Chemistry of Heterocyclic Compounds, Vol. 43, No. 2, 2007

FORMATION AND DEVELOPMENT OF THE LATVIAN INSTITUTE OF ORGANIC SYNTHESIS OVER 50 YEARS (1957-2006)

J. Stradins

Fifty years have passed since the foundation of the Latvian Institute of Organic Synthesis – the institute well known all over the world for investigations in the creation of new biologically active compounds and the solution of problems relating to the chemistry of heterocyclic compounds, the institute that for more than 40 years has been publishing the international journal "Chemistry of Heterocyclic Compounds".

The Background of the Institute Origin and its Principal Activities

The Institute of Organic Synthesis commenced its activities on January 1, 1957. More accurately, the formal date of the creation of the Institute must be considered December 20, 1956, when the Presidium of the Academy of Sciences of the Latvian SSR (at a session chaired by F. Deglavs, the Vice-President of the Academy of Sciences) adopted a resolution to form the Institute of Organic Synthesis of the Latvian Academy of Sciences. The Institute continued working in the Latvian Academy of Sciences up to 1993 and then became an independent scientific establishment under the aegis of the Ministry of Education and Science of the Latvian Republic.

The creation of the Institute 50 years ago was promoted by the strong chemical traditions of Latvia and Riga, the presence here of qualified chemists and medical men, and the need for accelerated development of chemical science in the USSR of that time (at that time up to 1991 annexed Latvia was a part of this power).

The traditions of chemical science in Latvia originated from the Nobel prize winner (1909) Riga-born Wilhelm Ostwald (1853-1932), who was a professor at Riga Polytechnic in 1881-1887); he conducted fundamental investigations here on chemical kinetics and catalysis, made a systematic study of organic acids and bases, and also laid effective foundations for comprehensive higher education in Riga.

No less important are the services of his student – Paul Walden (1863-1957), who seven times was put forward for a Nobel prize in chemistry, and whose name entered the history of chemistry in connection with the fundamental discoveries in the region of stereochemistry ("Walden inversion") and the search for novel nonaqueous solvents (determination of the fundamental relationships in the electrochemistry of nonaqueous solutions).

The direction of synthesis of organic chemistry in Riga was developed by Prof. Karl Adam Bishof (1855-1908), representative of the J. Wislicenus Leipzig School of organic chemists, who enriched stereochemistry with new ideas. Riga professor Waldemar Fisher (1881-1934), who was the first in Riga to be engaged in the study of derivatives of 1,3-indanedione, was a student of A. Hantsch in Leipzig. In the first period of existence of the Latvian Republic (1918-1940) chemistry research was conducted at the Chemical Faculty of the Latvian University; leading organic chemists at this time were Prof. Gustavs Vanags (1891-1965), famous for fundamental investigations in the chemistry of cyclic β-diketones, Pauls Kalniņš (1886-1955, student of F. Bergius), and Alfred Taurins (1904-1986, after the war professor in Montreal, a member of the

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 171-191, February, 2007.

Royal Society of Canada). The fundamental researches of Doctor of Chemistry Edwin Egriwe (1878-1944) on new organic analytical reagents, many of which have remained in the arsenal of organic analysis to this day, should be also mentioned.

The training of qualified chemists and their scientific work became a tradition for Latvia. In addition, unlike members of other professions, the majority of chemists in Latvia did not emigrate to the West in 1944 but stayed in their motherland.

The Academy of Sciences of the Latvian SSR, including the Institute of Chemistry (in which G. Vanags worked), the Institute of Experimental Medicine, and the extremely multifaceted and dynamic Institute of Forestry Problems [headed by student of P. Walden and A. Antropov Academician Arvīds Kalniņš (1894-1981) and where the at that time young chemist S. A. Hiller (1915-1975), future organizer of the Institute of Organic Synthesis, worked], and other institutes, was established in 1944.

At the end of the forties under the direct influence of Arvīds Kalniņš at the Institute of Forestry Problems investigations were started on the chemistry of furan. The choice of subject matter was based on the prospective use of pentosan-containing raw material, on which the Institute was working. Member of the Institute S. A. Hiller (student of Prof. P. Kalniņš) demonstrated the promise of this material for organic synthesis and in particular for the production of new biologically active compounds and drugs. The All-Union Council on pentosan-containing raw material was established at the Latvian Academy of Sciences in 1956. As early as 1951 a group of workers at the Institute received a Stalin prize for the development of the antitubercular preparation PASK and its introduction into medical practice (the "Riga method" for the production of PASK). Under the leadership of S. A. Hiller extensive researches were carried out on the synthesis and microbiological study of derivatives of the 5-nitrofuran series (State Prize of the Latvian SSR, 1957), which were considered at that time extremely promising in the fight against bacterial infections and have to some degree retained their significance to the present day.

All the foregoing created the prerequisites for the foundation of a new independent institute in Riga during the period of the "Khrushchev thaw". In those same years the "chemicalization of the national economy" was declared one of the priorities for the development of the USSR, and in addition the competence of the Union republics was extended. A. Kalniņš, S. A. Hiller, and others strongly popularized the idea that Latvia did not have the raw-material base for large-capacity chemical production but had available qualified specialized chemists. Here, therefore, it was necessary to develop fine organic synthesis with a view to the creation of new medical products and chemical agents for agriculture. The idea received support in Moscow, in the Academy of Sciences of the USSR, and in the State Committee for Science and Technology. The businesslike relations, energy, and helpfulness of the creator of the Institute S. A. Hiller were of great importance here. According to his plan, the new institute should have in its make-up specialists of various profiles – synthetic chemists, physical chemists, analysts, microbiologists, even medical clinicians. The principles of the organization and development of the new institute – amalgamation into a unified search for scientists of allied specialties, the combination of fundamental investigations with the solution of scientific applied problems, of "pure" chemistry with biology, pharmacology, and chemical technology, and finally the combination of science with experimental production – were observed both in the period of establishment of the Institute and during subsequent stages of its development. In this respect the Institute became a model in terms of the USSR of that time, where experience of such a kind was not particularly common.

Initially (in 1955) it was intended to create an independent Laboratory of Drugs and Biologically Active Substances of the Latvian SSR, but during subsequent development of this idea the new Institute was established and three scientific subdivisions, comprising 45 people from three already existing institutes of the Academy of Sciences of the Latvian SSR: The Institute of Forestry Problems – the Furfural Sector (headed by S. A. Hiller, Corresponding Member of the Academy of Sciences of the Latvian SSR,); the Institute of Chemistry – the Laboratory of General Organic Chemistry (headed by Prof. G. Vanags); the Institute of Experimental and Clinical Medicine – the Laboratory of Experimental Chemotherapy (headed by Prof. S. P. Zaeva) were provided to it.

The Evolution of the Institute and Its Principal Scientific Trends

S. A. Hiller was appointed a director of the new Institute and headed it for 18 years right up to its premature death in the summer of 1975. He determined the principal scientific trends and the principles of organization of the Institute. In 1962 the Institute's own building was constructed in the so-called Akademgorodok in the outskirts of Riga. Already by the end of 1957 the Experimental Vitamin Plant of the Institute of Medicine had been transferred to the competence of the Institute, and to this in 1973 the Riga Plant of Medical Products (producing antibiotics) was added. Thus, the foundations for a large experimental base had been laid for the Institute of Organic Synthesis, which was an unusual occurrence at that time in the large scale of the whole USSR. We note that the pharmaceutical company Grindeks was created on the basis of the Experimental Plant of the Institute of Organic Synthesis in 1991, and it is at present the largest company of its profile in the independent Baltic States.

