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Chemistry

ELECTROPHILIC INTRAMOLECULAR CYCLIZATION OF 1-(*N*-ALKENYL)-6-METHYLPYRIMIDINE-2,4-DIONES

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Abstract. *N*-Allyl(cinnamyl)substituted derivatives of 6-methyluracil were synthesized. The reactions of their bromo- and iodocyclization were performed which led to the formation of the derivatives of dihydrooxazolo-pyrimidinium and dihydrooxazinepyrimidinium. The factors that favor the regioselectivity of these reactions were suggested.

Keywords: electrophilic intramolecular cyclization, methyluracil, bromocyclization, iodocyclization, regio-selectivity, dihydrooxazolopyrimidinium, dihydro-oxazinepyrimidinium.

1. Introduction

Recently, the researchers have synthesized a series of heterocyclic compounds which are derivatives of oxazoles, thiazoles, imidazoles, pyridines, pyrimidines, benzimidazoles, benzothiazoles [1-6]. Such an interest in these heterocycles is caused by their rather high biological activity.

The solution of heterocycles and heterocyclic systems synthesis problems is a wider use of electrophilic intramolecular cyclization reactions [7, 8]. This is favored by the search for new variants of this reaction with still insufficiently studied functional groups of unsaturated compounds and the involvement of new electrophilic reagents. Recently, special attention is paid by the researchers to the reactions of electrophilic intramolecular heterocyclization of alkenyl- and alkynyl- substituted heterocycles [9-11]. The development of the synthesis methods for pyrimidine-based heterocyclic systems *via* its alkenyl derivatives intramolecular cyclization is of practical importance. The use of the latest techniques allows to obtain a range of compounds that are interesting in structure and properties and which can both be directly used and serve as synthetic blocks for more complex structures [12-14].

The objective of this study was the determination of the possible participation of oxygen atoms of 6-methylpyrimidine-2,4-dione alkenyl derivatives as nucleophilic centers in the electrophilic heterocyclization reactions and the study of the regiochemistry of the heterocycles formed as the result of these reactions.

2. Experimental

Commercially available materials were used without further purifications. 6-Methyluracil was produced by the oxidation of 6-methylthiouracil by 1,2-propyleneoxide [15].

The spectra of ^{1}H NMR of synthesized compounds were obtained on the device spectrometer Varian VXR-300 in DMSO-d_6 solution. The reaction process was controlled by a thin-layer chromatography on Silufor UV-254 in a solvent system chloroform–acetone 10:1.

2.1. General Procedure for the Preparation of Compounds 2, 3, 6

Let us take **2** for example. In a 250 ml round-bottom flask equipped with a reflux condenser, we poured 45 ml of ethyl alcohol, 1.5 g (0.012 mol) of 6-methyluracil, 0.83 g (0.015 mol) of KOH and 1.21 ml (0.015 mol) of allyl chloride. The reaction mixture was boiled for 3 h (controlled by TLC analysis), then KCl was filtered, alcohol was evaporated. The formed oil was rubbed with acetone. The formed precipitate was filtered and dried.

1-(*N*-Allyl)-6-methylpyrimidine-2,4-dione (**2**): Yield 0.89 g (45 %). mp 410–412 K. ^{1}H NMR in DMSO: δ 1.933 (s, 3H, $-CH_3$); 3.31 (d, 2H, NCH_2); 3.495 (d, 2H, CH_2=); 3.73 (m, 1H, CH=); 5.401 (s, 1H, 5-H). Found, %: C 57.67; H 5.97; N 16.53; S 19.16. $C_8H_{10}N_2O_2$. Calc., %: C 57.83; H 6.02; N 16.87; S 19.28.

1-(*N*-Cinnamyl)-6-methylpyrimidine-2,4-dione (**3**): Yield 0.98 g (40 %). mp 431–433 K. ^{1}H NMR in DMSO: δ 2.201 (s, 3H, $-CH_3$); 3.993 (d, 2H, NCH_2); 6.004 (s, 1H, 5-H); 6.418 (m, 1H, CH=); 6.715 (d, J=15.0, 1H, =CH–C_6H_5); 7.247–7.406 (m, 5H, H_{arom}). Found, %: C

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69.33; H 5.67; N 11.39; S 13.14. $C_{14}H_{14}N_2O_2$. Calc., %: C 69.42; H 5.79; N 11.57; S 13.22.

