REACTIONS OF SOME 2-(6-AZAURACIL-5-YL)PHENYLHYDRAZONES*

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Azo coupling of the diazotized 6-(2-aminophenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione with ethyl cyanoacetylcarbamate and diethyl malonyl-bis-carbamate has been used for preparation of the hydrazones *I* and *II*. The latter substances have been boiled in strongly acidic medium to give 2,3,4,6-tetrahydro-1,2,4-triazino[5,6-*c*]cinnoline-3-one (*III*) which has also been obtained by reduction of the mentioned diazonium salt with alkali sulphite and subsequent cyclization of the formed hydrazine sulphonate by boiling in acid medium. In alkaline medium the hydrazones *I* and *II* have been cyclized to the nitrile *IV* and to 2-[2-(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)-phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic acid (*V*), respectively.

Within the studies of cyclization reactions of hydrazones proceeding by two routes[1,2] attention has been focused in the present communication to preparation and cyclization of some 2-(6-azauracil-5-yl)phenylhydrazones.

Azo coupling of the diazotized 6-(2-aminophenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione with ethyl cyanoacetylcarbamate and diethyl malonyl-bis-carbamate in aqueous natrium acetate solution gave the corresponding hydrazones *I* and *II* in high yields. On boiling in strongly acidic medium the both hydrazones undergo hydrolytic splitting of the carbonyl component and subsequent cyclization of the formed hydrazino derivative to 2,3,4,6-tetrahydro-1,2,4-triazino[5,6-*c*]cinnoline-3-one (*III*). The derivative *III* was also obtained by another way, *viz*. reaction of the diazotized 6-(2-aminophenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione with alkali sulphite and boiling of the formed hydrazine sulphonate in strongly acidic medium. Hence, 6-(2-hydrazinophenyl)-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione represents a non-isolated intermediate in the both routes, its hydrazino group being condensed with the carbonyl at 5 position in the same way as the amino group in the analogous 6-(2-aminophenyl) derivative[3]. With the use of $Na^{15}NO_2$ we also prepared the corresponding isotopic hydrazone *I* and its cyclization product *III*, 5-^{15}N.

Out of the three possible tautomeric forms of the compound *III viz* 2,3,4,6,-2,3,5,6- and 1,2,3,4-tetrahydroform ($A-C$) the most probable appears to be the

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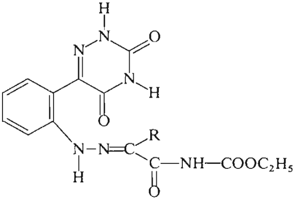
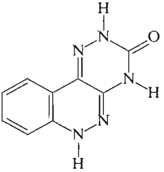
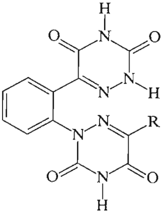
form *A* on the basis of IR and ^{1}H-NMR spectroscopy. In ^{1}H-NMR spectrum of this substance the NH groups appear at 11·83, 12·07 and 13·62 ppm as singlets, which excludes the structures *B* and *C* containing neighbouring NH groups. The signals at 11·83 and 12·07 ppm are due to NH protons neighbouring with a carbonyl group and bonded by intermolecular hydrogen bond with dimethyl sulphoxide molecules. Shielding effect of this hydrogen bond here is partially compensated by shielding effect of the carbonyl group anisotropy. The signal at 13·62 changes into doublet (8 Hz distance of the signals) on changing ^{14}N by ^{15}N at the position 5. It indicates spin coupling ^{1}H-^{15}N *via* an ^{14}N atom, *i.e.* the grouping ^{1}H—^{14}N—^{15}N. In case of direct ^{1}H—^{15}N interaction (as it is the case in the tautomer *B*) the above distance would be 60–90 Hz. In the IR spectrum the presence of the tautomer *A* is confirmed by the absorption band at 1465 cm^{-1}, due to valence vibration of C=N bond, which by the mentioned isotopic change is shifted to lower wave numbers by 3 cm^{-1}. The compound *III*, which so far is the first derivative of 1,2,4-triazino[5,6-*c*]cinnoline skeleton, behaves as a weak N—H acid forming well water-soluble alkali salts.