Created in 1957, the Institute has evolved swiftly and has attracted prominent specialists and mostly young scientists, both growing up in Riga (coming Academicians of the Latvian Academy of Sciences Margeris Lidaks, Gunars Chipens, Edmunds Lukevics, Elmars Grens, Gunars Duburs, Janis Freimanis, Ivars Kalvinsh, Vija Klusa, Paul Pumpens, Valdis Berzins, Edvards Liepinsh, Janis Stradins, Honorary Members of the Latvian Academy of Sciences Mariya Shimanska and Viesturs Baumanis, Corresponding Members of the Latvian Academy of Sciences Grigory Veinberg, Eriks Kupče, Peteris Trapencieris, Aivars Krauze, Nikolajs Sjakste, Foreign Member of the Latvian Academy of Sciences Regina Zhuk, Prof. Voldemars Grinšteins, Doctor of Medical Sciences Agris Ķimenis, Doctors of Chemical Sciences Karlis Venters, Valentina Slavinska, Janis Dregeris, Ludmila Leite, Eva Stankeviča, Honorary Doctor of the Latvian Academy of Sciences Janis Polis, and others) and from other scientific centers of the USSR. In particular, the well-known specialist in the chemistry of heterocyclic compounds Academician Mikhail Voronkov worked at the Institute, and in 1970 he headed an institute in Irkutsk; the NMR specialist Vadim Pestunovich, specialists in the structure of proteins G. V. Nikiforovich, S. G. Galaktionov, M. D. Shenderovich, and others were also co-workers at the Institute.

Great were the services of Academician G. Vanags in the evolution of the Institute during the initial stage of its existence. He laid the foundations for the development of synthetic organic chemistry, educated talented organic chemists, and worked successfully in the field of the chemistry of cyclic β-diketones (State Prizes of the Latvian SSR, 1959 and 1965). At the Institute of Organic Synthesis he developed some new blood anticoagulants for medicine, rodenticides, and a new type of psychotropic product *methindione* (A. Arens and S. Germane in conjunction with the prominent pharmacologist Prof. M. L. Belen'kii). Within the scope of these investigations E. Grens conducted the first quantum-chemical calculations in the Institute on the anions of dicarbonyl systems.

The traditions and the scientific directions of G. Vanags were continued at the Institute by Academician G. Duburs, who was distinguished in 2006 by a Gold Medal of WIPO (the Worldwide Intellectual Property Organization) as the most productive inventor in Latvia. Earlier, in 2005 Academician I. Kalvinsh, Director of the Institute of Organic Synthesis from 2004, had also been awarded a Gold Medal by WIPO.

Investigations on the chemistry of heterocyclic compounds, started under the leadership of the first director of the Institute S. A. Hiller, have been vigorously developed. Researches on furan chemistry (nitration, heterogeneous catalytic oxidation, etc.) were the earliest of all, and work on the furanidyl analogs of nucleosides, on the chemistry of aziridines, and others followed. These investigations, started in connection with the creation of potential antitumor and antibacterial agents, subsequently turned into independent studies of synthetic search. Under the leadership of S. A. Hiller such original drugs as the antitumor product *ftorafur* (*tegafur*), the nitrofuran antibacterial products *furagin*, *solafur*, and the myorelaxant *dioxonium* (State Prize of the Latvian SSR, 1965) were created, and the technology was developed for the production of many other drugs and herbicides (in particular, *phenazone*), for which an industrial plant was subsequently constructed (L. Avota and others, State Prize of the Latvian SSR, 1972).

S. A. Hiller was the initiator of the unfolding of bioorganic chemistry and molecular biology in Latvia and was one of the initiators in creation of the group of chemical pharmaceutical enterprises and the production of biochemical reagents in the new "chemical" city Olaine under Riga during the sixties and seventies of the twentieth century (the "Olainfarm and Biolar" companies). These establishments had great significance for the "former USSR"; they continue working under the conditions existing in independent Latvia, although with partly changed production profile. A substantial proportion (~40%) of the production at the Olaine plants is taken up by products created at the Institute. It must be said that at the beginning of the eighties 25% of all the original drugs produced in the USSR were developed at the Institute of Organic Synthesis. Although the Institute was not an industrial but an academic institute, it nevertheless had close connections with the pharmaceutical and chemical industry and medical establishments.

Beginning in 1964, together with classical organic chemistry the Institute of Organic Synthesis also began to develop fundamental investigations in the area of bioorganic chemistry and molecular biology, i.e. in the chemistry and structural and functional organization of peptides (Academician G. Chipens) and in the investigation of nucleic acids (Academician E. Grens), in the chemistry of enzymes (the production of L-asparaginase, R. Zhagats), and in the search for membrane-active compounds (Academician G. Duburs). These investigations were developed at the Institute particularly widely in 1975-1982, when the Institute was headed by G. Chipens, who was awarded with a State Prize of the Latvian SSR (1976) and a State Prize of the USSR (1981) for the development and applayment of techniques for peptide preparations (*angiotensin*, *oxytocin*, *pentagastrin*, and others) in practice. After 1976 comprehensive investigations were carried out at the Institute on synthetic analogs of natural prostaglandins (Academician J. Freimanis, State Prize of the Latvian SSR, 1987).

In 1991 the Department of Molecular Biology, headed by E. Grens, separated from the Institute as an independent Latvian Biomedical Research and Study Center. Consequently, the Institute of Organic Synthesis was the forefather of genetic engineering in Latvia.

An independent section was engaged in the synthesis and study of the reactivity of organosilicon, organogermanium, and organotin compounds, the potentialities of silylation methods in organic synthesis, and the use of complex metallic catalysts in organic and organometallic synthesis. Hydrosilylation and hydrogermylation were studied, methods were developed for the synthesis of organogermanium compounds of furan, thiophene, and nitrogen-containing heterocycles, and penta- and hexacoordinated compounds of the elements of group IVB, etc. were synthesized and studied. In particular, investigations commenced in 1962 on the organoelemental compounds of triethanolamine derivatives led to the creation of a new class of compounds with an intramolecular donor–acceptor bond N→M (where M = B, SiR, GeR, TiR, VO, MO_2, Fe), called *atranes*, followed by other atrane-like systems (M. Voronkov, E. Lukevics, G. Zelchans, L. Ignatovich, V. Gevorgyan, N. Erchak, and others).

The target synthesis of potential biologically active organosilicon compounds was the subject of scientific researches by Academician E. Lukevics (State Prize of the Latvian SSR, 1974) and the team headed by him. E. Lukevics was the third director of the Institute, after G. Chipens, from 1982 to 2003 inclusive. The numerous monographs and reviews written by him and his co-authors are widely known and cited.

Under the leadership of Honorary Member of the Latvian Academy of Sciences M. Shimanska (1922-1995) over many years methods were worked out for the heterogeneous vapor-phase catalytic oxidation, hydrogenation, and catalytic synthesis of various heterocyclic compounds (mostly derivatives of furan and pyridine), and new types of catalyst were developed. A technology was developed for the catalytic production of maleic anhydride from furfural, and in due course the appropriate pilot plant was in operation at the Riga Paint Plant (M. Shimanska, V. Slavinska, A. Avots, et al., State Prize of the Latvian SSR, 1965).

