CHEMISTRY OF HETEROCYCLIC COMPOUNDS AT THE INSTITUTE OF ORGANIC SYNTHESIS, LATVIAN ACADEMY OF SCIENCES

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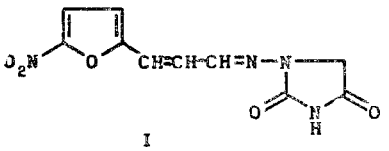
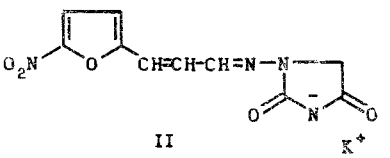
In the 35 years for which the Institute of Organic Synthesis of the Latvian Academy of Sciences has existed the chemistry of heterocyclic compounds has become one of the main subjects of its researches, which have included methods of synthesis, structure determination, and study of the reactivity and biological characteristics of the compounds for the creation of new medicinal products. The Institute has developed and introduced into medical practice 16 original products, of which ten are heterocyclic compounds.

The first steps in the search for biologically active substances were research into new antibacterial and antitumor substances. This led to the creation of new drugs from a series of oxygen- and nitrogen-containing heterocycles. Strong antibacterial activity and a wide spectrum of activity are exhibited by fugarine (I) and soluble fugarine (II), which are 1-[3-(5-nitro-2-furyl)allylideneamino]hydantoin and its potassium salt:



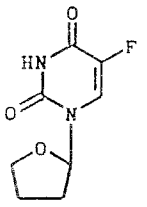
I



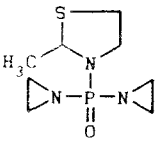
II

Fugarine is effective with respect to Gram-positive and Gram-negative microorganisms and also acts upon microorganisms resistant to antibiotics and sulfanilamides. The product is used for acute and chronic diseases of the kidneys and urinary tracts, during infections after operations on the organs of the urogenital system, for the treatment of suppurating wounds, and in ophthalmology for conjunctivitis, keratitis, and corneal ulcers. Soluble fugarine can be used in various medicinal forms, including intravenously, and this makes it possible to create a high concentration in the blood.

The antitumor product ftorafur [1-(2-tetrahydrofuryl)-5-fluorouracil (III)] has become widely known in world practice. Chemically it also belongs to the two classes of heterocyclic compounds (oxygen- and nitrogen-containing).



III



IV

Ftorafur is used in the treatment of cancer of the stomach, breast cancer, cancer of the rectum, the sigmoid colon, and the large intestine, and skin cancers and also as supportive therapy in cancer of the liver, the esophagus, and the ovaries, and brain tumors.

Whereas ftorafur belongs to the group of antimetabolites, the other antitumor agent imifos [di(1-aziridinyl)(2-methyl-3-thiazolidinyl)phosphine oxide (IV)] has alkylating action and is used for the treatment of erythremia.

In recent years two other products containing nitrogen-containing heterocycles have been introduced into oncological practice. These are the radioprotector dieton [2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine (V)] and the immunomodulator leakadin [2-carbamoylaziridine (VI)]:

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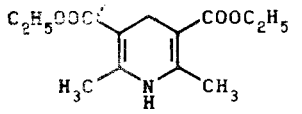
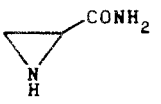


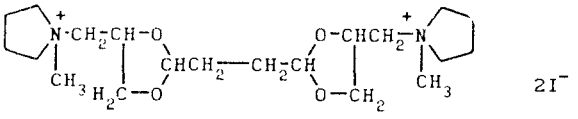
V



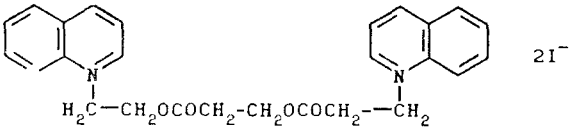
VI

Dieton is used for the prophylaxis and treatment of radiation injuries of the skin. Leakadin has an immunomodulating and antitumor action and regulates the immune status of the organism by normalization of the helper—suppressor ratio.

Nitrogen-containing heterocyclic compounds also include the myorelaxant dioxonium [1,2-bis(4-pyrrolidinomethyl-1,3-dioxolan-2-yl)ethane (VII)] and the anticholinesterase agent quinothilin [bis(β-quinolinoethyl) succinate diiodide (VIII).



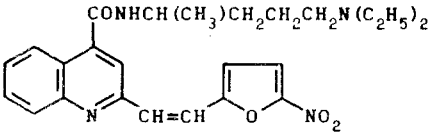
VII



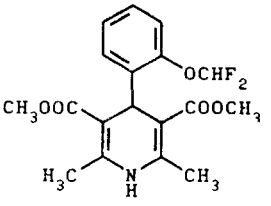
VIII

Dioxonium is a curare-like muscle relaxant, which blocks the passage of pulses in the neuromuscular synapses of the skeletal musculature. Quinothilin, on the other hand, is an antagonist of curare-like muscle relaxants and is used to remove the residual antidepolarization block of the neuromuscular transfer.

