664	
	CH ₃	CH ₃	1720	1680	

A second process previously unknown was also found for the preparation of the aminotriazine (**5**). Boiling in hydrazine hydrate of the methoxycarbonylhydrazone **6** gave **5**.

Concerning this reaction, it was presumed that **6** also existed in form of two stereoisomers and the cyclization started from the *Z* form. Indeed, **6** partially isomerized on heating thus the *Z* form could be separated and identified by preparative layer chromatography.

It is concluded that the preparation of **2** from **1** or **3** as well as the synthesis of **5** involve stereochemical conditions. The required stereochemical position has to be assured either in the starting material or realized under the reaction conditions. In general, it can be presumed that the stereochemical position of the α -oxo-carboxylic acid semicarbazones is decisive for the synthesis of 6-azauracils. In the case of 6-azathymine the energy of activation was so high that the isomerization occurred at the boiling point of ethylene glycol (**6**). From the appropriate isomer, 6-azathymine was formed at room temperature (**5**), a fact proving that isomerization, but not cyclization required the high temperature. In our experiments the stronger conditions could not be applied as 2-nitrophenylpyruvic acid derivatives were decomposed under such circumstances.

A few derivatives of **2** were also prepared (Scheme 2). Their structure was determined comparing the pK_a values and carbonyl frequencies with the literature data of analogous compounds (**7,8**).

EXPERIMENTAL

E Form of Ethyl 3-(2-Nitrophenyl)-2-semicarbazopropionate (**1-E**).

To the solution of ethyl 2-nitrophenylpyruvate (23.7 g, 0.1 mole) (**9**) in ethanol (50 ml), a mixture of semicarbazide hydrochloride (13.4 g, 0.12 mole) and water (30 ml) was added. The pH was adjusted to 8 with sodium carbonate and heated to the boiling point. The crystals precipitated on cooling were filtered and washed with water to give **1-E** (26.7 g, 91%), mp 184-186° after recrystallization from methoxyethanol (100 ml); ir (potassium bromide): 3500, 3380 (NH₂), 3200-3050 (NH), 1735, 1960

(C=O), 1520, 1350 (NO₂); nmr (DMSO-d₆): 1.20 (t 3, CH-CH₂, J = Hz), 4.23 (qa, 2, CH₃-CH₂, J = 6 Hz), 4.32 (s, 2, CH₂), 6.7 (s, 2, NH), 7.2 (d-d, 1, Ar-6-H, J_o = 7 Hz, J_m = 2 Hz), 7.5-7.9 (m, 2, Ar-4, 5-H), 8.2 (d-d, 1, Ar-3-H, J_o = 7 Hz, J_m = 2 Hz), 10.5 (s, 1, NH).

Anal. Calcd. for C₁₃H₁₄N₄O₅ (294.25): C, 48.98; H, 4.80; N, 19.04. Found: C, 48.72; H, 4.85; N, 18.96.

Z Form of Ethyl 3-(2-Nitrophenyl)-2-semicarbazopropionate (**1-Z**).

The methoxyethanol mother liquor (100 ml) used for the recrystallization of **1-E** was diluted to 500 ml with water and the precipitated crystals were filtered. The product (2.5 g) was dissolved in ethanol (12.5 ml) and the insoluble crystals (**1-E**) were filtered out. The filtrate was again heated to boil, let to cool and the mother liquor was decanted from the crystals at 50°. The procedure was repeated twice to yield **1-Z** (0.5-0.7 g), mp 149-150° contaminated with less than 1% of the *E*-isomer; ir (potassium bromide): 3460, 3280, 3140 (NH₂, NH), 1700 (C=O), 1520 (NO₂); nmr (DMSO-d₆): 1.18 (t 3, CH₃-CH₂, J = 6 Hz), 4.18 (s, 2, CH₂), 4.2 (qa, 2, CH₃-CH₂, J = 6 Hz), 6.58 (s, 2, NH₂), 7.35-7.8 (m, 3, Ar-4,5,6-H), 8.0 (d-d, 1, Ar-3-H, J_o = 7 Hz, J_m = 2 Hz), 11.1 (s, 1, NH).

Anal. Calcd. for C₁₃H₁₄N₄O₅ (294.26): C, 48.98; H, 4.80; N, 19.04. Found: C, 49.09; H, 4.76; N, 19.17.

6-(2-Nitrobenzyl)-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine (**2**).