Academician M. Lidaks (1928-2003) and his co-workers worked on the chemistry of purines, pyrimidines, and also nucleosides and their analogs and looked for antitumor and antiviral agents both among compounds of the above-mentioned classes and among the aziridines (*ftorafur*, *furavir*, *imiphos*, etc.).

In the field of aziridine chemistry S. A. Hiller, M. Lidaks, A. V. Eremeev, and others synthesized a multitude of new compounds of this class, including previously unknown heterocycles retaining the aziridine ring (diazabicyclohexanes). V. Pestunovich by PMR established the slow inversion of the nitrogen atom in the molecules of the N-aminoaziridines at room temperature and even at higher temperatures. This effect, which had been discovered earlier in other subjects by R. G. Kostyanovsky (Institute of Chemical Physics, Academy of Sciences of the USSR), was recognized in the USSR as a discovery by the issue of a diploma to S. A. Hiller, R. G. Kostyanovsky, A. V. Eremeev, V. A. Pestunovich, and other authors. The development of aziridine chemistry at the Institute was continued by I. Kalvinsh, P. Trapencieris, and others, who synthesized new bicyclic nitrogen-containing heterocycles and derivatives of aziridine-2-carboxylic acid.

S. A. Hiller, R. Zhuk, and I. N. Goncharova modeled nucleotides, nucleosides, and oligonucleosides, substituting the pentose fragments characteristic of the natural compounds by a tetrahydrofuran group or diol group. Although the plan was not fully realized (partly on account of the untimely death of S. A. Hiller), methods were developed for the synthesis of diols and their phosphates, and oligomers that selectively affect certain stages in the biosynthesis of nucleic acids and proteins were obtained. Stimulators of cell growth were found among these compounds. The synthesis of furanidylpyrimidines is also partly associated with these investigations (including the antitumor preparation *ftorafur*). Among the models of natural compounds it is possible to include purinyl- and pyrimidyl amino acids and peptides based on them, unique hybrids of polypeptides and polynucleotides, with which M. Lidaks was productively engaged in the last period of his life.

The extremely versatile chemist Academician J. Freimanis (1935-2006) synthesized and studied in detail the so-called molecular autocomplexes – compounds in which the donor part (an aromatic amine) and the acceptor part (an aromatic nitro compound or quinone) are joined in one molecule by a flexible bridge - an inert atomic grouping that controls the mutual spatial arrangement of the donor and acceptor parts.

Together with E. Markava and physical chemists (J. Stradins, L. Baumane, R. Gavars, V. Glezer, B. Turovska) J. Freimanis in 1984-1994 studied in detail the chemistry of N-arylquinone imines and N-arylquinone diimines, the electron affinity of these compounds, and the structure of the free radicals formed during their reduction. He made extensive searches for new organic semiconductors in conjunction with the physicist Academician E. Silinsh and his colleagues. In the last years of his life J. Freimanis was working on the problems of "organic clay".

Original methods for the synthesis of aminoadamantanes were developed by J. Polis, and new chemotherapeutic agents in this class were created – *adapromine*, *gludantane*, *midantane*, *remantadine* (State Prize of the Latvian SSR, 1989).

A wide range of investigations in partially hydrogenated nitrogen-containing heterocycles (dihydro- and tetrahydropyridines, dihydro- and tetrahydropyridones, dihydro- and tetrahydropyrimidines, dihydro- and tetrahydroindenopyridines, furo-, thieno-, and pyrrolodihydropyridines) and new heterocyclic systems (dihydrobenzothienopyridine, furopyrazolopyridines, thiazolopyridothiadiazines, dichromenopyridine, pyrroloacridine, etc.) was conducted (and is being conducted) under the leadership of G. Duburs. Multicomponent syntheses, chemical characteristics, and various types of reactions (isomerization, recyclization, the action of electrophilic reagents, oxidation, free-radical reactions, antiradical and antioxidant activity) were studied. G. Duburs and his colleagues are carrying out an extremely comprehensive search for new antagonists and agonists of calcium ions, antiarrhythmic and antidiabetic agents, radioprotectors, hepatoprotectors, neuroprotectors, antiamnestic and anti-inflammatory agents, immunomodulators, cryoprotectants, antimutagens, geroprotectors, and new agents for the transfection of genes. Extremely diverse fields of possible application of *diludin* (State Prize of the Latvian SSR, 1977), *diethone*, *foridone* (Prize of the Council of Ministers of the Latvian SSR, 1990), and also *cerebrocrast* and *glutapyrone* were studied.

Methods for the synthesis and biological testing of new inhibitors and substrates of β-hydroxylase and transaminase, the chemistry of aliphatic and heterocyclic amino- and hydrazinocarboxylic acids, and the synthesis and characteristics of γ-butyrobetaine, carnitine, and other betaines are being developed under the leadership of I. Kalvinsh. The cardio- and cytoprotector *mildronate* and the antitumor immunomodulator

leakadine (State Prize of the Latvian SSR, 1989) were created, and the mechanism of action and the clinical effect of the synthesized cytostatics and neuro- and cardioprotectors were studied. It should be noted that *mildronate* [3-(2,2,2-trimethylhydrazinium)propionate dihydrate] is one of the best-known products developed at the Institute in recent decades. (At the present time it accounts for about 70% of the profit of the Grindeks – largely on account of export trade.)

In 1965-1967 M. G. Voronkov, V. Udre, and others developed methods for the synthesis of sulfur heterocycles of the aromatic series containing thiophene, thienothiophene, 1,4-dithiadiene, and 1,2-dithiolene-3-thione rings coupled or condensed with an aromatic ring; these methods were based on the reactions of elemental sulfur with arylhaloalkanes. In particular, tetraphenylthiophene is formed from benzyl chloride and sulfur, while the reaction of sulfur with benzyl bromide gives 2-phenylthianaphthene.

It was shown that opening of one of the thiophene rings and nucleophilic substitution in the heteroaromatic ring at the point of cleavage of the S–C bond in the reaction of benzo[*b*]thieno[3,2-*b*]-benzo[*b*]thiophene disulfone with acyclic and cyclic amines followed by hydrolysis and dehydration of the obtained systems leads to derivatives of a new heterocyclic system (E. Lukevics, V. Udre, J. Bleidelis).

In the seventies Academician G. Chipens developed an original model of hormone–receptor interaction. According to this model the deciding significance in the hormone–receptor interaction is attributable only to certain sections of the peptide molecule, i.e., the so-called signatures. In order to check the theory model peptides (analogs and fragments of natural hormones angiotensin, bradikinine, and analogs of ACTH) were synthesized at the Institute and tested by molecular pharmacology, and their three-dimensional structure was determined by physical methods. A new analog of tuftsin – *rigin* (named after the town Riga) – was created, and cyclic analogs of linear peptides were synthesized on the basis of the calculated results. Corresponding Member of the Latvian Academy of Sciences G. Veinberg developed methods for the production of semisynthetic antibiotics of the β-lactam type, realized silyl methods for their synthesis, and carried out research into new antibiotics with antitumor activity.