1,3-(*N*,*N*-Cinnamyl)-6-methylpyrimidine-2,4-dione (**6**): Yield 0.65 g (62 %). mp 454–455 K. ^{1}H NMR in $CDCl_3$: δ 2.254 (s, 3H, $-CH_3$); 4.015 (d, 2H, NCH_2); 5.029 (d, 2H, NCH_2); 6.046 (s, 1H, 5-H); 6.265 (m, 1H, CH=); 6.404 (m, 1H, CH=); 6.649 (d, J=15.1, 1H, $=CH-C_6H_5$); 6.709 (d, J=15.1, 1H, $=CH-C_6H_5$); 7.239–7.431 (m, 10H, H_{arom}). Found, %: C 77.24; H 6.07; N 7.69; S 8.98. $C_{23}H_{22}N_2O_2$. Calc., %: C 77.09; H 6.15; N 7.82; S 8.94.

2.2. General Procedure for the Preparation of Compounds 4a, 5a, 7a

Let us take **4a** for example. In a 100 ml flat-bottom flask we dissolved 0.3 g (0.00181 mol) of 1-(*N*-allyl)-6-methylpyrimidine-2,4-dione in 7 ml of acetic acid (20 ml chloroform). Then 0.19 ml (0.00362 mol) bromine in 7 ml of acetic acid (10 ml chloroform) was slowly added to the solution under intensive stirring of the reaction mixture. After complete addition of bromine the stirring continued for 4 h, and then the mixture was left for one day. The formed precipitate was filtered, recrystallized from chloroform, and dried at 353–363 K.

2-Bromomethyl-5-methyl-2,3-dihydrooxazolo-8H-[3,2-b]pyrimidinium tribromide (**4a**): Yield 0.44 g (50 %). mp 492–494 K. ^{1}H NMR in DMSO: δ 2.245 (s, 3H, $-CH_3$); 3.82 (d, 2H, NCH_2); 4.26 (m, 2H, CH_2Br); 5.38 (m, 1H, 2-H); 6.39 (s, 1H, 6-H). Found, %: C 19.63; H 2.03; Br 65.64; N 5.53; S 6.46. $C_8H_{10}Br_4N_2O_2$. Calc., %: C 19.75; H 2.06; Br 65.84; N 5.76; S 6.59.

2-Phenyl-3-bromo-6-methyl-2,3-dihydrooxazine-9H-[3,2-b]pyrimidinium tribromide (**5a**): Yield 0.35 g (38 %). mp 501–503 K. ^{1}H NMR in DMSO: δ 2.230 (s, 3H, $-CH_3$); 3.762 (d, 2H, NCH_2); 5.222 (m, 2H, CH_2Br); 5.639 (d, J=15.0, 1H, $=CH-C_6H_5$); 6.053 (s, 1H, 7-H); 7.40–7.551 (m, 5H, H_{arom}). Found, %: C 29.78; H 2.43; Br 56.85; N 4.82; S 5.54. $C_{14}H_{14}Br_4N_2O_2$. Calc., %: C 29.9; H 2.49; Br 56.94; N 4.98; S 5.69.

2-Phenyl-3-bromo-6-methyl-9-(N-cinnamyl)-2,3-dihydrooxazine[3,2-b]-pyrimidinium tribromide (**7a**): Yield 0.52 g (68 %). mp 505–507 K. ^{1}H NMR in $CDCl_3$: δ 2.254 (s, 3H, $-CH_3$); 3.821 (d, 2H, NCH_2); 5.028 (d, 2H, NCH_2); 5.246 (m, 2H, CH_2Br); 5.712 (d, J=15.3, 1H, $=CH-C_6H_5$); 6.092 (s, 1H, 7-H); 6.285 (m, 1H, CH=); 6.671 (d, J=15.1, 1H, $=CH-C_6H_5$); 7.239–7.506 (m, 10H, H_{arom}). Found, %: C 40.84; H 3.17; Br 47.44; N 4.19; S 4.84. $C_{23}H_{22}$ $Br_4N_2O_2$. Calc., %: C 40.73; H 3.25; Br 47.17; N 4.13; S 4.72.