Compound **1-Z** (8.81 g, 0.3 mole) was stirred in a solution of sodium ethoxide (8.0 g, 0.35 mole sodium in 100 ml of dry ethanol) for 1 hour at room temperature. The crystals precipitated were filtered and immediately suspended in 5% hydrochloric acid (60 ml). The white crystals were filtered and washed with water and ethanol to give **2** (5.78 g, 77.5%), mp 211-212°; ir (potassium bromide): 3320, 3140 (NH), 1670 (C=O), 1525, 1340 (NO₂); nmr (DMSO-d₆): 4.2 (s, 2, CH₂), 7.35-7.8 (m, 3, Ar-4,5,6-H), 8.0 (d-d, 1, Ar-3-H, J_o = 7 Hz, J_m = 2 Hz), 12.1 (s, 2, NH).

Anal. Calcd. for C₁₀H₈N₄O₄ (248.19): C, 48.39; H, 3.25; N, 22.56. Found: C, 48.31; H, 3.40; N, 22.59.

E-3-(2-Nitrophenyl)-2-semicarbazopropionylhydrazone (**3**).

Compound **1-E** (29.4 g, 0.1 mole) was heated in 96% hydrazine hydrate (42 ml) till boiling. The solution obtained was cooled, the crystals precipitated were filtered and washed with water to give **3** (19.4 g, 69.2%), mp 206-207°; ir (potassium bromide): 3420-3260 (NH₂, NH), 1680, 1660 (C=O), 1520, 1350 (NO₂); nmr (DMSO-d₆): 4.25 (s, 2, CH₂), 6.15 (s, 2, NH), 6.9 (d-d, 1, Ar-6-H, J_o = 7 Hz, J_m = 1 Hz), 7.15 (s, 2, NH₂), 7.25-7.65 (m, 2, Ar-4,5-H), 7.95 (d-d, 1, Ar-3-H, J = 7 Hz, J_m = 2 Hz), 9.8 (s, 1, NH), 10.00 (s, 1, NH).

Anal. Calcd. for C₁₀H₁₂N₄O₄ (280.25): C, 42.85; H, 4.32; N, 29.99. Found: C, 42.94; H, 4.45; N, 29.96.

Reaction with Hydrazine Hydrate of *E* Ethyl 3-(2-Nitrophenyl)-2-semicarbazopropionate (**1-E**).

A mixture of 96% hydrazine hydrate (42 ml) and **1-E** (28.0 g, 0.1 mole)

was boiled for 15 minutes, cooled at 0° for 2 hours and the crystals precipitated were filtered and washed with water to yield 2-hydrazono-3-(2-nitrophenyl)propionylhydrazine (**4**) (3.78 g, 15.8%), mp 149-150°; ir (potassium bromide): 3360, 3310, 3180 (NH₂, NH), 1650 (C=O), 1520, 1355 (NO₂); nmr (DMSO-d₆): 4.18 (s, 2, CH₂), 4.1 (br, 2, NH), 7.05 (d-d, 1, Ar-6-H, J_o = 7 Hz, J_m = 2 Hz), 7.35 (s, 2, NH₂), 7.25-7.7 (m, 2, Ar-4,5-H), 8.0 (d-d, 1, Ar-3-H, J_o = 7 Hz, J_m = 2 Hz), 8.76 (s, 1, NH).

Anal. Calcd. for C₉H₁₁N₅O₃ (237.22): C, 45.56; H, 4.67; N, 29.55. Found: C, 45.51; H, 4.48; N, 29.50.

The filtrate obtained after isolation of **4** was diluted to 300 ml with water and let stand at 0° for 2 hours. The crystals were filtered and washed with water. The product (7.85 g) was recrystallized from the mixture of water (100 ml), ethanol (50 ml) and sodium hydrogen carbonate (0.5 g) to give 4-amino-6-(2-nitrobenzyl)-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine (**5**) (5.92 g, 22.5%), mp 184-185°; ir (potassium bromide): 3315-3150 (NH₂, NH), 1735, 1700, 1680 (C=O), 1525, 1345 (NO₂); nmr (DMSO-d₆): 4.2 (s, 2, CH₂), 5.65 (s, 2, NH₂), 7.35-7.80 (m, 3, Ar-4,5,6-H), 8.0 (d-d, 1, Ar-3-H, J_o = 7 Hz, J_m = 2 Hz), 12.5 (s, 1, NH).