In the field of physical organic chemistry the electronic and molecular structures, intra- and intermolecular effects, redox characteristics, and reactivity of extremely varied types of organic compounds were systematically studied. In the region of NMR spectroscopy methods of multinuclear NMR spectroscopy (including 2D spectroscopy) were introduced, and new multinuclear methods (including ultrahigh resolution spectra) were developed. Researchers at the Institute E. Liepinsh and E. Kupče, who subsequently worked in Switzerland, Sweden, and Great Britain, became internationally recognized NMR experts. Cyclic voltammetry, polarography methods, and rotating disc electrode with ring technique were used for systematic study of the mechanism and kinetics of the electrochemical reduction and oxidation of heterocyclic nitro compounds (mostly derivatives of 5-nitrofuran), quinoidal systems (quinone imides, etc.), 1,3-diketones, heterocyclic aldehydes and ketones, various dihydropyridines and dihydropyrimidines, silatranes, etc., and the electron affinities were determined (J. Stradins, State Prize of the Latvian SSR, 1980). In the physical organic chemistry laboratory the method involving electrochemical generation of free radicals directly in the resonance cavity of the ESR spectrometer while the ESR spectra were recorded was worked on methodically and widely used, and the density of the unpaired electron was calculated. The subjects of investigation were various heterocyclic nitro compounds and indanediones. The main authors in the field of molecular electrochemistry were J. Stradins, R. Gavars, V. Kadysh, L. Baumane, V. Glezer, and B. Turovska. A procedure was worked out in conjunction with J. Freimanis for the calculation of the complex formation and thermodynamic constants of so-called molecular autocomplexes synthesized at the Institute (Honorary Doctor of the Latvian Academy of Sciences I. Turovskis).

The structure of a large number of crystalline organic compounds was established by X-ray crystallographic analysis (J. Bleidelis, A. Kemme, A. Mishnev, S. Belyakov). Methods were developed for the gas-liquid chromatography and liquid chromatography of organic amines (A. Andersons), and the methodology was worked out for the use of liquid chromatography in the chemistry of drugs (V. Shatz).

In due course the computational approaches and the procedures for predicting biological activity in organic compounds developed at the Institute gained a wide reputation (V. Golender, A. Rozenblit).

Products Created at the Institute

At the Institute in the middle of the eighties the technology for the production of about 65 medicinal preparations, herbicides, and pesticides (of them 37 products of a widespread medical application approved in the USSR) was introduced at two of its Experimental plants; 12 of the medicinal products among them were original. Besides the various nitrofuran products the Institute gained the greatest reputation due to the product *ftorafur*.

Ftorafur (5-fluoro-1-tetrahydrofuryl-2-uracil) can be regarded as a unique transport form of 5-fluorouracil, distinguished from the latter by its substantially lower toxicity. The low toxicity together with high activity makes it possible to use *ftorafur* for the treatment of cancer of the rectum and large intestine, stomach, and gullet (effective in 20-40% of the investigated clinical cases); encouraging results were also obtained during the treatment of brain tumors, breast cancer, and tumors of the ovary. The chronology of *ftorafur* describes the period in which the product passed from the first synthesis of the active substance in 1964 to the completion of clinical trials, the development of the experimental technology, and the start of foreign exports (to Japan) in 1972 – 6-8 years, which can be considered a relatively short period in the investigation and introduction of products. *Ftorafur* was used in oncological practise not only in the former USSR but also in Japan, the Federal Republic of Germany, the USA, and other countries and for a long time occupied the most important position in the export of synthetic drugs from the USSR. Beginning in 1972 several international conferences of oncologists and clinicians devoted specially to *ftorafur* were arranged.

After 1969, when the product was first introduced into Japan, it achieved a widespread application in the arsenal of chemotherapeutic antitumor products, particularly in the post-operative period to prevent the formation of metastases. The Institute had to sustain a whole "patent war" over its invention and as a result was able to win a judicial process in Japan.

The export of *ftorafur* to Japan by the Institute's Experimental Plant enabled the Institute to earn monetary resources, which was uncharacteristic of the academic institutes of the USSR. The export operations made it possible to equip the Institute with fairly modern scientific equipment, reagents, etc., and this in turn contributed to the scientific development of the Institute and the carrying out of serious scientific investigations in organic and medicinal chemistry, bioorganic chemistry, molecular biology, and genetic engineering, including also the chemistry of heterocyclic compounds.

Many of the technologies for the production of "resynthesized" drug preparations for various uses, developed at the Institute and introduced into industry, were also of great importance for medicine under the conditions in the USSR, where purchases of foreign products were restricted.

By 1987 the list of original preparations created at the Institute included the following original substances: *Gludantane* – for the treatment of Parkinson's disease; *dioxonium* – for weakness of the muscular system during anesthetization; *imiphos* – for the treatment of erythremia; *leakadine* – in immunological disturbances in oncological patients; *methindione* – for epilepsy; *mildronate* – for the prophylaxis of ischemic myocardial damage; *omephin* – for the prophylaxis and treatment of thromboembolic diseases; *foridone* – in hypertonic disease; *ftorafur* – in oncology; *furagin* – in inflammatory diseases of the urinary tracts; *soluble furagin* – for heavy forms of infectious and inflammatory diseases; *furamag* – for the prophylaxis of infections and the treatment of infectious inflammatory diseases; *quinotilin* – for the removal of residual antidepolarizing block of nerve–muscle transmission, in total 13 products, and also three products for animal husbandry and veterinary science – *diludin*, *ratindan*, and *ratindan-2*. The last two products of the 2-acylindanedione series, agents developed by G. Vanags for the killing of rodents, are used in the fight against ground squirrels, particularly in the Ukraine.

The resynthesized products included antitumor agents (L-*asparaginase*, *bleomicetin*, *thiophosphamide*, *cyclophosphane*, *cytarabine*), chemotherapeutic agents for the treatment of bacterial and viral infections (*adapromine*, *remantadine*, *furadonin*, *furazolidone*, *furazoline*, *cefalexin*), products for the treatment of cardiovascular diseases (*ditrimine*, *carbochromen*, *streptodecase*, *fenigidine*, *fenilin*), psychopharmacological

and analgesic agents (*benperidol*, *damilene maleinate*, *droperidol*, *midantane*), peptide bioregulators (*angiotensinamide*, *deaminooxytocin*, *pentagastrin*), mucolytic agents (*acetylcysteine*, *bromhexine*), the sugar-lowering agent *glibutide*, the laxative *bisacodyl*, enzymatic preparations for the treatment of gastroduodenal diseases – *solizyme* and *somilase*, and the cholinergic product *dipyroxime*.

The preparations for veterinary use included *desoxyfur*, *divezide*, *oxytocin*, *piperazine silicofluoride*, *furagin*, *furazolidone*, *furacilin*, *cyazide*, and *cyazone*, and preparations for plant cultivation included *GMK-T* and *GMK-Na*, *DYAK*, and *fenazone*.

Scientific-Managerial Projects at the Institute

Beginning in the sixties the Institute established scientific relations with scientific establishments of the USSR in Moscow, Leningrad, Kiev, Kharkov, Sverdlovsk, Irkutsk, Novosibirsk, etc., with the institutes of the Academy of Sciences of the USSR, the Academy of Medical Sciences of the USSR, the Cardiological and Oncological Centers in Moscow, and with various universities. The number of partners of the IOS in the creation of drugs was about 150-200. To be sure the development of broader scientific connections with the scientists of the West was restricted by the isolationist scientific policy of the USSR. Fairly strong obstacles were set up to scientific exchange, with lengthy probation periods, participation in conferences abroad, and publication of scientific papers in foreign international journals. This was also reflected in the citability of the Institute's scientists. Admittedly, these obstacles peculiar to the period of the cold war were less pronounced in the case of the Institute of Organic Synthesis than for other institutes of the USSR; it is even possible to say that the Institute of Organic Synthesis operated in its own type of "regime of special treatment".

