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Polydental Anions of 2-Amino-6-Methylpyrimidin-4-One

H. I. Nurboev [1]

Abstract

The article presents the results of studying the alkylation reaction of 2-amino-6-methylpyrimidin-4-one with higher alkyl halides (C4-C9) in absolute alcohol. When electron density is distributed in the 2-amino-6-methylpyrimidin-4-one anion, alkylation products of N-.1, N-3 or the exocyclic amino group are not formed.

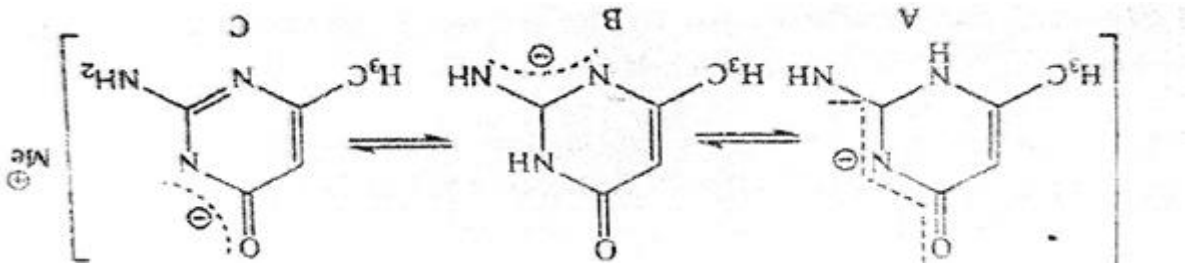
Key words: 2-amino-6-methylpyrimidin-4-one, alkyl halides C4.-C9, N-, O- alkylation isomers.

[1] Samarkand Medical University, Department of Biological Chemistry

The alkylation of 2-oxo, -thioxo, -selenoxo-6-methylpyrimidin-4-ones has been well studied in the literature [1-4]. Unlike 2-oxo- -thioxo-, -selenoxopyrimidin-4-ones, the amino group of 2-amino-6-methylpyrimidin-4-one is predominantly in the amino form, where the double bond is located between the N^1 and C^2 atoms of the ring, and in position 3 there is hydrogen atom.

Therefore, to study the comparative reactivity and direction of the alkylation reaction of these compounds, in our opinion, it was necessary to study the interaction of 2-amino-6-methylpyrimidin-4-one (1) with C_4-C_9 alkyl halides.

In salts of 2-amino-6-methylpyrimidin-4-one (1) The electron density is delocalized between several atoms. And its anion is polydental [1]. Five (O^4-C^4-N^3-C^2-N^2 fragment) or three (N^1-C^4-N^2 or O^4-C^4-N^3 fragments) atoms of the pyrimidine ring are involved in the delocalization of electron density.



For this system there are potential reaction centers: N^3, N^2, N^1, O.

In the IR spectrum of the sodium salt of 2-amino-6-methylpyrimidin-4-one there is no absorption band at 1680 cm, characteristic of the CO of the parent molecule. This indicates the coordination of the metal with the oxygen atom, that is, the carbonyl group takes part in salt formation. In this regard, an anion is realized during alkylation.

Objects and methods of research. The object of study is 2-amino-6-methylpyrimidin-4-one, iso-butyl chloride, BT-butyl iodide, n-pentyl chloride, n-hexyl chloride and n-heptyl iodide. Research methods include analysis of the structures of synthesized compounds using IR and PMR spectra.

IR spectra were taken on a UR-20 spectrophotometer in KBr tablets and on a PERKIN device

ELMER System 2000 FT-IR, mass spectra on an MX-1303 spectrophotometer, PMR spectra. Tesla BS-567 A (internal standard GMDS, δ scale) Rf values are determined on “Silufol? UV-254. System acetone methanol (3:1). Developer: iodine vapor.

Solvents (acetonitrile, alcohol, DMF, DMSO) were purified and absolute according to the standard procedure [7].