Anal. Calcd. for C₁₀H₉N₅O₄ (263.21): C, 45.63; H, 3.45; N, 26.61. Found: C, 45.81; H, 3.54; N, 26.46.

The filtrate obtained after isolation of **5** was acidified to pH 2 by concentrated hydrochloric acid. The crystals precipitated were filtered and washed with water. The product (7.55 g) was dissolved in the hot solution of sodium hydrogen carbonate (4 g) and water (70 ml) and let stand at 0° for 2 hours. The crystals were filtered (**5**, 0.8 g) and the filtrate was acidified to pH 2 by concentrated hydrochloric acid to give 6-(2-nitrobenzyl)-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine (**2**), (6.45 g, 26%) the properties of which were the same as those of the substance prepared from **1-Z**.

E Ethyl 2-(Methoxycarbonylhydrazono)-3-(2-nitrophenyl)propionate (**6**).

To the solution of ethyl 2-nitrophenylpyruvate (**9**) (23.7 g, 0.1 mole) in ethanol (250 ml), the solution of methyl carbazate (15.0 g, 0.16 mole) in water (25 ml) was added, the mixture was heated to boiling and set aside overnight at room temperature. The crystals precipitated were filtered and washed with water and ethanol; ir (potassium bromide): 3200 (NH), 1740, 1710 (C=O), 1530, 1350 (NO₂); ir (chloroform): 3280 (NH), 1760, 1710 (C=O), 1525, 1350 (NO₂); nmr (DMSO-d₆): 1.15 (t, 3, CH₃-CH₂, J = 7 Hz), 4.12 (qa, 2, CH₃-CH₂, J = 7 Hz), 3.7 (s, 3, CH₃), 4.22 (s, 2, CH₂), 7.0 (d-d, 1, Ar-3-H, J_o = 7 Hz, J_m = 2 Hz).

Anal. Calcd. for C₁₃H₁₅N₃O₃ (309.27): C, 50.28; H, 4.89; N, 13.59. Found: C, 50.53; H, 4.88; N, 13.53.

Z Ethyl 2-(Methoxycarbonylhydrazono)-3-(2-nitrophenyl)propionate (**6-Z**).

Compound **6-E** (1 g) was melted and kept at 200° for 10 minutes. After cooling the oil was dissolved in ethanol, clarified and precipitated with water. The yellow oil was dissolved in chloroform and dried on anhydrous magnesium sulphate. The filtered solution was developed on a Kieselgel 60 F₂₅₄ preparative layer in the system of chloroform-benzene-methanol (70:30:20). The substance with higher R_f value was collected together with the layer material and extracted with chloroform. After evaporation of the latter solution **6-Z** (0.3 g) was obtained. In the above system **6-Z** appeared with a 0.68 R_f value, while **6-E** with 0.52; ir (liguid film): 3280 (NH), 1760, 1730, 1690 (C=O), 1530, 1350 (NO₂) ir (chloroform): 3280 (NH), 1755, 1700 (C=O), 1530, 1360 (NO₂); nmr (deuteriochloroform): 1.2 (t, 3, CH₃-CH₂, J = 7 Hz), 3.8 (s, 3, CH₃), 7.15-7.85 (m, 3, Ar-4,5,6-H), 7.9 (d-d, 1, Ar-3-H, J_o = 7 Hz, J_m = 2 Hz), 12.0 (s, 1, NH).

Reaction with Hydrazine Hydrate of **6-E**.

Compound **6-E** (30.9 g, 0.1 mole) was boiled with 96% hydrazine hydrate (50 ml) for 15 minutes, then cooled at 0° for 2 hours. The crystals were filtered to give **4** (1.2 g, 5.0%). The characteristics were in agreement with those of the substance prepared from **1-E**.

The filtrate was poured on ice (1000 g) and acidified to pH 2 by concentrated hydrochloric acid. The crystals precipitated were filtered and

washed with water to give **5** (15.5 g, 58.9%) the characteristics of which agreed with those of the compound prepared from **1-E**.

2,4-Dimethyl-6-(2-nitrobenzyl)-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine (**7**).