Thus, even in 1965 the Institute was afforded the right to publish the international journal "Chemistry of Heterocyclic Compounds", which from the very beginning was also published in parallel in English "from cover to cover" in the USA.

For the contribution to the development of new drugs (*ftorafur*, *diludin*, and others) workers at the Institute were with awarded with Prizes of the Council of Ministers of the USSR and the Council of Ministers of the Latvian SSR, and for the development of the production process they were awarded with the International "Gold Mercury" Prize for international economic collaboration (1980).

Already at the beginning of the sixties the Institute organized numerous All-Union scientific conferences on important branches of chemical and medical science, and from 1967 it also organized international scientific conferences. (The first was the First International Symposium of Socialist Nations on the Structure and Function of Proteins and Peptides.) Up to 1990 the Institute organized more than 80 conferences, congresses, and symposiums on problems associated with the subject matter covered by the Institute.

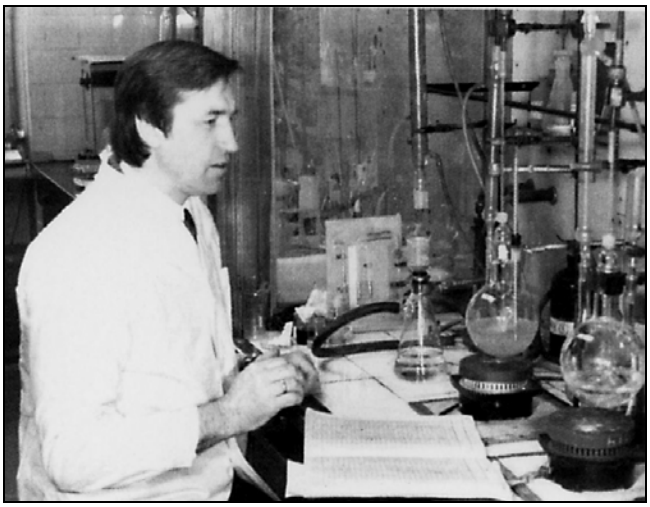
The most significant event was the VII International Symposium of IUPAC on the Chemistry of Natural Compounds with four pre-symposiums, in which 1900 scientists from 40 countries participated. At the symposium, the organizers of which were the Academy of Sciences of the USSR, the Institute of the Chemistry of Natural Compounds of the Academy of Sciences of the USSR (currently Academicians M. M. Shemyakin and Yu. A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences), the Academy of Sciences of the Latvian SSR, and the Institute of Organic Synthesis of the Academy of Sciences of the Latvian SSR. Plenary lectures were delivered by H. G. Khorana, R. G. Woodward, D. Barton, C. Djerassi, V. Prelog, K. Nakanishi, M. M. Shemyakin, and others. (Members of the Institute of Organic Synthesis presented 12 oral reports at the symposium.) This impressive international forum, larger than any held anywhere in Riga, gave rise to extensive international response. (H. G. Khorana reported on the first synthesis of an artificial gene, R. B. Woodward on the completed most important stage in the total synthesis of vitamin B_{12}.) It is also necessary to mention the IX IUPAC Symposium on the Chemistry of Organic Compounds of Sulfur (1980) organized by the Institute, the International Conference "Bioorganic Chemistry and the Design of Medicaments"

FUTURE ACADEMICIANS AND PROFESSORS
AT THE BEGINNING OF THE ROAD

From left to right: E. Grens, J. Freimanis, G. Chipens, E. Lukevics

J. Stradins

R. Zhuk (left)



I. Kalvinsh

E. Stankeviča and G. Duburs

FROM OUR PHOTO ARCHIVE
(The Sixties)

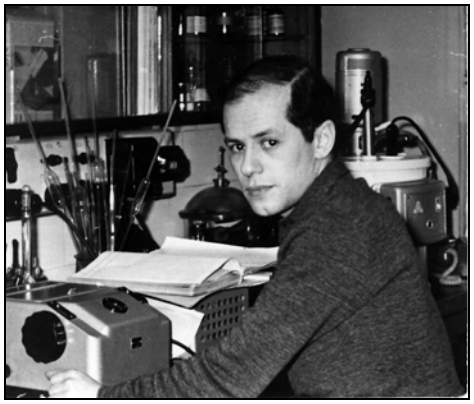
L. Avota

B. Kurgane

K. Venters

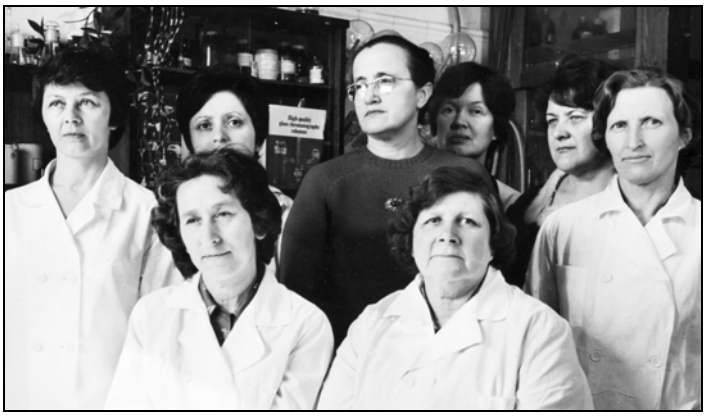
R. Kalnberga

N. Saldābola

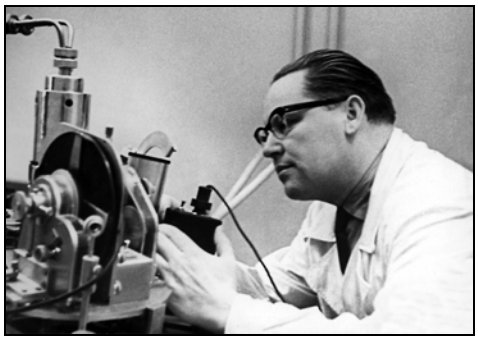


G. Veinberg

The Laboratory of Catalytic Synthesis, the eighties

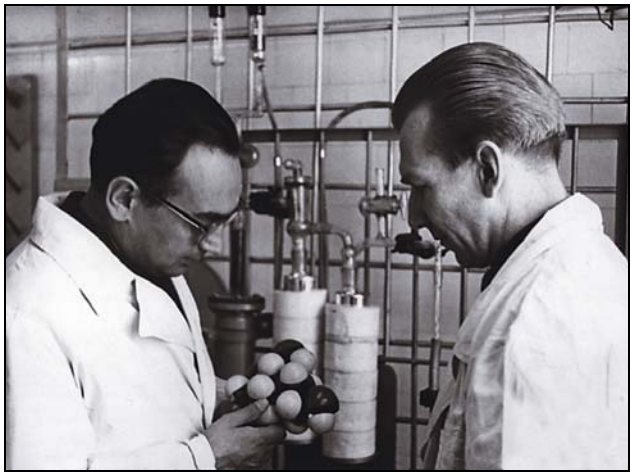


The Liquid-Phase Catalytic Reactions Group, 1982



J. Bleidelis sets up the camera to photograph the reciprocal lattice of crystals, 1965

Colleagues at the Laboratory of Physical Organic Chemistry, 1982



M. Voronkov and G. Zelchans examine a model of a new structure found by them, the sixties

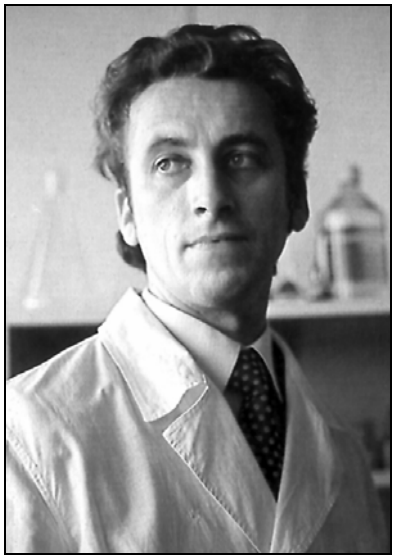
Leader of the Laboratory of Organic Analysis and Standardization of Products V. Egerts, 1980