I, R = CN
II, R = CONHCOOC$_2$H$_5$



III



IV, R = CN
V, R = COOH

A quite different course was observed for cyclization of the hydrazones *I* and *II* in alkaline medium, when a further 6-azauracile cycle is closed. On heating in alkali carbonate solution the hydrazone *I* is converted to 2-[2-(3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (*IV*) which was acid hydrolyzed to the acid *V*. The latter compound was also obtained by heating the hydrazone *II* with alkali hydroxide solution when both cyclization and hydrolytic splitting of the carbamate group take place[5].

EXPERIMENTAL

The melting points were determined with a Boetius apparatus and are not corrected. The IR spectra were measured with a UR-20 spectrophotometer (Zeiss, Jena) in Nujol suspension or in KBr. The ^{1}H-NMR spectra were measured with a 60 MHz spectrometer T-60 in hexadeuteriodimethyl sulphoxide using tetramethylsilane as internal standard. The UV spectra were measured with Unicam SP 1800 spectrophotometer in $5\cdot0 . 10^{-5}$M solutions in ethanol.

Ethyl 2-(3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)phenylhydrazonocyanoacetylcarbamate (*I*)

Solution of 4·20 g (20·57 mmol) 6-(2-aminophenyl)-2,3,4,5-tetrahydro-1,2-triazine-3,5-dione[4] in 24 ml 37% HCl and 180 ml water was cooled at 0—3°C, crushed ice was added thereto, and diazotization was carried out by addition of solution of 1·38 g (20·0 mmol) $NaNO_2$ in 20 ml ice water. The mixture was left to stand 30 min at 0—3°C, and then it was added with stirring to a mixture prepared from 4·00 g (25·62 mmol) ethyl cyanoacetylcarbamate dissolved in 1000 ml hot water, cooled to 0—3°C, and treated with 40 g sodium acetate and crushed ice. After 24 h the crystalline solid was collected by suction, washed with water and dried in air. Yield of the monohydrate 7·22 g (91%). After recrystallization from mixture ethanol–water yellow crystals were obtained, m.p. 211—213°C. For $C_{15}H_{15}N_7O_6$ (389·3) calculated: 46·27% C, 3·88% H, 25·18% N; found: 46·20% C, 3·87% H, 25·41% N. After drying at 105°C the weight decrease corresponded to 1 molecule H_2O. For $C_{15}H_{13}N_7O_5$ (381·3) calculated: 48·52% C, 3·53% H, 26·41% N; found: 48·62% C, 3·64% H, 26·26% N. IR spectrum (Nujol, cm^{-1}): 424 m, 434 m, 483 m, 498 m, 543 m, 551 m, 590 s, 611 m, 627 m, 648 w, 683 m, 730 m, 745 s, 760 s, 783 m, 807 s, 840 w, 866 w, 954 m, 993 sh, 1010 m, 1050 s, 1095 w, 1116 m, 1160 m, 1175 s, 1195 sh, 1217 s, 1257 m, 1290 m, 1315 m, 1357 w, 1400 m, 1435 m, 1505 s, 1575 m, 1587 w, 1605 w, 1667 s, 1692 s, 1725 s, 1653 s, 2219 w, 3150 m, 3240 m. Recrystallization of the anhydrous hydrazone from ethanol gave its adduct with the solvent. For $C_{17}H_{19}N_7O_6$ (417·3) calculated: 48·92% C, 4·59% H, 23·49% N; found: 48·74% C, 4·60% H, 23·39% N. The adduct is converted to the original hydrazone on heating at 100°C. The above-described procedure using $Na^{15}NO_2$ gave the corresponding hydrazone *I* with ^{15}N isotope.