2.3. General Procedure for the Preparation of Compounds 4b, 5b, 7b

Let us take **4b** for example. In a 100 ml flat-bottom flask we dissolved 0.4 g (0.00241 mol) of 1-(*N*-allyl)-6-methylpyrimidine-2,4-dione in 10 ml of ethanol, and 1.224 g (0.00482 mol) of iodine dissolved in 15 ml of ethanol were added by small portions under stirring and cooling to 273–278 K during 1 h. The reaction mixture was left for two days. The formed precipitate was filtered and dried at 353–363 K.

2-Iodomethyl-5-methyl-2,3-dihydrooxazolo-8H-[3,2-b]pyrimidinium triiodide **(4b):** Yield 0.64 g (39.5 %). mp 471–473 K. ^{1}H NMR in DMSO: δ 2.023 (s, 3H, $-CH_3$); 3.799 (d, 2H, NCH_2); 3.96 (m, 2H, CH_2I); 5.329 (m, 1H, 2-H); 6.363 (s, 1H, 6-H). Found, %: C 14.17; H 1.34; I 75.23; N 4.02; S 4.64. $C_8H_{10}I_4N_2O_2$. Calc., %: C 14.24; H 1.48; I 75.37; N 4.16; S 4.75.

2-Phenyl-3-iodo-6-methyl-2,3-dihydrooxazine-9H-[3,2-b]pyrimidinium triiodide **(5b):** Yield 0.73 g (59 %). mp 484–485 K. ^{1}H NMR in DMSO: δ 2.212 (s, 3H, $-CH_3$); 3.217 (d, 2H, NCH_2); 5.318 (m, 2H, CH_2I); 5.713 (d, J=15.0, 1H, $=CH-C_6H_5$); 6.106 (s, 1H, 7-H); 7.245–7.409 (m, 5H, H_{arom}). Found, %: C 22.28; H 1.63; I 67.65; N 3.62; S 4.14. $C_{14}H_{14}I_4N_2O_2$. Calc., %: C 22.4; H 1.87; I 67.73; N 3.73; S 4.27.

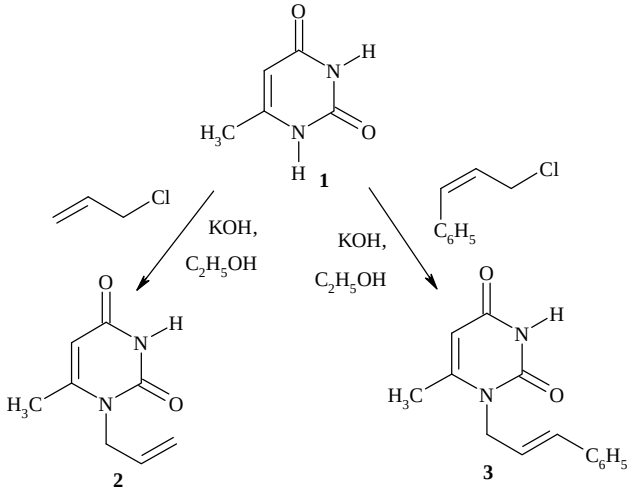
2-Phenyl-3-iodo-6-methyl-9-(N-cinnamyl)-2,3-dihydrooxazine[3,2-b]-pyrimidinium triiodide **(7b)**: Yield 0.67 g (74 %). mp 512–514 K. ^{1}H NMR in $CDCl_3$: δ 2.255 (s, 3H, $-CH_3$); 3.829 (d, 2H, NCH_2); 5.027 (d, 2H, NCH_2); 5.310 (m, 2H, CH_2I); 5.762 (d, J=15.3,1H, $=CH-C_6H_5$); 6.110 (s, 1H, 7-H); 6.269 (m, 1H, CH=); 6.709 (d, J=15.1, 1H, $=CH-C_6H_5$); 7.247–7.504 (m, 10H, H_{arom}). Found, %: C 31.81; H 2.67; I 58.98; N 3.39; S 3.84. $C_{23}H_{22}I_4N_2O_2$. Calc., %: C 31.87; H 2.54; I 58.66; N 3.23; S 3.70.

