Chemistry of Heterocyclic Compounds, Vol. 33, No. 2, 1997

THE FORTIETH ANNIVERSARY OF THE LATVIAN INSTITUTE OF ORGANIC SYNTHESIS

E. Lukevics

The Institute of Organic Synthesis, Latvian Academy of Sciences, was founded on January 2, 1957. Its organizer and first director was Academician S. A. Giller (1915-1975), who successfully steered the activity of the Institute for 18 years. Under his leadership the Institute became a unique scientific complex, which included not only chemical laboratories and laboratories for biological trials on the synthesized compounds but also a pilot plant for the development of the technology and manufacture of medical products and agents for the chemicalization of agriculture. Such a complex was capable of fulfilling the whole cycle of operations involved in the creation of drugs from the initial concept and chemical synthesis in the laboratory to industrial manufacture in the finished medical form. Giller organized the first export of the antitumor product Ftorafur, created at the Institute, to Japan. Being a specialist in heterocyclic chemistry, Giller became the first editor of the journal "Chemistry of Heterocyclic Compounds" (Khimiya Geterotsiklicheskikh Soedinenii).

From 1975 to 1982 the Institute was headed by Academician G. Chipens (peptide chemistry). During this period the trend toward bioorganic chemistry (peptides, prostaglandins, nucleic acids) began to develop at the Institute.

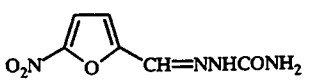
From October 1982 the Institute was directed by Prof. E. Lukevics, who works in the field of organosilicon and organogermanium compounds and their heterocyclic derivatives.

The Institute continues to conduct fundamental researches in the field of organic chemistry (O-, S-, and N-heterocycles, betaines), heteroorganic chemistry (the organic derivatives of silicon, germanium, and tin, metal-complex catalysis), bioorganic chemistry (peptides, prostaglandins, membrane-active substances), physical organic chemistry (NMR, ESR, mass spectrometry, x-ray crystallographic analysis, electrochemistry), and pharmacology.

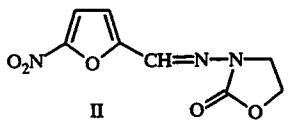
As well as the scientific researches, the organization of international conferences, and the publication of the international journal "Chemistry of Heterocyclic Compounds" the Institute has undertaken many other activities promoting the development and assimilation of new medicines; it established a laboratory of technology, the development of finished drugs, and the standardization of products; it created the first plant for the manufacture of peptide, prostaglandin, and cephalosporin products; it organized scientific and technical collaboration with pharmaceutical companies in Japan, Germany, France, the USA, and Finland and began to export its own products to Japan, France, Czechoslovakia, Bulgaria, and other countries; it promoted the introduction of the patent protection of chemical substances into the former USSR; it used computer technology to predict the biological activity of the synthesized compounds; it initiated the construction of a biological complex with a nursery for laboratory animals for preclinical trials conforming to international requirements.

Over the years the Institute has created 17 original medical products for the treatment of cardiovascular, infectious, tumorous, and other diseases and has developed techniques for the production of 47 other products. Most of them were developed on the basis of heterocyclic compounds.

A special place in the arsenal of antibacterial agents is occupied by the products from the condensation of the aldehyde group of 5-nitrofurfural with compounds containing an amino (hydrazino) group or an active methylene group. On the basis of its own safer technology for the production of 5-nitrofurfural and its diacetate the Institute developed a technique for the production of **furacyllin** (I) and **furazolidone** (II) and also the original antimicrobial product **quinifuril** (III).



I



II

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 147-150, February, 1997.

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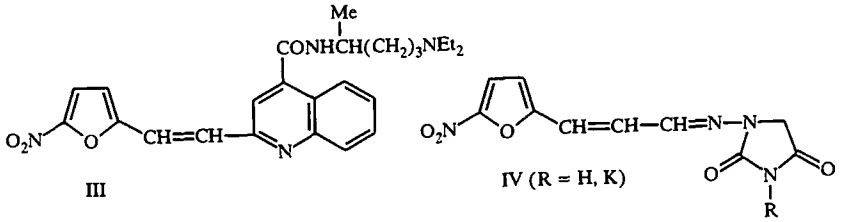
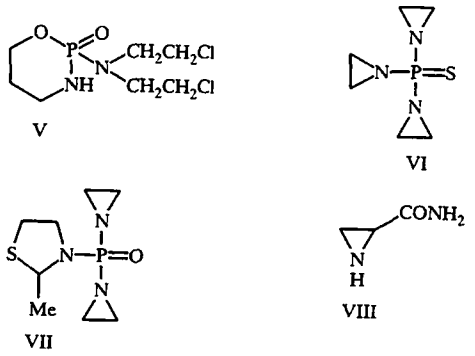


III IV (R = H, K)

The antibacterial activity of a compound can be increased by increasing the number of double bonds between the nitrofuran ring and the nitrogen atom. The more active vinylog of nitrofurantoin **furagine** (IV) (R = H) and its water-soluble salt **solafur** (IV) (R = K) were produced on this basis from 5-nitrofurylacrolein.