Synthesis of 2-amino-6-methylpyrimidin-4-one. (l). 26 g (0.2 mol) of acetoacetic ether (solution 1) was added to a solution of sodium ethoxide (from 4.6 g of sodium and 120 ml of absolute ethanol).

To another solution prepared from 4.6 g (0.2 mol) of sodium and 6 ml of absolute ethanol, 1.92 g (0.2 mol) of guanidine hydrochloride was added and heated in a boiling water bath for 30 minutes under reflux. The precipitated sodium chloride was filtered off, and the filtrate containing free guanidine was added to a solution of the sodium derivative of acetoacetic ester (to solution I). The reaction mixture was heated with stirring for 3 hours. The alcohol was distilled off, 50 ml of boiling water was added to the residue, neutralized with glacial acetic acid to pH = 5.0, the precipitate was cooled, filtered, washed with water, alcohol, and sulfuric ether. Yield of 2-amino-6-methylpyrimidin-4-one 18 g (72%). T, pl. 260^0C (ethanol). Alkylation of 2-amino-6-methylpyrimidin-4-one with methyl iodide. Synthesis 2 (R-CH3) A mixture of 1.25 g (10 mmol) of 2-amino-6-methylpyrimidin-4-one (1), dissolved in 70 ml of alcohol, 0.64 g (10 mmol) of potassium hydroxide, 1.42 g (10 mmol) methyl iodide was boiled for 2 hours. A precipitate appears. The reaction mixture was diluted with water and dried. After recrystallization from alcohol, 0.9 g (64%) of 3,6-dimethyl-2-aminopyrimidin-4-one (2, R=CH3,) was obtained: T, pl. 236-230ºC. IR spectrum: A 1665 (ν C=0) 3360 (υ CNH_2). PMR spectrum (CH_3COOH): 2.03 ppm. (3H, C, C^6-CH_3), 3,30 ppm. (3H, C,N^3-CH_3,), 5.90 ppm. (1HI,C, C^5-H), 754 ppm. (2H, C^2-NH_2).

Alkylation of 2-amino-6-methylirimid-4-one. To a solution containing 0.35 g (2.8 mmol) of 2-amino-6-methylpyrimidin-4-one (1) in 10 ml of absolute alcohol, 0.14 g (2.5 mmol) of potassium hydroxide and 1.8 mmol of an alkylating agent were added in 2 ml of solvent. The reaction was carried out at room temperature (24 hours). The reaction mixture was decomposed with 50 ml of cold water. The resulting precipitate was filtered off, the filtrate was extracted with chloroform, the organic layer was dried over anhydrous sodium sulfate. Chloroform was distilled off, and the residue was washed with ether.

Alkylation of 2-amino-6-methylpyrimidin-4-one with sec-butyl iodide. The reaction was carried out in 20 ml of absolute alcohol. From 0.28 g (5.0 mmol) KOH, 0.64 g (5.0 mmol) 2-amino-6-methylpyrimidin-4-one and 0.47 ml (5.0 mmol) sec-butyl iodide, we obtained 0.80 g (89%) 4-sec-butyloxy-2-amino -6-

methylpyrimidine. (3, R = sec.-C4H9) M.p. 160-162°C (ethanol).

IR spectrum: 1650 (υ CN), 1610 (υ C=C).

4-n-pentyloxy-2-amino-6-methylpyrimidine (3, R=n-C5H11). From 0.64 g (5.0 mmol) of 2-amino-6-methylpyrimidin-4-one, 0.5 ml (5.0 mmol) n-pentyl chloride, 0.28 g (5.0 mmol) potassium hydroxide in 18 ml of absolute alcohol, 0.53 g (52%) of the product was obtained 3, e m.p. 220-222°C (ethanol).

IR spectrum: 1650 (υ CO).

