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Stable σ-adducts of 5-azauracil with C-nucleophiles

Yurii A. Azev,*[a] Sergei V. Shorshnev[b] and Detlef Gabel[c]

[a] *Urals Scientific Research Institute of Technology of Medical Preparations, 620219 Ekaterinburg, Russian Federation. Fax: +7 3432 22 0781; e-mail: azural@dialup.utk.ru*
[b] *ChemBridge, 119435 Moscow, Russian Federation. Fax: +7 095 956 4948*
[c] *Department of Chemistry, University of Bremen, D-28334 Bremen, Germany. Fax: +49 421 218 2871; e-mail: Gabel@chemie.uni-bremen.de*

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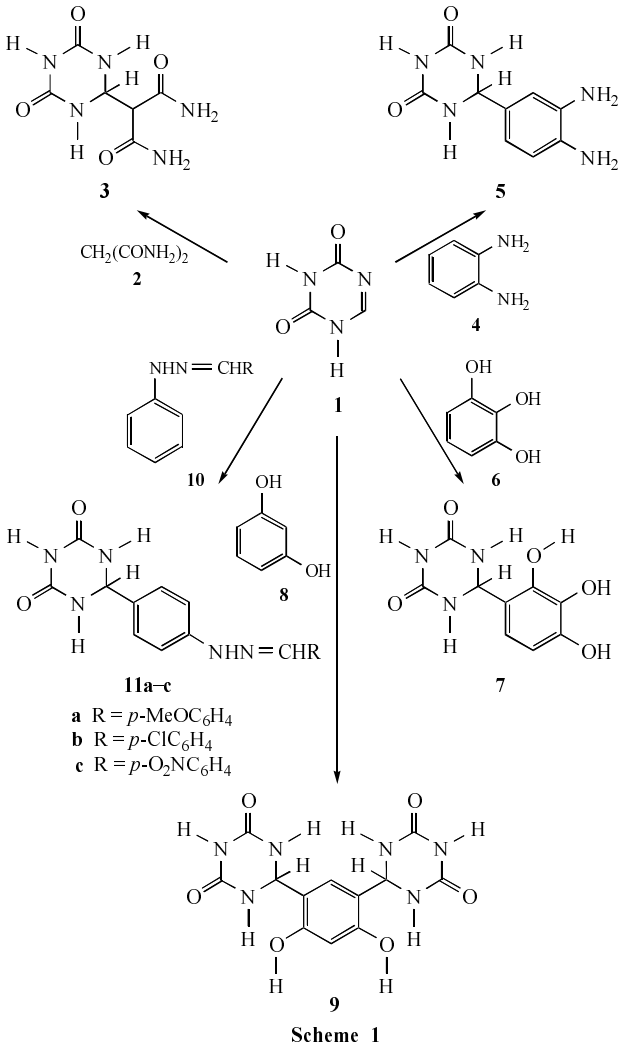
The heating of 5-azauracil 1 with malonamide in butanol resulted in 1,2,3,4,5,6-hexahydro-6-(dicarbamoylmethyl)-1,3,5-triazine-2,4-dione 3. Under conditions of acid catalysis, compound 1 reacted with *o*-phenylenediamine, pyrrogallol, resorcinol and phenylhydrazine derivatives to form the corresponding 6-derivatives of 1,2,3,4,5,6-hexahydro-1,3,5-triazine-2,4-dione.