Colleagues at the Laboratory of Organometallic Chemistry greet the new millennium with optimism

Colleagues at the Laboratory of Membrane-Active Compounds and β-Diketones after a colloquium, 2006

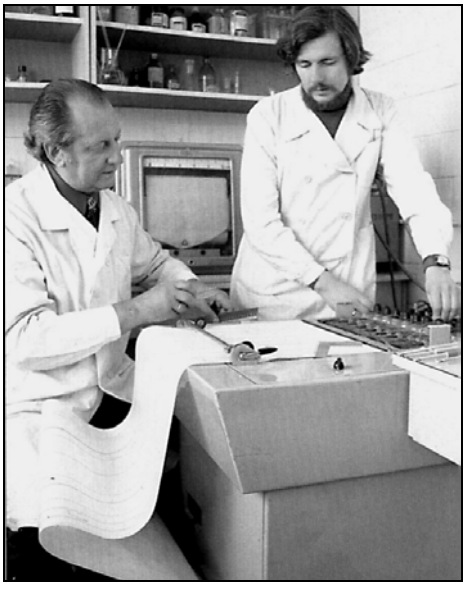
The path from chemical compound to medicine can only be surmounted by the joint efforts of various specialists

A new anticancer product is synthesized. M. Lidaks, R. Paegle, and I. Ulane, the sixties



J. Polis synthesized antiviral products of the adamantane series

Pharmacologists S. Germane (photo below, left), A. Zīdermane (photo, middle), and A. Ķimenis and M. Veveris (photo, below right)



USSR State Prize winners (left to right):
G. Chipens, V. Klusa, A. Pavārs, F. Mutulis, and A. Štālberga

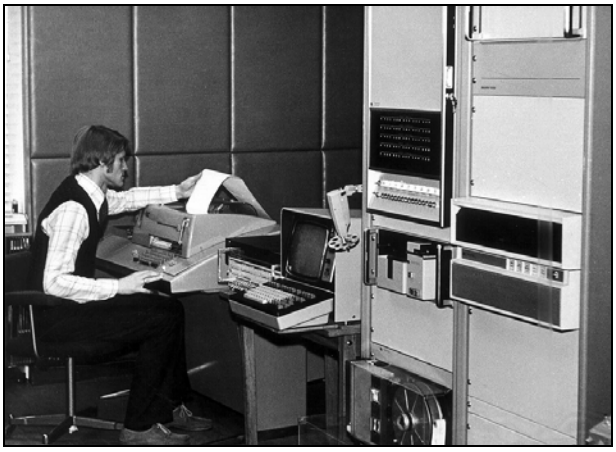
E. Grens – Pioneer of molecular biology and genetic engineering in Latvia

Chemist O. S. Papsuevich, pharmacologist V. Klusa, and mathematician S. Galaktionov discuss the results of a joint investigation, the eighties

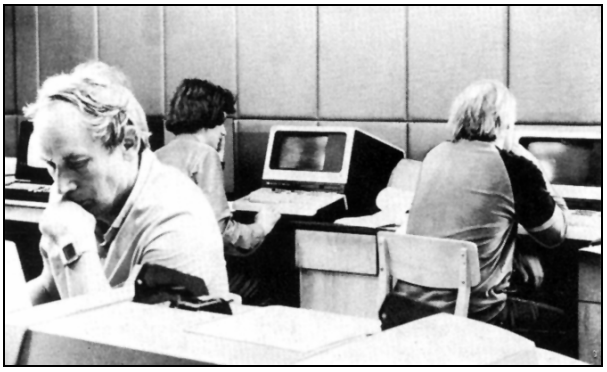
"Peptide enthusiasts at the IOS, September 25, 1994," so named this photograph the journal "The European Peptide Society News Letter." At the center Director of the IOS E. Lukevics and Section Leader G. Chipens

Mathematics in the Service of Chemistry and Medicine.
The Computer Center of the IOS in Various Years

I. Liepiņa, V. Sīle, and P. Mellis



U. Pinka



A. Rozenblit, I. Freivalde, J. Bētiņš

A. Gutcait and I. Kalvinsh

In the Experimental Plant Organic Technology Section Leader A. Avots (left), seventies

At the Experimental Plant of the IOS

Colleagues of the Institute E. Lukevics and A. Fogel after successful application for patent right for *ftorafur* in Japan, 1977

In the laboratory of Prof. Vataru Ando (Tsukuba, Japan, 1990)

Collaboration with Nippon Soda continues (Riga, 1992)

After signing a new contract with Taisho Pharmaceuticals (Tokyo, 1998)

The management of the Institute and Grindeks in the "place of honor" at the Iskra company (Tokyo, 1998)

In 1980 the IOS was awarded with the Gold Mercury Award

Director of the IOS S. Hiller introduces guests from Moscow to the Institute's new premises. From left to right: S. Hiller, Academician A. P. Aleksandrov, President of the Academy of Sciences of the USSR Academician M. V. Keldysh, Academician J. Peive, Vice-President of the Council of Ministers of the USSR K. Rudnev, 1962

Director of the IOS, Academy of Sciences of the Latvian SSR, G. Chipens and Deputy Director Corresponding Member of the Latvian Academy of Sciences E. Lukevics acquaint President of the Academy of Sciences of the USSR Academician A. P. Aleksandrov and Vice-President of the Academy of Sciences of the USSR Yu. A. Ovchinnikov with the work of the Institute, 1980

Prof. E. Garfield (Institute of Scientific Information, USA) chats with Editor-in-Chief of the journal "Chemistry of Heterocyclic Compounds"
Prof. J. Stradins (Riga, 1981)

Springer Editorial Director K. Derham (center) with representatives of the two journals published in Riga near the building, in which the IOS was located up to 1962 (2005)

Seventh International Symposium on the Chemistry of Natural Compounds (Riga, 1970)

The conference hall

Session chairpersons: Academician of the Academy of Sciences of the Latvian SSR S. Hiller and Academician of the Academy of Sciences of the USSR S. E. Severin

Prof. S. Hiller and Prof. H. G. Khorana chat in the break-time

Jubilee Session of the Science Council on Organosulfur Compounds (Riga, 1980)

Photographic reminiscence

IX International Symposium on the Organic Compounds of Sulfur (Riga, 1980)

VI FECHEM Conference on Organometallic Chemistry (Riga, 1985)

Academician M. E. Volpin greets Academician G. A. Razuvaev on the 90th anniversary

THE EDITORIAL STAFF OF "CHEMISTRY OF HETEROCYCLIC COMPOUNDS"

Beginning of the eighties.
Left to right: T. I. Groceva, P. Krasnevich, Secretary of the Board I. N. Goncharova, Editor-in-Chief J. Stradins

The Editorial Team in 2000 (top) and 2007 (bottom)

(1982), the VI European Conference on Organometallic Chemistry (1985), the V International Symposium on the Chemistry of Furan (1988), the VII International Conference on the Chemistry of Organic and Coordination Compounds of Germanium, Tin, and Lead (1992), not counting the numerous All-Union conferences and bilateral symposiums USSR–GDR, USSR–India, and USSR–Switzerland organized by the IOS.