3. Results and Discussion

The objects of the investigation were the alkenyl derivatives of 6-methyluracil (**2, 3**) synthesized *via* the alkylation of 6-methyluracil with allyl and cinnamyl chlorides. 1-(*N*-allyl)-6-methyluracil **2** was obtained as a result of the compound **1** alkylation with allyl chloride; 1-(*N*-cinnamyl)-6-methyluracil **3 –** with cinnamyl chloride (Scheme 1).

The composition and structure of the synthesized compounds were proved by elemental analysis and ^{1}H NMR spectroscopy. The signals of allyl substitute were identified in the spectrum of compound **2**: doublet arising from two protons of NCH_2 group (δ 3.31), doublet

from two protons of CH_2= group (δ 3.49), multiplet from the –CH= group (δ 3.73); these reliably confirm the structure of this heterocycle. The presence of cinnamyl substitute is indicated by the following signals in the spectrum of compound **3**: doublet arising from two protons of NCH_2 group (δ 3.99), multiplet from the –CH= group (δ 6.41) proton, doublet from the proton of =CH–C_6H_5 group (δ 6.715), multiplet signal of five aromatic protons (δ 7.24, 7.32, 7.40).



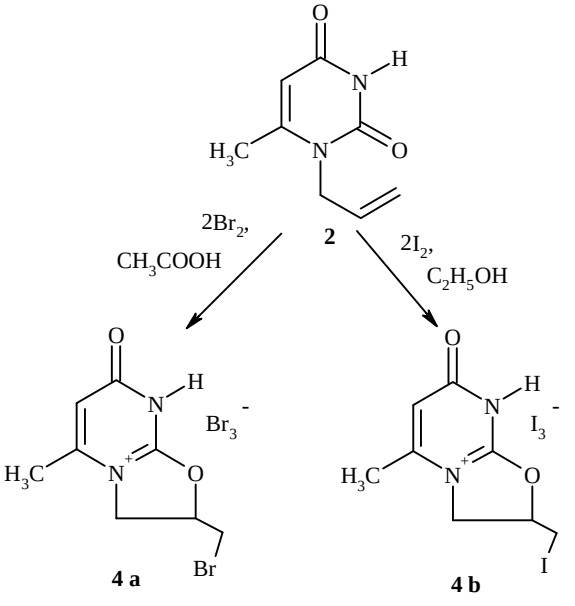
Scheme 1. The synthesis of 1-(N-alkenyl)-6-methyluracil **2, 3**

The reaction of alkenyl-substituted compounds **2, 3** with bromine in acetic acid produced 2-bromomethyl-5-methyl-2,3-dihydrooxazolo-8H-[3,2-b]pyrimidinium tribromide **4a** and 2-phenyl-3-bromo-6-methyl-2,3-dihydrooxazine-9H-[3,2-b]pyrimidinium tribromide **5a**, respectively (Schemes 2, 3).

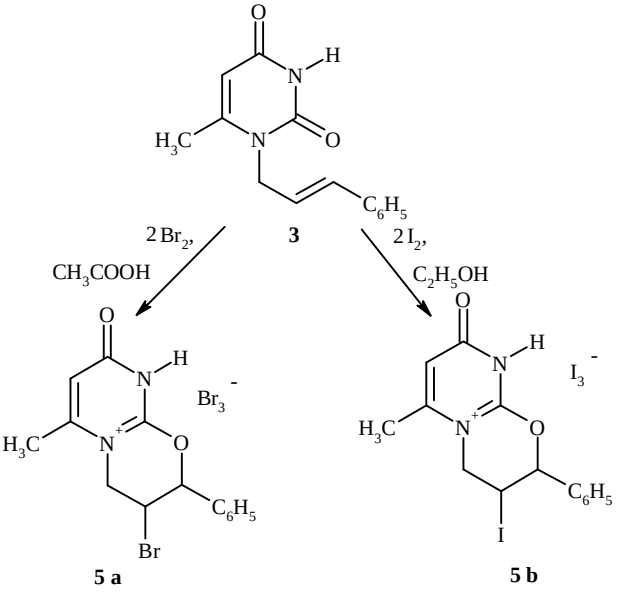
Iodocyclization of compounds **2** and **3** in THE ethanol solution takes AN analogous route and leads to the formation of respective triiodides **4b, 5b**. The formation of trihalogenides is confirmed by ^{1}H NMR spectroscopy data.

