

Hydroxyalkylation of 6-Aminouracil

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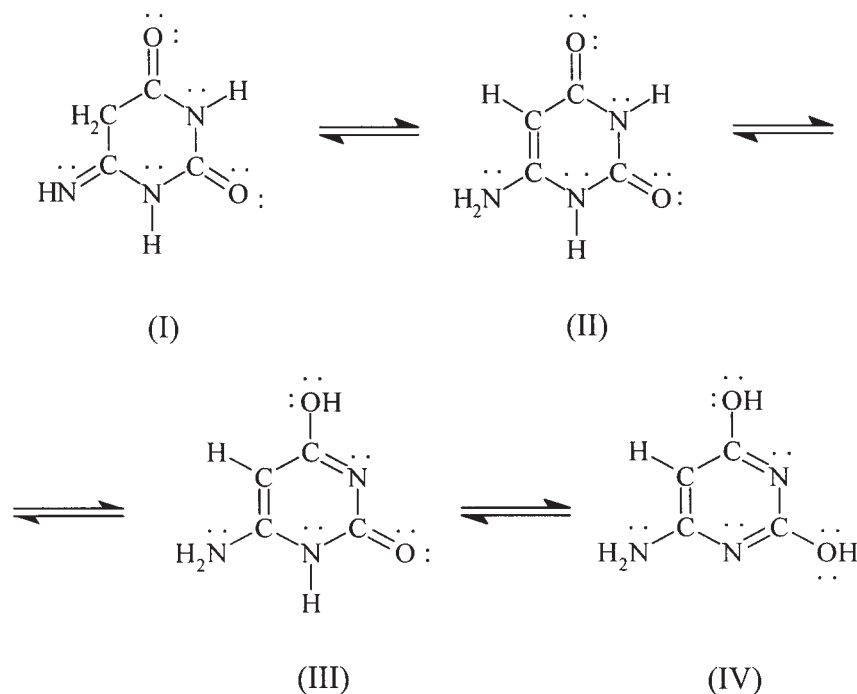
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ABSTRACT: Reactions of 6-aminouracil with formaldehyde, ethylene and propylene oxide, and ethylene carbonate were studied. Hydroxyalkyl derivatives of 6-aminouracil were prepared. The structure of the products were established by elemental analysis, $^1\text{H-NMR}$, and IR techniques.
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Key words: ring-opening polymerization; heteroatom-containing polymers; NMR; 6-aminouracil; hydroxyalkylation

INTRODUCTION

6-Aminouracil (6-amino-1H,3H-pyrimidine-2,4-dione, 6-AU) is a tetrafunctional compound, present in various tautomeric forms:



In the solid state, form (II) of 6-AU dominates.^{1,2} 6-AU is a white solid, which decomposes without melting at temperatures higher than 300°C. It dissolves well in 10% aq. NaOH, slightly in DMSO, and

in mineral acids.³ 6-AU gives barbituric acid when heated with concentrated hydrochloric acid or with sulfuric(VI) acid.^{3,4}

6-AU and its alkyl-, aryl-, and hydroxyalkyl-derivatives are semiproducts in the synthesis of drugs used for heart diseases,^{5–8} asthma,^{9,10} tumor,^{11–13} allergy,^{14,15} and depression.¹⁶ Hydroxyalkyl derivatives of 6-AU can be prepared in the reaction of cyanoacetic acid with *N*-(2-hydroxyethyl)urea (1- or 3-substituted derivatives)⁶ and

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in the reaction of 6-chlorouracil, or 6-AU, or their 1,3-dialkyl derivatives with aminoalcohols, e.g., 2-aminoethanol or 3-aminopropanol (substituted derivatives at N atom of amine group).^{7,17-21} In this work, the possibilities of synthesis of hydroxyalkyl derivatives of 6-AU in the reactions of 6-AU with formaldehyde, oxiranes, and ethylene carbonate are presented. These derivatives can be used as precursors in the synthesis of oligoetherols of improved thermal stability.

EXPERIMENTAL

Reaction of 6-AU with formaldehyde

To a round-bottomed flask (100 cm³) equipped with a reflux condenser, thermometer, and stirrer, 2.4 g (0.1 mol) of 6-AU (pure, Sigma-Aldrich, Germany) was introduced with a proper amount of formalin (pure, PPH POCh, Gliwice, Poland). The initial molar ratio of 6-AU to formaldehyde was equal to 1 : 4, 1 : 6, or 1 : 8. The content was heated, with continuous stirring. Temperature and time of reaction course depended on the initial molar ratio of 6-AU to formaldehyde, namely, 50°C and 10–20 min. for the ratio 1 : 4; 85°C and 10 h for the ratio 1 : 6; and finally, 85°C and 4–5 h for the ratio 1 : 8. In the first case, a precipitate was obtained as a product, which was washed with acetone and dried; in the second case, a precipitate and a solid resin-like substance were obtained as products (water was distilled off from the filtrate at a of pressure 2.7 kPa); and in the third case, a solid resin was obtained.

