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Transformations of 5-azauracil in reactions with some nucleophiles

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Heating 5-azauracil 1 with 3-methyl-1-phenylpyrazol-5-one 2 in boiling butanol gave dipyrazolylmethane 3 and biuret 4; under similar conditions, indoles 5 react with 1 to yield stable 6-indolyl derivatives of 2,4-dioxohexahydro-*s*-triazine 6.

In the presence of a base, 1,3-dimethyl-*s*-triazine-2,4(1*H*,3*H*)-dione reacts with guanidine yielding 5-azacytosine; upon reaction with urea, it is converted into 5-azauracil; the reaction with malonamide affords uracil 5-carboxamide, while that with cyanogen amide gives rise to 5-cyanouracil.[1] When 1,3-dimethyl-5-azauracil reacts with fluoroacetamide in the presence of lithium diisopropylamide, it is converted into 5-fluorouracil.[2] However, no reactions of this sort for unsaturated 5-azauracil are known.

We found that 2,4-dioxo-1,2,3,4-tetrahydro-*s*-triazine (5-azauracil, **1**) reacts with 3-methyl-1-phenylpyrazol-5-one **2** on heating in butanol yielding dipyrazolylmethane **3** and biuret **4** (Scheme 1).

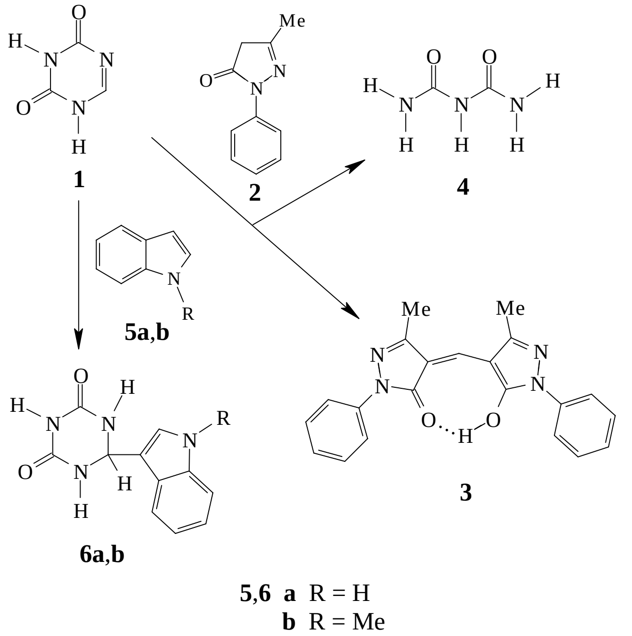
Dipyrazolylmethane **3** is identical to the product that we obtained and studied by X-ray diffraction analysis previously.[3]

Evidently, the dipyrazolylmethane **3** is formed *via* intermediate I_1 resulting from nucleophilic addition of pyrazolone **2** at the C(6) atom of the azauracil **1** (Scheme 2).

The C(6)–N(1) [or C(6)–N(5)] bond is then cleaved, and intermediate I_2 is attacked by the second pyrazolone molecule, and compounds **3** and **4** are thus formed.[†] The fact that the process leads to biuret **4** confirms that the primary nucleophilic attack by pyrazolone is directed at the C(6) atom of 5-azauracil.

The reaction of 5-azauracil with indoles **5** follows a different pathway. When **1** was heated with the indoles **5** in boiling butanol, stable adducts **6** were obtained in high yields.

In addition to the intense molecular ion peak, mass spectra of the compounds **6** exhibit peaks of the $(M-H)^+$, $(M-H-CONH)^+$, $(M-H-HNCONH)^+$ and $(M-H-HNCONH-CO)^+$ ions corresponding to the decomposition of the triazine nucleus. It is noteworthy that this type of decomposition involving abstraction of carbonyl groups is possible only if indole adds at the C(6) atom of the triazine ring.



5,6 **a** R = H
b R = Me

Scheme 1

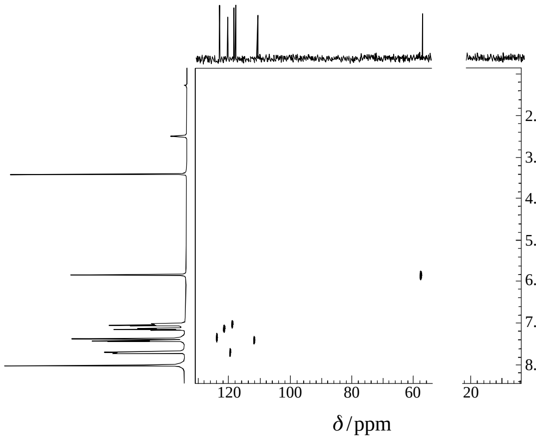


Figure 1 CH correlation for **6a**.

The ^{1}H NMR spectra of **6a**,**b**[‡] contain singlets corresponding to H-6 at 5.8 ppm, whereas the signal for H-6 in the spectrum of the initial 5-azauracil is observed at 8.2 ppm (Figure 1). The signals for the protons of the 1-NH and 3-NH groups are observed at 8.0 ppm as one singlet. This is possible only in the case where the molecule is symmetrical with respect to the axis that passes through the N(2) and C(6) atoms.