1,3-Dimethyl-5-azauracil reacts with guanidine or urea in the presence of a base to form 5-azacytosine or 5-azauracil, respectively.[1] 1,3-Dimethyl-5-azauracil also reacts with malonamide or cyanamide to form 5-aminocarbonyl- or 5-cyano derivatives of uracil, respectively.[1] More recently,[2] it was found that 1,3-dimethyl-5-azauracil reacts with fluoroacetamide in the presence of lithium diisopropylamide to afford 5-fluorouracil, which is a well-known anticancer drug. Note that it is believed that σ-complexes with the addition of C-nucleophiles at the C-6 atom of a triazine ring are formed as intermediates in the above reactions of 1,3-dimethyl-5-azauracil. Addition of indole at the C-6 atom of a triazine ring was reported previously.[3]

In this work, we prepared the σ-adduct of 5-azauracil **1** with a β-dicarbonyl compound.† Thus, 1,2,3,4,5,6-hexahydro-6-(dicarbamoylmethyl)-1,3,5-triazine-2,4-dione **3** is formed on heating compound **1** with malonamide **2** (Scheme 1). The ^{1}H NMR spectrum of compound **3** is consistent with the proposed structure. Indeed, a doublet of the nodal proton of a malonamide moiety of the molecule is observed at 3.43 ppm (*J* 8.8 Hz). The nodal H-6 atom of the triazine nucleus is observed at 4.8 ppm as a doublet of doublets of doublets because of the spin–spin interaction with a proton of the malonamide moiety (*J* 8.8 Hz) and NH protons of the triazine nucleus (*J* 4.1 Hz, *J* 4.1 Hz).

It is interesting that σ-adduct **3** was formed even on mixing the reactants in a DMSO solution at room temperature. Thus, the appearance and buildup of σ-adduct **3** in an equimolar mixture of the reactants can be monitored in time by ^{1}H NMR spectroscopy.

We found an unusual reaction between compound **1** and *o*-phenylenediamine **4** in ethanol on heating in the presence of hydrochloric acid, which afforded 1,2,3,4,5,6-hexahydro-6-(3′,4′-diaminophenyl)-1,3,5-triazine-2,4-dione **5**.



Scheme 1

It is likely that the blocking of N-nucleophilic centres in amino groups because of protonation is responsible for the above orientation and reaction of **4** as an 'aromatic' C-nucleophile.

We failed to prepare an unsubstituted hydrazine derivative under analogous conditions. However, the derivatives of 1,2,3,4,5,6-hexahydro-6-(*p*-hydrazinophenyl)-1,3,5-triazine-2,4-dione **11a–c** were smoothly formed in the reaction of **1** with various hydrazones of phenylhydrazine **10**.

The found reaction of **1** with phenols provides an opportunity to prepare another series of 5-azauracil σ-adducts. Thus, 1,2,3,4,5,6-hexahydro-6-(2′,3′,4′-trihydroxyphenyl)-1,3,5-triazine-2,4-dione **7** was formed by the short-term heating of compound **1** with pyrogallol **6** in ethanol in the presence of hydrochloric acid.

† *Reaction of* **1** *with malonamide.* 5-Azauracil **1** (2.0 mmol) was refluxed with 2.0 mmol of malonamide in 10 ml of butanol for 3 h. The reaction mixture was cooled to 20–25 °C; the precipitate of **3** was filtered off and recrystallised from water. Yield 35%, mp 220–221 °C. Found (%): C, 33.4; H, 4.2; N, 32.3. Calc. for $C_6H_9N_5O_4$ (%): C, 33.5; H, 4.2; N 32.5.

General preparation procedure for σ-adducts **5**, **7**, **9** *and* **11**. 5-Azauracil **1** (1.0 mmol) was refluxed with 1.0 mmol of a C-nucleophile in 5 ml of ethanol in the presence of 0.2 ml of concentrated HCl for 1 h. The reaction mixture was cooled to 20 °C; the precipitate formed was filtered off. The hydrochloride of product **5** was dissolved in a minimum amount of water, and the solution was treated with a saturated sodium acetate solution to a neutral pH value. After cooling in an ice bath for 2 h, free product **5** was filtered off. Products **7** and **11** were purified by repricipitation from DMF with water. Adduct **9** was repricipitated from DMSO with water.

For **5**: yield 35%, mp 318–320 °C. Found (%): C, 49.1; H, 4.9; N, 31.6. Calc. for $C_9H_{11}N_5O_2$ (%): C, 48.9; H, 5.0; N, 31.7.