Diethyl 2-(3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)-phenylhydrazonomalonyl-bis-carbamate (*II*)

The diazonium salt solution prepared in the same way as in the above case was added portionwise with stirring to a mixture prepared by dissolution 8·00 g (32·49 mmol) diethyl malonyl-bis-carbamate and 40 g sodium acetate in 600 ml water, cooling to 0—3°C and addition of crushed ice. The separated solid was, after 24 h, collected by suction, washed with water and dried in air.

Yield of the dihydrate 9·68 g (97%). After recrystallization from ethanol and drying at 80°C yellow anhydrous hydrazone was obtained melting at 262—264°C (decomp.). For $C_{18}H_{19}N_7O_8$ (461·4) calculated: 46·86% C, 4·15% H, 21·25% N; found: 46·84% C, 4·12% H, 21·12% N.

2,3,4,6-Tetrahydro-1,2,4-triazino[5,6-*c*]cinnoline-3-one (*III*)

a) Mixture of 390 mg (1·00 mmol) hydrazone *I* monohydrate, 20 ml 37% HCl and 10 ml water was refluxed 3 h and cooled. On the other day the precipitated solid was collected by suction, washed with water and dried at 150°C. Yield 150 mg (74%). After two crystallizations from aqueous ethanol crystalline solid was obtained not melting up to 360°C. For $C_9H_7N_5O$ (201·2) calculated: 53·75% C, 3·51% H, 34·81% N; found: 53·62% C, 3·50% H, 34·76% N. The same procedure was applied for preparation of *III* 5-^{15}N from the hydrazone *I* monohydrate with ^{15}N.

b) Mixture of 465 mg (1·01 mmol) hydrazone *II*, 60 ml acetic acid and 60 ml 37% HCl was refluxed 6 h, concentrated, diluted with 10 ml water, and cooled. The precipitated solid was collected by suction after several hours, washed with water, and dried at 150°C. Yield 160 mg (79%). After two crystallizations from aqueous ethanol the product was identical in all respects (inclusive of IR spectrum) with the compound prepared by the above-mentioned procedure.

c) The diazonium salt solution was prepared as in the case of preparation of the hydrazone *I*, and solution of 24 g (190·4 mmol) Na_2SO_3 in 400 ml water was added thereto. The solution was left to stand at 0—3°C 24 h, heated on 80°C water bath 15 min, acidified with 38 ml 37% HCl and refluxed 2 h. The mixture was cooled, and the separated solid was collected by suction after several days standing, then it was washed with water and dried at 150°C. Yield 2·36 g (57%). After two crystallizations from aqueous ethanol the product was identical in all respects with the compounds prepared by the above-described procedures. IR spectrum (KBr, cm^{-1}): 427 m, 483 m, 532 m, 602 m, broad, 643 w, 743 m, 766 m, 783 sh, 902 m, 959 s, 1004 m, 1033 sh, 1050 m, 1085 m, 1124 w, 1152 m, broad, 1127 m, 1261 w, 1343 m, 1378 m, 1465 m, 1488 m, 1510 sh, 1558 w, 1580 w, 1605 sh, 1622 m, 1700 s, broad. Exchange of ^{14}N by the isotope ^{15}N at the position 5 resulted in the following wave-number decrease: 532 cm^{-1} by 2 cm^{-1}, 602 cm^{-1} by 4 cm^{-1}, 902 cm^{-1} by 2 cm^{-1}, 959 cm^{-1} by 2·5 cm^{-1}, 1085 cm^{-1} by 3 cm^{-1}, 1152 cm^{-1}, by 6 cm^{-1}, 1227 cm^{-1} by 2 cm^{-1}, 1261 cm^{-1} by 4 cm—^{1}, 1465 cm^{-1} by 3 cm^{-1}. ^{1}H-NMR spectra (hexadeuteriodimethyl sulphoxide, δ, ppm): 7·0—7·6 (3 H) multiplet, 8·15 (1 H) doublet, 11·83 (1 H) singlet, 12·07 (1 H) singlet, 13·62 (1 H) singlet. Exchange of ^{14}N by the ^{15}N isotope at the position 5 caused the signal at 13·62 ppm to be converted into doublet with the peaks distance 8 Hz. UV spectrum (ethanol) λ_{max} (log ε): 213 nm (4·33), 237 nm (4·03), 267 nm (3·79), 275 nm (3·86), 305 nm (4·08), 313 nm (3·93).