Reaction of 6-AU with oxiranes

To a glass pressure reactor (250 cm³) equipped with a stirrer, 6.4 g (0.05 mol) 6-AU and 25 cm³ DMSO (pure Aldrich, Germany) were introduced with a proper amount of catalyst and oxirane (see under Amounts of oxiranes). The content was heated and stirred. Temperature and time of reaction depended on the type of oxirane; namely, 50–70°C and 55–89 h for EO; 60–80°C and 78–178 h for PO. 6-AU was gradually dissolved during the reaction course, and the reaction mixture became brown. The end of the reaction was established by determining the epoxy number of the reaction mixture. Next, the solvent and catalyst were distilled off at reduced pressure (2.7 kPa). The product had a resin appearance.

Amounts of oxiranes

1. Ethylene oxide (EO; pure, Fluka, Switzerland) 8.8 g (0.2 mol), 17.6 g (0.4 mol).
2. Propylene oxide (PO; pure, Fluka, Switzerland) 11.6 g (0.2 mol), 23.2 g (0.4 mol).

In the reactions with EO and PO, 1 and 2 cm³ of triethylamine (TEA; p.a., Fluka, Switzerland) were used as a catalyst, respectively.

Reaction of 6-AU with ethylene carbonate

To a round-bottomed flask (100 cm³) equipped with a reflux condenser, thermometer, and stirrer, 6.4 g (0.05 mol) 6-AU and 17.6 g (0.2 mol) or 35.2 g (0.4 mol) ethylene carbonate (EC; pure, Fluka, Switzerland), and 0.2 g potassium carbonate as a catalyst were introduced. The contents were heated to 160°C, with continuous stirring. The reaction was conducted for 6.5–8 h at this temperature. The reaction course was controlled by determining the amount of unreacted EC. The resin-like product had dark brown color.

Analytical methods

In the anhydrous products of the reactions of 6-AU with formaldehyde, the amount of nonpermanently bonded formaldehyde in the form of *N*- and *O*-hydroxymethyl groups was determined iodometrically.²² The epoxy number was determined by titrating a sample with a dioxane solution of hydrochloric acid.²³ The acid number was determined by titrating a sample dissolved in 20 cm³ DMSO and 5 cm³ H₂O with 0.1M NaOH. An amount of unreacted EC was determined with barium hydroxide.²⁴ Elemental analysis of products (C, H, N, S) was performed using EA-1108 (FISONS, Italy) analyzer. The infrared spectra were recorded on a Fourier transform IR PARAGON 1000 spectrometer (PerkinElmer, Norwalk, CT). The samples for IR analysis were prepared in the form of capillary films or as KBr tablets. The ¹H NMR spectra of products were recorded on an 80 MHz BS-586A spectrometer (Tesla, Czechoslovakia). The solvent was d₆-DMSO with HMDSO internal standard.

RESULTS AND DISCUSSION

Reactions of 6-AU with formaldehyde were carried out by directly mixing 6-AU with the proper amount of formalin for variable initial molar ratios of substrata. Two types of products were obtained: precipitate and/or solid resin-like substance. Determined amounts of formaldehyde in the products are half of these, calculated from the initial molar ratio of substrates (see Table I). In the reaction, in which the initial molar ratio 6-AU and formaldehyde is equal to 1:6, two products were obtained: di- or tetra-(hydroxymethyl) derivatives of 6-AU (see Table I). The structure of the products were studied more precisely by using IR and ¹H NMR spectroscopy. In comparison with the IR spectrum of pure 6-AU, the IR spectra of the products of the reaction of 6-AU with formaldehyde (Fig. 1)

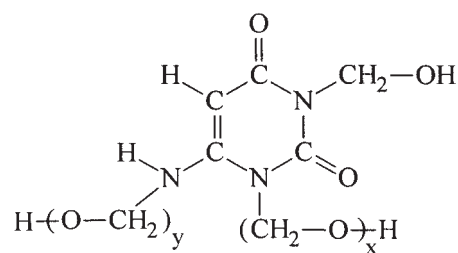
TABLE I
Content of Formaldehyde in Hydroxymethyl
Derivatives of 6-AU