Within the framework of the USSR the Institute was a leader in several fields on the scale of the superpower at that time, and three All-Union Scientific Councils operated at the Institute: The Scientific Council on the Utilization of the Pentosan-Containing Raw Material (in the eighties it became a section of the All-Union Council on Timber); the Scientific Council of the State Committee of the USSR on "Chemistry and Technology of Organic Compounds of Sulfur" (from 1969); the Section of Chemical Cybernetics of the All-Union Council on Cybernetics. The activity of the Council on Organic Compounds of Sulfur had a special significance. The Council coordinated all the investigations being carried out in the USSR on the processing of sulfur-containing oil and high-sulfur oil, the identification and study of organic compounds of sulfur in fossil fuels, the development of products for medicine and agriculture on the basis of organic compounds of sulfur, the ecological aspects of the production and use of organic compounds of sulfur and sulfur-containing fuels, and the theoretical and synthetic chemistry of organic compounds of sulfur.

Traditional for the Institute are the Gustavs Vanags memorial lectures (from 1966) and also the symposiums in memory of the Institute's founder S. A. Hiller devoted to the search for new drug products (held between 1975 and 1991). In 1990 the S. A. Hiller medal was established as the highest award of the Institute (up to the present more than 80 people have received it). In 2003 the Latvian Academy of Sciences (in collaboration with the Grindeks company) set up an official S. A. Hiller prize for biomedicine and the creation of new drugs, which has so far been awarded to Academicians I. Kalvinsh and E. Grens. The G. Vanags Prize of the Latvian Academy of Sciences for chemistry has been awarded since 1971, and 11 specialists at the Institute have been given it.

In 1980 546 people were working at the Institute (of them 340 were researchers, including 15 doctors and 129 candidates of sciences). Toward the end of the eighties the number of doctors of sciences (20) and candidates of sciences (180) increased. At the beginning of the eighties scientists at the Institute annually received 25-30 author's certificates of the USSR and up to 10 patents from various countries.

The Development of the Institute since 1991

After the collapse of the USSR and restoration of the independence of Latvia (many workers at the Institute were active participants in the struggle for liberation) the work conditions at the Institute changed significantly. There was not only a transition from a totalitarian state to a democratic state, but working in a superpower changed to working in a small state with substantially different financial resources and state priorities. The conditions and principles for financing the scientific investigations changed, and there was a transition to financing scientific projects (grants) instead of financing complex scientific programs. (The latter were cancelled completely in the first years of independence in Latvia and were only partly restored as from 1996.) Many previously traditional scientific links with Russia, Ukraine, etc. were disrupted (science there had endured no better times), but then wider possibilities appeared for inclusion in the international community, ties with the countries of Western and Northern Europe, USA, Canada, Japan, and Taiwan, and joint projects arose with the scientists of these countries. Most of the traditional directions in the field of chemistry at the Institute continued, although in a somewhat different perspective and often in reduced scope, and the possibilities of publication in foreign journals and appearance at conferences in other countries improved. However, the emigration of some of the Institute's scientists to the USA, Sweden, Israel, and other countries soon became evident, and a significant number of workers turned to contract syntheses at the order of foreign firms or scientific centers (alongside with investigations on the main subject, which were financed quite poorly by the Latvian Council of Science and partly by the international Soros Research foundation and European funds). The Institute did not (like most of the former institutes of the Latvian Academy of Sciences) become part of the

Latvian University but kept its independence. (At present it has the status of a state scientific-research institute.) The number of workers at the Institute has decreased: in 1991-597 (including 225 researchers, among them there are 196 doctors and habilitated doctors of science): in 1997-310 (including 188 researchers, among them there are 130 doctors and habilitated doctors of science). Admittedly, this is partly explained by the transfer of molecular biologists to the new institute created by them and also by subsequent transfer of the Pharmacology department and part of the medical scientists to other establishments or to the Latvian University.

The Institute was separated from the Latvian Academy of Sciences, while in turn its Experimental Plant was separated from the Institute and formed the basis of the Joint Stock Company Grindeks, which was named after the first Latvian chemist and pharmacist of the eighteenth century David Hieronymus Grindel (1776-1836) and the word *experimental.*

The founder of Grindeks was Valdis Jakobsons, who previously worked as a deputy director of the Institute of Organic Synthesis (now – Honorary Member of the Latvian Academy of Sciences, to 2007 – Chairman of the Board of Grindeks). The highest award of this firm since 1995 is the Grindel medal, with which many scientists at the Institute of Organic Synthesis have been awarded. In 2006 in connection with the fiftieth anniversary the IOS was awarded with this distinction as an institute as a whole for services in the development of drugs and in the creation of the Grindeks holding. Consequently, the bonds between the Institute and this pharmaceutical firm are becoming stronger, and the collaboration between the Institute and Latvian University, Riga Technical University, and Riga Stradins University on the training of specialists in the field of chemistry and pharmacy is being strengthened.

Despite all the perturbation of the time, the Institute of Organic Synthesis remains as before the most multitudinous and qualified scientific-research institution of the independent Latvian Republic. Although the difficulties of the transitional period were substantial, the Institute was able to retain its scientific potential to a considerable degree. Admittedly, along with other things there was a natural change of generations, and certain directions at the Institute (such as the chemistry of peptides and enzymes, which was strong in the eighties) practically died out. The theoretical work on the chemistry of heterocyclic compounds was also somewhat curtailed.

Along with the theoretical investigations in the region of chemistry and biomedicine a substantial effect has been credited to the applied investigations directed at creating new medicinal preparations. Since 2004 the Institute has been headed by I. Kalvinsh, famous for the creation of a series of original drugs – immuno-modulators, antitumor agents, and psychopharmacological agents.

After 1991 workers at the Institute were awarded with the Prize of the Cabinet of Ministers of the Latvian Republic (G. Dubur, 1999; J. Stradins, 2001; E. Lukevics, 2004; I. Kalvinsh, 2006), the Grand Medal of the Latvian Academy of Sciences (J. Stradins, 1993; E. Lukevics, 1996), P. Walden medals (Riga Technical University) (J. Stradins,1988; G. Duburs, 1994; E. Lukevics, 2000; I. Kalvinsh, 2003), O. Schmideberg medals, and other scientific prizes and government awards of the Latvian Republic, France, Italy, Estonia, Ukraine, and other countries.

In 2006 the D. I. Mendeleev Russian Chemical Society, the International Charitable Fund "Scientific Partnership," and the M. V. Lomonosov Moscow State University awarded the journal "Chemistry of Heterocyclic Compounds" with a medal in memory of Prof. A. N. Kost. E. Lukevics, A. Skorova, and J. Stradins were awarded with the corresponding honorary diplomas for achievements in the chemistry of heterocyclic compounds. Earlier, in 2003 the Scientific Partnership Fund awarded the journal with a Gold Medal "For Contribution to Science and the Scientific Partnership".