The quinoline and nitrofuran fragments are also combined in the antibacterial product quinifuril (IX):



IX



X

As a result of investigations in the region of dihydropyridines a new calcium antagonist foridon [2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2′-difluoromethoxyphenyl)-1,4-dihydropyridine (X)], which has hypotensive and coronary dilating action, was created. The product is used for the treatment of hypertonic and ischemic heart disease.

Of the series of nitrogen-containing heterocycles the institute continues to research the synthesis of partially hydrogenated rings (dihydropyridines, dihydropyrimidines, dihydroindenopyridines, furo-, thieno-, and benzothienodihydropyridines) and also new heterocyclic systems of the dihydrobenzothienopyridine, dichromenopyridine, and pyrroloacridine types. Methods are being developed for the synthesis of cyclic and acyclic analogs of nucleosides, and research is being conducted into partial oxidation catalysts and the creation of catalytic methods for the synthesis of various derivatives of N-heterocycles.

Processes are being developed for the synthesis of organosilicon and organogermanium derivatives of furan, thiophene, and nitrogen-containing heterocycles, the direction of substitution and addition of furan derivatives of silicon, germanium, and tin is being studied, and the possibility of using alkenylsilanes in the synthesis of nitrogen-containing heterocycles is being investigated. An asymmetric synthesis of chiral alkylheteroarylcarbinols has been achieved by reduction of the corresponding prochiral ketones; optically active synthons have been obtained by means of chiral heterocyclic intermediates (oxazolidines and indazolidines).

The chemical modification of β-lactam antibiotics is being conducted in the search for new antimicrobial agents, and silyl methods are being developed for their synthesis.

Phase-transfer catalysis and ultrasonic acceleration of the reaction are widely used at the institute for the synthesis of new heterocyclic compounds. The obtained compounds are studied by multinuclear magnetic resonance, including ^{15}N, ^{17}O, ^{29}Si, and ^{73}Ge NMR spectroscopy and mass spectrometry. The stereochemical structure of the molecules of the nitrogen-containing heterocycles and the nucleoside derivatives in the crystals is determined by x-ray crystallographic analysis. A list of the publications of workers at the Institute of Organic Synthesis of the Latvian Academy of Sciences on the chemistry of heterocyclic compounds is included in the annual bibliography of the Institute's work [1,2]. Some of the new results are published in articles in the present issue of the journal.

LITERATURE CITED

1. Latvijas Zinatņu Akademijas Organiskas Sintezes Instituts, Bibliografija, 1990, Riga (1991).
2. Latvijas Zinatnu Akademijas Organiskas Sintezes Instituts, Monografijas, Rakstu Krajumi, Autoreferati, 1987-1990, Riga (1991).

SYNTHESIS OF FTORAFUR (REVIEW)

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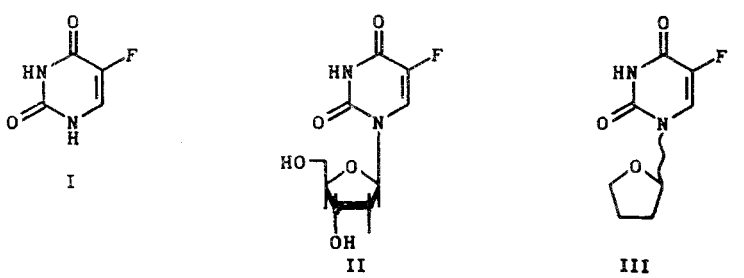
UDC 547.854.4'722+615.012.1.(048.8)

Published data on methods for the synthesis of the antitumor compound "Ftorafur" by the tetrahydrofurylation of 5-fluorouracil and its derivatives and also by fluorination, cyclization, solvolysis, oxidation, and other reactions are reviewed.

One method of fighting tumor diseases involves the use of antimetabolites. The therapeutic effect of antimetabolites (analogs of nucleic acid components [1]) both of bases (e.g., 5-fluorouracil [2-4]) and of nucleosides (e.g., 2′-deoxy-5-fluorouridine) is due to the possibility of their inclusion in the nucleic acids. This takes place when the products are substrates for DNA or RNA polymerases, which use them in the form of the triphosphates of the respective deoxyribosides or ribosides. The analogous nucleic bases or nucleosides are converted by the cell enzymes into modified nucleotides. In the tumor cell the action of the individual enzymes is changed, the synthesis of isoenzymes is often observed, and the inclusion of the analogs in the nucleic acids may therefore be much stronger than in normal cells. The so-called lethal synthesis, which disrupts replication and transcription when the modified deoxynucleoside is included in the DNA or disrupts the translation and protein synthesis processes when the modified riboside is included in the RNA, is observed more frequently in tumor cells than in normal cells. Modification of the base can be achieved by substitution of a hydrogen atom in the ring by a fluorine atom [as in 5-fluorouracil (I) and 2′-deoxy-5-fluorouridine (II)], while modification of the sugar can be achieved by substitution of the 1-β-D-pentosyl residue by a 2-tetrahydrofuryl fragment.



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