To a suspension of **2** (24.8 g, 0.1 mole) in water (170 ml) methyl sulphate (22.6 g, 0.18 mole) was added and 10% sodium hydroxide solution (60 ml) was dropped to the mixture. The temperature increased to 55-60°. It was stirred for 1 hour, then cooled, the crystals were filtered and washed with water to give **7** (22.5 g, 82.6%), mp 122-123°; ir (potassium bromide): 1710, 1670 (C=O) 1525, 1390 (NO₂); nmr (DMSO-d₆): 3.15 (s, 3, CH₃), 3.31 (s, 3, CH₃), 4.2 (s, 2, CH₂), 7.35-7.75 (m, 3, Ar-4,5,6-H), 7.95 (d-d, 1, Ar-3-H, J_o = 8 Hz, J_m = 2 Hz).

Anal. Calcd. for C₁₂H₁₂N₄O₄ (276.25): C, 52.17; H, 4.38; N, 20.28. Found: C, 52.26; H, 4.47; N, 20.25.

2-Methyl-6-(2-nitrobenzyl)-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine (**8**).

To the solution of **2** (24.8 g, 0.1 mole) in water (200 ml) and 40% sodium hydroxide (40 ml), methyl sulphate (11.3 g, 0.09 mole) was dropped at 10°. The crystals precipitated (**8-Na**) were filtered, dissolved in water (300 ml) and the insoluble material was filtered out. The solution was acidified to pH 2 by concentrated hydrochloric acid, the precipitate was filtered and washed with water to give **8** (13.3 g, 50.7%), mp 205-206°; ir (potassium bromide): 3180, 3050-2830 (NH), 1720, 1670 (C=O), 1540, 1360 (NO₂); nmr (DMSO-d₆): 3.3 (s, 3, CH₃), 4.18 (s, 2, CH₂), 7.35-7.80 (m, 3, Ar-4,5,6-H), 7.95 (d-d, 1, Ar-3-H, J_o = 8 Hz, J_m = 2 Hz), 12.2 (s, 1, NH).

Anal. Calcd. for C₁₁H₁₀N₄O₄ (262.22): C, 50.38; H, 3.84; N, 21.37. Found: C, 50.52; H, 3.96; N, 21.28.

4-Methyl-6-(2-nitrobenzyl)-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine (**9**).

The solution, obtained after filtering out the sodium salt of **8** (see above), was acidified to pH 2 by concentrated hydrochloric acid. The aqueous phase was decanted from the separated oil, the oil was dissolved in hot ethanol (4 ml) and the solution was poured into ice. The crystals obtained were filtered and washed with ethanol to give **9** (0.13 g, 0.5%), mp 187-188°; ir (potassium bromide): 3240 (NH), 1730, 1650 (C=O), 1515, 1350 (NO₂); nmr (DMSO-d₆): 3.15 (s, 3, CH₃), 4.18 (s, 2, CH₂), 7.35-7.80 (m, 3, Ar-4,5,6-H, J_o = 8 Hz, J_m = 2 Hz), 8.0 (d-d, 1, Ar-3-H), 12.3 (s, 1, NH).

Anal. Calcd. for C₁₁H₁₀N₄O₄ (262.22): C, 50.38; H, 3.84; N, 21.37. Found: C, 50.46; H, 3.95; N, 21.23.

2-Acetyl-6-(1-nitrobenzyl)-3,5-dioxo-2,3,4,5-tetrahydro-*as*-triazine (**10**).

The solution of **2** (24.8 g, 0.1 mole) in acetic anhydride (100 ml) was boiled 30 minutes, then clarified and let stand at 0° for further 30 minutes. The crystals were filtered and washed with ethanol to yield **10** (19.3 g, 66.4%), mp 189-190°; ir (potassium bromide): 3200-3000 (NH), 1775, 1725, 1685 (C=O); nmr (DMSO-d₆): 2.18 (s, 3, CH₃), 4.27 (s, 2, CH₂), 7.35-7.80 (m, 3, Ar-4,5,6-H), 8.0 (d-d, 1, Ar-3-H, J_o = 7 Hz, J_m = 2 Hz), 12.4 (s, 1, NH).

Anal. Calcd. for C₁₂H₁₀N₄O₅ (290.23): C, 49.66; H, 3.47; N, 19.31. Found: C, 49.85; H, 3.62; N, 19.25.

The melting points are uncorrected. The ir spectra were recorded in cm⁻¹ on a Perkin-Elmer 157G spectrometer, the nmr spectra were taken up on a Hitachi Perkin Elmer R 24A 60 MHz device. Chemical shifts were measured in ppm (δ) with respect to TMS.

Acknowledgement

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