Initial molar ratio 6-AU:CH ₂ O	Content of formaldehyde (wt %)		Molar ratio 6-AU:CH ₂ O in product
	Calculated	Found	
1:4	48.56	33.20	1:2.1
1:6 (precipitate)	58.61	31.40	1:2.1
1:6 (resin)	58.61	48.37	1:4
1:8	65.38	48.70	1:4

showed changes in the range 3400–2700 cm⁻¹. The changes correspond to the appearance of stretching vibrations of hydroxy groups and methylene groups, and the disappearance of N—H vibrations in ⁺NH₃ groups (from zwitter-ion of 6-AU), and those of N(1)—H groups and N(3)—H groups. The changes show that nitrogen-attached hydrogen atoms in the ring were substituted by hydroxymethyl groups. Absence of bands of deformation vibrations of N(1)—H groups and N(3)—H groups at 1291 and 1237 cm⁻¹, respectively, also confirms the substitution of hydrogen atoms. Instead, the band of stretching vibrations of C—O in primary alcohols at 1022 cm⁻¹ appears.

In the ¹H NMR spectra of these compounds (Fig. 2), the resonances from H—C= protons at 4.4 ppm, methylene groups protons at 4.5–4.9 and 5.2 ppm, amine groups protons at 6.2–6.5 ppm were observed. The signal from protons in hydroxy groups partially overlaps with the signal from protons in methylene groups (5.0–6.0 ppm). This was confirmed by spectra with D₂O added to the sample. Signal of protons in N(1)—H groups and N(3)—H groups (at 10 ppm) was absent. It indicated again that these nitrogen atoms are substituted by hydroxymethyl groups.

The structure of the obtained hydroxymethyl derivatives of 6-AU can be presented as



(V)

where: $x = 1, y = 0$ or $x + y = 3$

Reactions of 6-AU with oxiranes were conducted in DMSO solutions, using TEA as a catalyst. The simplest oxirane, that is EO and PO, were used for synthesis. Consistency of the obtained resins depends both on the kind and amount of the substituted oxirane. The structure of the products were studied by using elemental analysis, IR, and ¹H NMR spectra. In the IR spectra of the products, the analogous changes as previously described are observed. Additionally, bands of methylene group stretching and deformation vibrations appear. Analysis of ¹H NMR spectra of the products indicates the presence of three hydroxyl groups and one nonsubstituted hydrogen atom in amine group (in the higher products of substitution e.g., those obtained at the ratio 1:8, as well). Ratios of areas of the signals from protons of methylene or methyl groups, protons of H—C= groups, and protons of hydroxyl and amine groups indicate quantitative addition of oxirane to 6-AU (in contrast to reactions with formaldehyde). The structure of the obtained hydroxyalkyl derivatives of 6-AU can be presented as

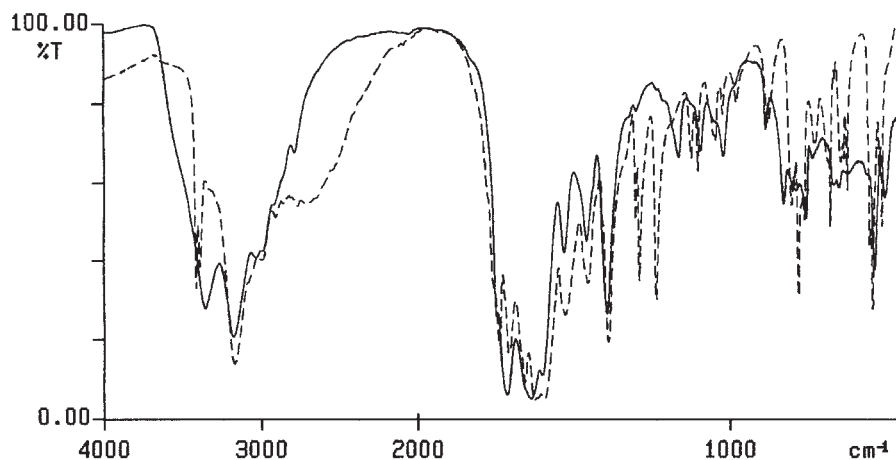


Figure 1 IR spectra of 6-AU (---) and of the product of the reaction of 1 mol of 6-AU with 4 mol of formaldehyde (—).

where: $4 \leq w + x + y + z \leq 8$

CONCLUSIONS

In the reactions of 6-AU with 4, 6, and 8 mol of formaldehyde di-, di- and tetra-, and tetra-(hydroxymethyl) derivatives of 6-AU are obtained, respectively. 6-AU reacts with an excess of oxiranes, that is EO and PO, in DMSO solutions and in the presence of TEA as a catalyst. The products are the proper hydroxyalkyl derivatives of 6-AU and are oligoetherols. 6-AU reacts with EC without any solvent but in the presence of potassium carbonate as a catalyst. The products are resins which have a structure similar to the products of the reactions of 6-AU with EO.

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