The ^{13}C NMR spectrum of compound **6a** (Figures 1, 2) exhibits a signal at 58.04 ppm due to the sp^3-hybridised C(6) atom. This proves unambiguously that indoles add at the C(6) atom of the triazine nucleus of 5-azauracil. The chemical shifts of C(2) and C(4) atoms are identical; this confirms the

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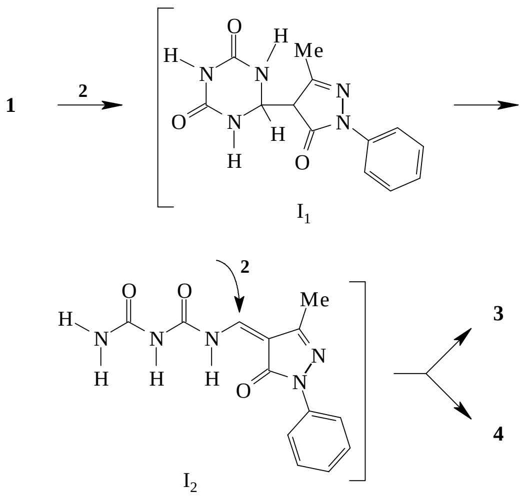
[†] *An example of the preparation of di*(3-*methyl*-1-*phenyl*-5-*oxopyrazol*-4-*yl*)*methane* **3** *and biuret* **4**. 5-Azauracil (131 mg, 1.0 mmol) was refluxed with 3-methyl-1-phenylpyrazol-5-one **2** (348 mg, 2.0 mmol) in 5 ml of butanol for 2 h. The reaction mixture was cooled, and the resulting precipitate of dipyrazolylmethane **3** was filtered off and recrystallised from ethanol to give 250 mg (70%) of **3**. Mp 181–182 °C. The melting point and IR spectra of the product **3** were identical to those of the sample prepared previously.[3]

The mother liquor of the reaction mixture was concentrated to dryness *in vacuo*. The solid residue was recrystallised from ethanol to give 37 mg (36%) of compound **4**. Mp 189–190 °C. The melting point and the IR spectrum of the product were identical to those of an authentic biuret sample.

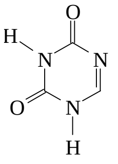
[‡] *An example of the preparation of* 6-*indolyl-derivatives of* 2,4-*dioxohexahydro-s-triazine* **6a**,**b**. 5-Azauracil **1** (1.0 mmol) and the corresponding indole **5a**,**b** (1.0 mmol) were boiled in 3 ml of butanol for 1 h. The reaction mixture was cooled, and the precipitate was filtered off and reprecipitated from dimethylformamide with water to give 75 mg (34%) of compound **6a**. Mp > 250 °C. MS: 230 (M^+), 229 $(M-H)^+$, 186 $(M-H-CONH)^+$, 171 $(M-H-HNCONH)^+$, 143 $(M-H-HNCONH-CO)^+$; ^{1}H NMR ($[^2H_6]$DMSO) δ 5.8 (s, 1H, 6-H), 7.0–7.7 (m, 5H, indole CH), 8.0 (s, 2H, 2×NH), 9.3 (s, 1H, NH), 11.1 (s, 1H, indole NH); ^{13}C NMR ($[^2H_6]$DMSO) δ 58.04 (C6–H), 111.69, 114.10, 118.83, 119.41, 121.44, 124.08, 124.65, 136.64 (indole C), 153.25 (triazine C2, C3). Yield of **6b** 102 mg (42%). Mp > 250 °C. MS: 244 (M^+), 243 $(M-H)^+$, 200 $(M-H-CONH)^+$, 185 $(M-H-HNCONH)^+$, 157 $(M-H-HNCONH-CO)^+$; ^{1}H NMR ($[^2H_6]$DMSO) δ 3.8 (s, 3H, CH_3), 5.8 (s, 1H, 6-H), 7.0–7.7 (m, 5H, indole CH), 8.0 (s, 2H, 2×NH), 9.3 (s, 1H, NH).



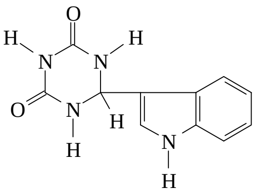
Scheme 2

conclusion that this molecule is symmetrical, which was based on an examination of the ^{1}H NMR spectrum of this compound.

It should be noted that the reactions described above are the first examples of transformation of the 1,3,5-triazine ring in NH-acidic 5-azauracil without charge activation of the reactants. Apparently, the extreme ease of the addition of nucleophiles to 5-azauracil without activation of the substrate or the reagents by a charge is due to the high degree of localisation of the C(6)=N(5) double bond and to the high electrophilicity of the C(6) atom.



1



6a

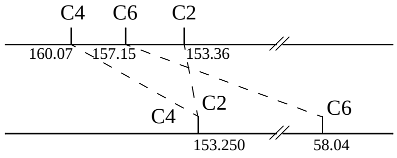


Figure 2 Chemical shifts of the carbon atoms of the triazine ring in **1** and **6a**.

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