2-[2-(3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (*IV*)

Mixture of 780 mg (2·00 mmol) hydrazone *I* monohydrate, 400 mg (3·77 mmol) Na_2CO_3 and 15 ml water was heated on boiling water bath 30 min, cooled to the room temperature, and acidified to pH 0 with conc. hydrochloric acid. After several hours the precipitated solid was collected by suction, washed with little water and dried at 70°C. Yield of the monohydrate 660 mg (96%). After two crystallizations from water and drying at 70°C the obtained crystals lose crystal water at 180°C and melt at 277—279°C. For $C_{13}H_9N_7O_5$ (343·3) calculated: 45·49% C, 2·64% H, 28·57% N; found: 45·41% C, 2·58% H, 28·35% N. Drying in vacuum at 165°C results in a weight decrease corresponding to one molecule of H_2O. For $C_{13}H_7N_7O_4$ (325·2) calculated: 48·01% C, 2·17% H, 30·15% N; found: 47·85% C, 2·33% H, 30·01% N. IR spectrum (Nujol, cm^{-1}): 416 m, 430 sh, 452 w, 475 m, 501 w, 557 m, 580 m, 602 m, 630 w, 640 w, 665 m, 705 m, 727 sh, 745 s, 760 m, 773 m, 800 m, 820 w, 870 w, 956 w, 1016 m, 1030 m, 1068 w, 1100 sh, 1115 m, 1145 m, 1183 s, 1250 s, 1290 m, 1305 m, 1320 m, 1385 m, 1405 s, 1425 s, 1450 s, 1467 s, 1493 m, 1537 m, 1580 sh, 1630 sh, 1695 sh, 1665 sh, 1675 s, 1705 s, 1730 sh, 2228 w.

2-[2-(3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazin-6-yl)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carboxylic Acid (*V*)

a) Mixture of 350 mg (1·02 mmol) nitrile *IV* monohydrate, 20 ml 37% HCl, and 5 ml water was refluxed 4 h and evaporated. The evaporation residue was treated with 3 ml water, the precipitated solid was collected by suction after several hours, washed with little ice water, and dried in air. Yield 370 mg (95%) dihydrate. After two crystallizations from water the product melted at 218–221°C with decomposition, the crystal water being lost first. For $C_{13}H_{12}N_6O_8$ (380·3) calculated: 41·06% C, 3·18% H, 22·10% N; found: 41·27% C, 3·03% H, 21·92% N. IR spectrum (Nujol, cm^{-1}): 425 m, 474 w, 497 m, 512 w, 560 m, 580 s, 600 s, 630 m, 676 m, 744 s, 780 m, 797 m, 807 m, 824 m, 880 w, 960 w, 1017 s, 1059 m, 1122 m, 1168 s, 1228 m, 1258 s, 1290 s, 1310 sh, 1333 m, 1410 s, 1500 m, 1536 sh, 1553 s, 1581 m, 1603 sh, 1632 sh, 1645 sh, 1660 sh, 1678 s, 1707 s, 1722 s. 3170 s, 3250 m, 3510 s.

b) Mixture 470 mg (1·02 mmol) hydrazone *II*, 500 mg KOH, and 5 ml water was refluxed 20 min, acidified to pH 0 with conc. hydrochloric acid, and cooled. The separated solid was collected by suction after several days, washed with little ice water, and dried in air. Yield of the dihydrate 280 mg (72%). After two crystallizations from water the product was identical in all respects (m.p., elemental analysis, IR spectrum) with the dihydrate prepared by the above procedure. Drying in vacuum at 120°C results in a weight decrease corresponding to 2 H_2O molecules.

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