For **7**: yield 55%, mp 215–216 °C. Found (%): C, 45.1; H, 3.9; N, 17.6. Calc. for $C_9H_9N_3O_5$ (%): C, 45.2; H, 3.8; N, 17.6.

For **9**: yield 30%, mp 260–262 °C. Found (%): C, 42.7; H, 3.6; N, 24.8. Calc. for $C_{12}H_{12}N_6O_6$ (%): C, 42.9; H, 3.6; N, 25.0.

For **11a**: yield 55%, mp 275–277 °C. Found (%): C, 60.4; H, 5.0; N, 20.4. Calc. for $C_{17}H_{17}N_5O_3$ (%): C, 60.2; H, 5.1; N, 20.6.

For **11b**: yield 60%, mp 273–275 °C. Found (%): C, 55.8; H, 4.3; N, 20.2. Calc. for $C_{16}H_{14}ClN_5O_2$ (%): C, 55.9; H, 4.1; N, 20.4.

For **11c**: yield 45%, mp 284–286 °C. Found (%): C, 54.0; H, 3.2; N, 23.6. Calc. for $C_{16}H_{14}N_6O_4$ (%): C, 54.2; H, 3.4; N 23.7.

The reaction of compound **1** with resorcinol **8** proceeds differently. In this case, 2,4-bis(2,4-dioxo-1,2,3,4,5,6-hexahydro-1,3,5-triazine-6-yl)-1,5-dihydroxybenzene **9** was obtained under analogous conditions.

Note that σ-adducts with aromatic C-nucleophiles are formed only under conditions of acid catalysis.

The ^{1}H NMR spectra‡ of 5-azauracil σ-adducts with aromatic C-nucleophiles exhibit a typical singlet at 4.8–5.7 ppm due to the H-6 proton at the sp^3-hybridised carbon atom. The *para* addition to a triazine ring is supported by the spin–spin splitting of the protons of aromatic nuclei of *o*-diaminophenyl and phenylhydrazine moieties in compounds **5** and **11**. At the same time, in the case of pyrogallol derivative **7**, two doublets due to aromatic *o*-protons are indicative of the *ortho* addition to an aromatic nucleus.

Resorcinol derivative **9** exhibits two signals due to *p*-protons at the aromatic nucleus and a doubled number of protons at the triazine ring (Figure 1).

The mass-spectrometric fragmentation of the σ-adducts proceeded *via* specific characteristic mechanisms. Thus, all of the above adducts exhibited peaks due to the ions $[M - 2CONH]^{+\cdot}$ or $[M - H - 2CONH]^{+\cdot}$. Note that unsubstituted 5-azauracil does not exhibit fragmentation of this kind.

In addition to an intense peak due to the molecular ion, diaminophenyl and hydrazinophenyl derivatives also exhibit the ions $[M - H]^{+\cdot}$. It is likely that loss of a proton followed by expulsion of carbamide groups takes place in the decomposition of diaminophenyl derivatives.

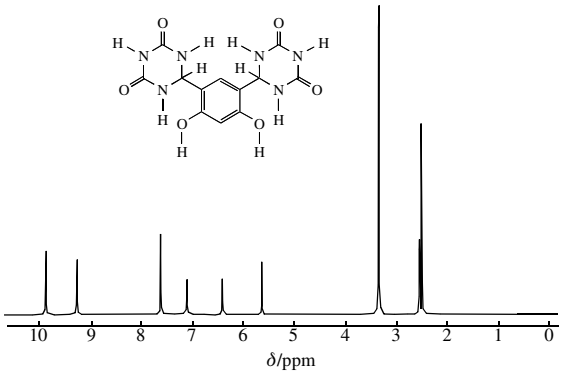


Figure 1 ^{1}H NMR spectrum for compound **9**.