4-n-heptyloxy-2-amino-6-methylpyrimidine (3, R=n-C6H13). Similarly to the above, from 0.64 g (5 mmol) of compound 1 and 0.7 ml (5.0 mmol) hexyl chloride in 18 ml of absolute alcohol, 0.28 g (5.0 mmol) of potassium hydroxide we obtained 0.52 g (51%) of product 3 (R=n-C6H13) m.p.p. 150-152°C (ethanol).

IR spectrum: 1647(υCN),1518(υC=C), 1588(υC=N), 3378, 3098 (υNH).

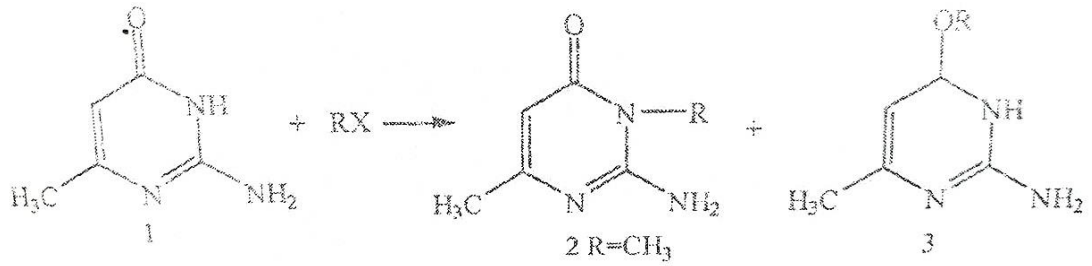
4-n-heptyloxy-2-amino-6-methylpyrimidine (3, R=n-C7H15). From 0.64 g (5.0 mmol) of the starting compound 1, 0.8 ml (5.0 mmol) of heptyl iodide, similarly to that described above, we obtained 0.98 g (100%) of product 3 m.p. 138-140°C (ethanol).

IR spectrum: 1647 (υ CN), 1520 (υ C=C), 1587 (υ C=N), 3376, 357 (υ NH).

Mass spectrum, m/z($I_{отн}$ %): 223 (M^+: 23), 206(M^+:-17;7), 194(M^+-29;20), 180(M^+-43; 21), 152(M^+--71, 23), 149 (M^+-74;30) 140(- 83; 10), 138(M^+-85; 43), 129(M^+- 94; 16), 125(M^+-98, 100),109(M^+ -114;23)

Results and its discussion. A study of the methylation reaction of 2-amino-6-megylpyrimidin-4-one salts showed that it occurs mainly at the nitrogen atom in position 3 [2], and only in some cases was the product of alkylation of the oxygen atom at C-4 found. 2-amino-4-methoxy-6-methylpyrimidine (5-10%). Of interest was the process of studying the alkylation of 2-amino-6-methylpyrimidin-4-one (1) with higher alkyl halides (C_4-C_8). The study of this reaction with isomeric butyl bromides and butyl chlorides, n-hexyl bromide and n-heptyl iodide showed that in all cases the formation of O-alkylation products - 2-amino-4-alkoxy-6-methylpyrimidines (3) occurs. To determine isomeric N-3 and O-4 methyl products, the NMR spectrum is successfully used, where the methyl group at N-3 gives a proton signal at 3.30 ppm, and the OCH_3 group at 4.41 ppm. We used this method to interpret the ratio of N_3/O_4 isomers [l].

Their PMR spectrum is characterized by the presence of a triplet proton signal centered at δ 3.92 to 4.12 ppm. It can be classified as O-CH_2 protons. In addition to these signals, the NMR spectrum of 2-amno-4-hexyl (heptyl) hydroxy-6-methylpyrimidines contains a signal from the protons of the terminal methyl group in the form of a triplet at 0.60 (0.64), a broadened singlet of 3 CH_2 groups at 1.00 (1.00), broadened multiplet at 1.64 (1.67), singlet of the C_6-CH_3 group at 2.02 (2.00), methylene protons of the O-CH_2 group at 4.10 (4.12) in the form of a doublet-doublet and the H-5 proton in the form of a singlet at 5.91 (5.9) m.d. respectively.