The size of the obtained cycle is determined by the structure of the alkenyl substitute thus leading to the regioselective formation of a five-member (oxazol) cycle in tribromide (triiodide) **5a, 5b**, or a six-member (oxazine) cycle in tribromide (triiodide) **6a, 6b**.

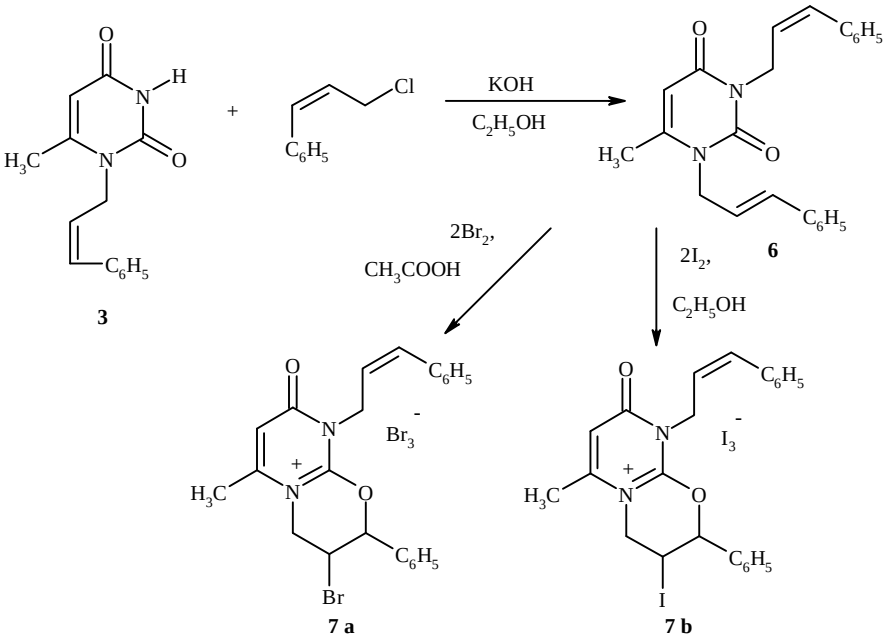
Further alkylation of compound **3** with cinnamyl chloride leads to the formation of the product of N^3-substitution, 1,3-(*N*,*N*-cinnamyl)-6-methyluracil **6** (Scheme 4). NMR spectrum of this compound, in addition to the signal of the cinnamyl substitute at N^1 atom, also features the signal of the cinnamyl substitute at N^3 atom, namely shifted to the weaker region doublet of two protons of NCH_2 group (δ 5.029), multiplet from the –CH= group (δ 6.265) proton, doublet from the proton of =CH–C_6H_5 group (δ 6.649), which reliably confirm the formation of dialkenylsubstituted derivative of 6-methyluracil.



Scheme 2. The synthesis of oxazolo[3,2-b]pyrimidinium tribromide (triiodide) **4a, 4b**



Scheme 3. The synthesis of oxazine[3,2-b]pyrimidinium tribromide (triiodide) **5a, 5b**



Scheme 4. The synthesis of 9-(N-cinnamyl)-2,3-dihydrooxazine[3,2-b]-pyrimidinium tribromide (triiodide) **7a, 7b**

The action of bromine in acetic acid or iodine in ethanol on compound **6** produces respective trihalogenides **7a, 7b**. The halogencyclization reaction was performed for 3 h under constant stirring and cooling the reaction mixture with ice. The reaction could be expected to result in the formation of tricyclic heterocycle with two cinnamyl substitutes (at N_1 and N_3) and two oxygen atoms (in positions 2 and 4). However, the products isolated as a result of bromo- and iodocyclization correspond to structures **7a** and **7b** leading us to the conclusion that only one cinnamyl substitute and one oxygen atom take part in the reaction. This is also confirmed by the reaction stoichiometry, since only 2 mol of bromine or iodine participate in the reaction. This result may be explained by a weaker nucleophilicity of oxygen atoms in the position 4. The formation of one oxazine cycle in compounds **7 a,b** is confirmed by the data of ^{1}H NMR spectroscopy.