At the Institute techniques were developed for the production of a series of other heterocyclic antimicrobial and antiviral products (acyclovir, cephalexin, furadonin, furazoline, ribamidyl, silafungin).

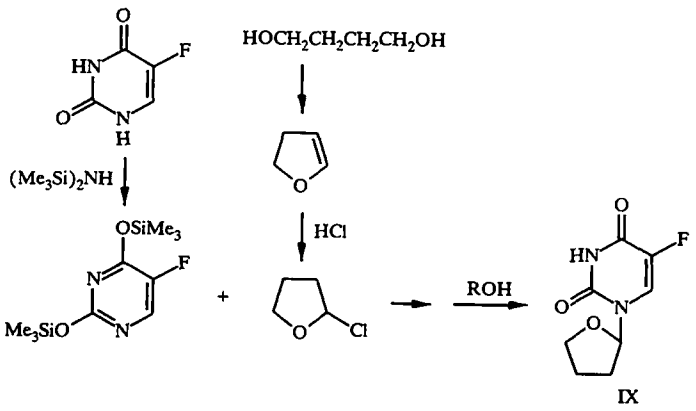
One of the directions in the creation of drugs at the Institute involved the development of a technique for the production of antitumor agents. After the introduction of **cyclophosphamide** (V) and **thiotef** (VI) the original product **imiphos** (VII), used for erythremia, and the antitumor immunomodulator **leakadin** (VIII) were created.



V VI VII VIII

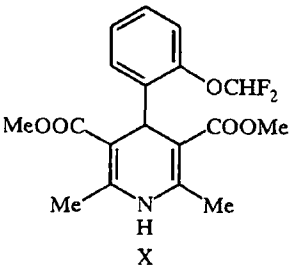
The bases of nucleic acids were used in the synthesis of antitumor and antileukemia preparations (cyclocytidine, cytarabine, thioguanine). On the basis of 5-fluorouracil an original antitumor product **ftorafur** (IX) (tegafur), which has been produced by the pilot plant of the Institute for more than 20 years (for the last five years by the firm Grindeks), was created.

The first stage in the production of ftorafur is the silylation of 5-fluorouracil by hexamethyldisilazane in the presence of trimethylchlorosilane. The silylated 5-fluorouracil then enters into reaction with 2-chlorotetrahydrofuran, and the remaining trimethylsilyl group is removed during crystallization from 2-propanol.

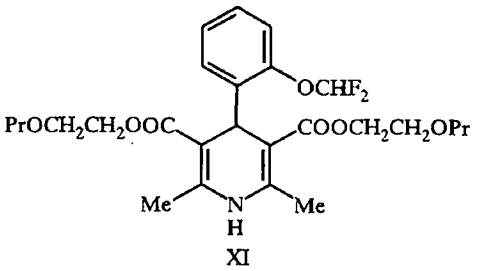


IX

Among the other products based on heterocyclic compounds it is necessary to mention the original myorelaxant dioxonium and the anticholinesterase agent quinotiline, the anticholinesterase reactivator dipyroxime, and the laxative bisacodyl. Original antihypertensives are the derivatives of 1,4-dihydropyridine **phoridone** (X) (rhyodipine) and **cerebrocrast** (XI).



X



XI

The reorganization of the scientific research system, conducted in Latvia over the last five years, has also affected the Latvian Academy of Sciences and its institutes. The Academy was changed from an organization with many scientific-research institutes into a private academy with active, corresponding, honorary, and foreign members, and the institutes were incorporated into the universities or brought under the authority of the Ministry of Education and Science. The Institute of Organic Synthesis of the Latvian Academy of Sciences became the Latvian Institute of Organic Synthesis, in which the number of members was reduced by half. The Department of Molecular Biology became the Biomedical Center of Latvian University, while the Pilot Plant of the Institute was converted into the independent pharmaceutical company Grindeks, which included a series of the former laboratories of the Institute: The department of toxicology and pharmacokinetics; the laboratory of technology and finished drugs; the department of the care of laboratory animals.

The Institute in turn has intensified its international activity. New agreements have been signed with pharmaceutical companies in Japan, Germany, Switzerland, and the USA on the biological screening of compounds synthesized at the Institute. Contracts have been made with companies in the USA, Japan, and Switzerland on the development of the essential synthetic methods. Agreements have been reached on the joint search for new drugs with companies in Japan.

On entering the fifth decade of its existence, the Latvian Institute of Organic Synthesis continues to combine fundamental research in the search for new drugs with the education of masters and doctors of chemistry.

The results of a series of the most recent researches on the chemistry of heterocyclic compounds, carried out at the Institute and also in conjunction with Riga Technical University, are presented in the articles in this issue of the journal.