In the other cases, the expulsion of carbamide groups from molecular ions takes place. Pyrogallol and malonamide derivatives **7** and **3**, respectively, do not exhibit peaks due to molecular ions. However, the mass spectra contain peaks that support the degradation of the triazine nucleus in the σ-adducts (ions with *m/z* $[M - 86]^{+\cdot}$). At the same time, the spectra of these σ-adducts exhibit intense peaks due to ions of mass corresponding to the initial components. This fact is indicative of the mass-spectrometric (or thermal) dissociation of these adducts into the parent components under conditions of mass-spectrometric measurements.

Thus, we found new reaction paths and the applicability of 5-azauracil as C-nucleophile acceptor for the formation of stable σ-adducts. The resulting σ-adducts are of interest as model compounds for studying intermediates and reaction mechanisms in the transformations of a triazine ring.[4]

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‡ Spectroscopic data (Bruker AMX 400).

For **3**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.43 (d, 1H, CH malonamide, *J* 8.8 Hz), 4.80 (ddd, 1H, H-6 triazine, *J* 8.8 Hz, *J* 4.1 Hz, *J* 4.1 Hz), 7.27 (br. s, 2H, NH_2), 7.30 (br. s, 2H, NH_2), 7.69 (d, 1H, 1-NH triazine, *J* 4.1 Hz), 7.70 (d, 1H, 5-NH triazine, *J* 4.1 Hz), 9.28 (br. s, 1H, 3-NH triazine).

For **5**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.5 (s, 4H, $2NH_2$), 5.2 (s, 1H, H-6), 6.4 (d, 1H, CH arom., *J* 7.8 Hz), 6.5 (d, 1H, CH arom., *J* 7.8 Hz), 6.6 (s, 1H, CH arom.), 7.8 (s, 2H, 2NH), 9.2 (s, 1H, NH).

For **7**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 5.6 (s, 1H, H-6), 6.3 (d, 1H, CH arom., *J* 7.8 Hz), 6.5 (d, 1H, CH arom., *J* 7.8 Hz), 7.6 (s, 2H, 1,3-NH), 8.4 (br. s, 1H, OH), 8.6 (s, 1H, OH), 9.2 (br. s, 2H, NH, OH).

For **9**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 5.6 (s, 2H, H-6, H-6′), 6.4 (s, 1H, CH arom.), 7.1 (s, 1H, CH arom.), 7.6 (s, 4H, 1,5,1′,5′-NH), 9.2 (s, 2H, 3,3′-NH), 9.8 (s, 2H, 2OH).

For **11a**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 3.8 (s, 3H, OMe), 5.4 (s, 1H, H-6), 6.9 (d, 2H, *J* 8.3 Hz, CH arom.), 7.1 (d, 2H, CH arom., *J* 8.7 Hz), 7.2 (d, 2H, CH arom., *J* 8.3 Hz), 7.6 (d, 2H, CH arom., *J* 8.7 Hz), 7.8 (s, 1H, CH=N), 7.9 (s, 2H, 1,5-NH), 9.3 (s, 1H, NH), 10.2 (s, 1H, NH).

For **11b**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 5.4 (s, 1H, H-6), 7.1 (d, 2H, CH arom., *J* 7.9 Hz), 7.2 (d, 2H, CH arom., *J* 7.9 Hz), 7.4 (d, 2H, CH arom., *J* 8.3 Hz), 7.7 (d, 2H, CH arom., *J* 8.3 Hz), 7.8 (s, 1H, CH=N), 8.0 (s, 2H, 1,3-NH), 9.3 (s, 1H, NH), 10.5 (s, 1H, NH).

For **11c**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 5.5 (s, 1H, H-6), 7.2 (d, 2H, CH arom., *J* 8.3 Hz), 7.3 (d, 2H, CH arom., *J* 8.3 Hz), 7.9 (d, 2H, CH arom., *J* 8.5 Hz), 8.0 (s, 1H, CH=N), 8.1 (s, 2H, 1,5-NH), 8.2 (d, 2H, CH arom., *J* 8.5 Hz), 9.3 (s, 1H, NH), 11.0 (s, 1H, NH).