A characteristic feature of these reactions cyclization is the adherence to Markovnikov's rule, *i.e.* the addition of the electrophile to the more hydrogenised carbon atom in the case of non-symmetric alkenes or alkenyl substitutes. In the case of symmetrical alkenes, the electrophilic part is added to the carbon atom of the double bond in such a fashion that the most stable carbocation is formed. Thus pyrimidine derivatives with *N*-allyl substitute form a five-member cycle in oxazolopyrimidine, whereas compounds with a cinnamyl substitute form oxazinepyrimidines – heterocycles with six-member cycles.

4. Conclusions

Based on the reaction of electrophilic intramolecular cyclization, we developed the methods of the synthesis of functionally substituted heterocyclic systems of 2,3-dihydrooxazolo[3,2-b]pyrimidinium and 2,3-dihydrooxazine[3,2-b]-pyrimidinium. It was shown that the direction of halogencyclization of 1-(*N*-alkenyl)-6-methyluracils is substantially affected by the structure of S-alkenyl substitute which leads to the regioselective formation of oxazolopyrimidinium or oxazinepyrimidinium derivatives. Obtained results of the regiochemistry of closing five- or six-member heterocycles in the reaction of halogencyclization of alkenylsubstituted 6- methyluracils in the overall context could be explained on the basis of the theoretical concepts of Markovnikov's rule.

References

[1] Sukach V., Thachuk V., Rusanov E. *et al.:* Tetrahedron, 2012, **68**, 8408. https://doi.org/10.1016/j.tet.2012.07.099
[2] Vaskevych R., Khrypak S., Stanynets V. *et al.*: Ukr. Khim. Zh., 2000, **66**, 47.
[3] Bentya A., Vaskevych R., Stanynets V.: Ukr. Khim. Zh., 2008, **74**, 94.
[4] Gevaza Yu., Stanynets V.: Ukr. Khim. Zh., 2002, **68**, 67.
[5] Kim D., Shmygarev V.: Khimiya Heterotsikl. Soed., 1995, **2**, 211.
[6] Zborovskyi Yu., Orysyk V., Dobos A. *et al.:* Ukr. Khim. Zh., 2002, **68**, 95.
[7] Slyvka N., Gevaza Yu., Stanynets V., Korolchuk S.: Ukr. Khim. Zh., 2010, **76**, 102.
[8] Slyvka N., Gevaza Yu., Stanynets V.: Khimiya Heterotsikl. Soed., 2004, **5**, 776.

[9] Vaskevych A., Bentya A., Staninets V.: Zh. Org. Khim., 2009, **45**, 1848.
[10] Saliyeva L., Slyvka N., Vaskevych R., Vovk M.: Ukr. Khim. Zh., 2016, **82**, 64.
[11] Dyachenko I., Vaskevych R., Vovk M.: Zh. Org. Khim., 2014, **50**, 270.
[12] Sukach V., Thachuk V., Shoba V. *et al.*: Eur. J. Org. Chem., 2014, **7**, 1452. https://doi.org/10.1002/ejoc.201301542
[13] Dyachenko I., Vaskevych R., Vovk M. *et al.*: Zh. Org. Khim., 2016, **52**, 745.
[14] Shoba V., Thachuk V., Sukach V. *et al.*: [in:] Attanazi O., Spinelli D. (Eds.), Targets in Heterocyclic Systems: Chemitry and Properties. Vol. 17. Italian Society of Chemistry, Roma 2013, 147.
[15] Novakov I., Orlinson B., Navrotskii M.: Zh. Org. Khim., 2005, **41**, 607.

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ЕЛЕКТРОФІЛЬНА ВНУТРІШНЬОМОЛЕКУЛЯРНА ЦИКЛІЗАЦІЯ 1-(*N*-АЛКЕНІЛ)-6-МЕТИЛПІРИМІДИН-2,4-ДІОНІВ

Анотація. *Синтезовано N-аліл(цинаміл)заміщені похідні 6-метилурацилу та проведено реакції їх бромо- та йодоциклізації, які приводять до утворення похідних дигідрооксазолопіримідинію та дигідрооксазинопіримідинію. Запропоновано чинники, які сприяють регіоселективному протіканню цих реакцій.*

Ключові слова: *електрофільна внутрішньомолекулярна циклізація, метилурацил, бромоциклізація, йодоциклізація, регіоселективність, дигідроксоазолопіримінідіум, дигідроксиазинпіримінідіум.*