Similar results were obtained in the alkylation of 2-amino-b-methyllyrimidn-4one with sec-butyl iodide. The PMR spectrum of the product basically coincides with that for alkylation products with alkyl halides of normal structure, and has the following values: 0.80 ppm. (triplet, terminal CH_3,). 1.25 (doublet CH-CH_3) 1.50 (multiplet, CH_2), 2.08 ppm. (C_6-CH_3), 3.92 (multiplet, OCH_2), 6.12 ppm. (N-5). The value of the chemical shift of the multiplet at 3.92 ppm. indicates the presence of a s-butyl residue at the oxygen

atom at C-4.

The interpretation of the PMR spectra of the products of alkylation of 2-amino-6-methylpyrimidin-4-one with alkyl halides is confirmed by the data obtained for 2-aminopyrimidin-4-ones having a methyl group in various positions. Thus, if in 2-amino-6-methylpyrimidin-4-one itself the methyl group gives a signal at 1.97 ppm, and the H-5 proton at 5.70 ppm, then the cholesterol values of the methyl groups of 2-amino-3 ,6-dimethyliirimidin-4-one (R=CH_3) were at 1.99 ppm. and 5.82 ppm respectively. The methyl group protons at N-3 appear at 3.22 ppm. In the case of 2-methylamino-6-methylpyrimidin-4-one, these values were: 1.90 ppm. (C_6-CH_3, singlet), 5.81 ppm. (N-5, singlet). The methyl group protons located at the exocyclic amino group are observed as a singlet at 3.13 ppm. A comparison of the direction of the alkylation reaction of 2-amino-6-methylpyrimidin-4-one with its methylation with methyl iodide and methyl tosylate shows that the direction of the reaction between them is sharply different. In the case of methyl iodide and methyl tosylate, the reaction occurs predominantly at the N_3 atom. When alkylated with C_4-C_9 alkyl halides, the reaction occurs at the O^4 oxygen atom, which indicates a significant influence of the volume of the alkyl residue and its structure. In this case, alkylation of the N-3 center, that is, the formation of compound 2, does not occur.

In contrast to the alkylation of 2-amino-6-methylpyrimidin-4-one with methyl iodide and methyl tosylate in various solvents, where predominant N-alkylation occurs, the methylation of 2-amino-6-phenylpyrimidin-4-one also produces the O^4-methyl product (reaction with methyl tosylate in DMF). The authors of [1] explain this fact by the thermodynamic controllability of the O-alkylation process. This can also explain the predominant O-alkylation in the case of the interaction of 2-amino-6-methylpyrimidin-4-one with C_4-C_9 alkyl halides. Dual reactivity, that is, alkylation of N^3: and O^4 centers, was discovered in the reaction of 2-oxo- and -thioxo-b-methylpyrimidin-4-one with C_4-C_9 alkyl halides [3,4].

Exclusive N^3-methylation occurs during the alkylation of 2-aminopyrimidin-4-one fused with a benzene ring, 2-aminoquinazolin-4-one, in various solvents [5,6]. Increasing the polarity of the solvent or the “hardness” of the alkylating agent and the reaction conditions leads to an increase in the yield of the N^3 alkylation product without changing the direction of the reaction. In this case, the main factor determining the direction of the reaction, as in other cases, is the thermodynamic stability of the O^4 product [5].

The introduction of both electron-donating and electronegative substituents, as well as substituents with an I-effect into the 2-aminoquinazolin-4-one molecule, changing the basicity of the reaction centers, changes the direction of the reaction and leads to the formation of a mixture of N^3 and O^4 methyl products [6].

Conclusion: This article presents studies of the alkylation reaction of 2-amino-6-methylpyrimidin-4-one with higher alkyl halides. When the electron density is distributed in the 2-amino-6-methylpyrimidin-4-one anion, no cyclic amino groups are formed.

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