In 2006 I. Kalvinsh was elected a Honorary Member of the Ukrainian Medico-Stomatological Academy. In 2004 J. Stradins was given the highest award of the Saxony Academy of Sciences (in Leipzig) – the Wilhelm Ostwald medal, was elected an Active Member of the German Academy of Naturalists "*Leopoldina*" and the European Academy of Sciences and Arts, and a Foreign Member of the Academies of Sciences of Latvia, Estonia, and Georgia. The founder of the Institute S. A. Hiller was elected a member of the German Academy of Naturalists "*Leopoldina"* as far back as 1972. E. Lukevics is a member of editorial boards and the editing councils of many international chemical journals.

Many workers of the older generation continue their research activity, but the role of scientists of the middle and younger generations is increasing all the time (Doctors of Science O. Pugovich, P. Trapencieris, V. Kauss, V, Lūsis, A. Krauze, A. Jirgensons, E. Abele, E. Sūna, N. Sjakste, M. Dambrova, and others).

The Laboratory of CNS-Active Compounds (Dr. chem. I. Kauss) is conducting a targeted search for and study of compounds of noncompetive action that control allosterically the function of metabotropic glutamate receptors (mGluR) of the central nervous system. The aim of the investigation is to develop new therapeutic agents for the treatment of such progressive neurological disorders as Alzheimer's and Parkinson's diseases.

The Laboratory of Organic Chemistry (laboratory leader Dr. chem. P. Trapencieris) is engaged in theoretical investigations and the development of synthetic methods in various fields of organic chemistry. The main direction of the theoretical investigations on asymmetric synthesis is being conducted in classes of non-natural amino acids, including various heterocyclic systems (aziridines, oxaziridines, 1,2-oxazines, pyrroles, indoles). New methods have been developed for the synthesis of indoles and aziridines, and investigations are being conducted on their functionalization. Practical investigations in the field of hydrazinecarboxylic acids are being conducted with the aim of seeking new cyclic and linear betaine systems – analogs of the natural betaines carnitine and γ-butyrobetaine, suitable for use as agents for cardiovascular diseases.

The laboratory for the analysis of biologically active compounds (Dr. chem. A. Drivina) was created in 1996. The main direction of the work of the laboratory is investigation of the stability of ready-made drug forms and also the active substances in order to obtain data for registration of the products in accordance with the requirements of EDQM (European Directorate of the Quality of Medicines). The laboratory is also engaged in the development and testing of essential new analytical procedures for the achievement of the above-mentioned aim. In order to ensure the reliability and authenticity of the obtained results a quality control system conforming to the standard EN ISO/IEC17025 was installed in the laboratory.

The laboratory of carbofunctional compounds (Dr. habil. chem. I. Kalvinsh) is engaged in the targeted development of new antitumor agents based on inhibitors of histone-deacetylase, heat-shock proteins, and other proteins drawn into malignant transformation. Workers at the laboratory found a new class of compounds that complex heavy metals and zinc and are based on derivatives of aziridines. They exhibit a high specific activity against tumors of the pancreas and are being developed as a new drug. The antitumor product PXD-101 synthesized under the leadership of Dr. chem. E. Loža is at stage II of clinical trials in the USA and EU. In the laboratory new methods are being developed for the synthesis of heterocyclic compounds, including enantiomerically pure synthons for the synthesis of medicines.

A state program on the creation of medicines and novel drugs, and biocorrection agents is also being undertaken under the guidance of Academician I. Kalvinsh.

Recently after the return of E. Liepinsh from abroad (where he worked with Nobel Prize winner K. Wüthrich and his successors) correlation methods (2D-HSQC, 2D-TOCSY, 2D-NOESY, 2D-ROESY, etc.) were introduced to routine NMR work, and this made it possible to substantially improve the accuracy of correlation of the NMR signals. The acquisition of new NMR spectrometers (400 and 600 MHz with cryosensors) by the Institute enabled to analyze the spectra of small fragments of proteins and to use NMR to determine the stereochemical structure of these natural compounds in their natural medium – in aqueous media. As examples it is possible to cite the previously established structures of the protein WIF (156 amino acids) and the enzyme inhibitor–human WFIKKN protein. In this way a new step was taken in the study of the mechanism of potential medicinal preparations synthesized at the Institute at the molecular level. New possibilities were opened up for the analysis of mixtures and the search for biomarkers by NMR. The cycle of investigations by E. Liepinsh on determination of the stereochemical structure of proteins in aqueous media by multidimensional NMR was named among the 10 best scientific papers executed in Latvia in 2006 – such a list is traditionally compiled by the Latvian Academy of Sciences.

The journal "Chemistry of Heterocyclic Compounds" is published as before (Editor-in-Chief Academician E. Lukevics). The other periodical published by the Institute – "Experimental and Clinical Pharmacotherapy" – ceased publication at the beginning of the nineties. The number of scientific monographs and to some degree scientific papers published by workers at the Institute has been reduced, but a substantial part of the scientific results is patented jointly with foreign partners. The number of patents bearing the names of workers at the Institute increases with each year.

The Institute continues to be a location for holding scientific forums, the most brilliant of which was the third *Balticum Organicum Syntheticum* symposium (BOS-2004). Beginning in 1998, the Institute regularly organizes the international Walden symposiums on organic chemistry (once every two years).

The oak planted in front of the Institute's building in 1984, which was brought from the home farm of the founder of stereochemistry P. Walden at Vidzem, is growing. The younger generation of students-chemists, educated in Riga and improved at scientific centers abroad, take part in the investigative work.

The list of young scientists who received the title of doctor of sciences abroad in the last decade is extensive: A. Antipova (Prague, Czechoslovakia), M. Dambrova (Uppsala, Sweden), A. Amolinsh (Bern, Switzerland), A. Sobolev (Wageningen, the Netherlands), I. Liepiņa (Gdansk, Poland), A. Drivina (Chiba, Japan), R. Zemribo (Mississippi, USA), Yu. Fotins (Cincinnati, USA), V. Vyater (Halle, Germany), R. Zhalubovskis (Stockholm, Sweden). Useful foreign experience after defence of a thesis was obtained by: A. Jirgensons (Perugia, Italy), R. Zemribo (Bozeman, USA; Sodertalje, Sweden); V. Ozola (Wurzburg and Bonn, Germany), B. Turovska (Århus, Denmark), M. Katkevičs (Kyoto, Japan), L. Ignatovich (Sendai and Hanno, Japan), A. Gutcait (Taipei, Taiwan). Now their experience contributes to the implementation of the complex developments at the contemporary level.

On the other hand, a number of former collaborators at the Institute have left Latvia; E. Kupče, Yu. Goldberg, B. Simkhovich, R. Zhuk, V. Golender, V. Glezer, O. Daugulis, V. Gevorgyan, N. Erchak, L. Baider, and others are working at universities, companies, and scientific establishments in the USA, Canada, Israel, Sweden, Great Britain, Russia, Belarus, and other countries. Some of them, who achieved successes in science and in the creation of fundamentally new methods of investigation (e.g. E. Kupče at the firm Varian on the development of an NMR spectrometer at 1000 MHz, the Laukien prize of 2006 for the creation of new methodology for the accelerated production of multidimensional NMR spectra), continue to maintain a connection with Institute.

The entry of Latvia into the European Union in 2004 led to a change of government policy with regard to science. This raises hope for the expansion of scientific investigations and for the realization of innovative processes, which was the speciality of the Institute of Organic Synthesis even from the very beginning of its existence. New prospects of development, regeneration of traditions and approaches, and the focused search for new medicines set by the founder of the Institute S. A. Hiller have been opened up before the Institute. The possibility of creating original medicines and developing fundamental science in a small country is a special topic, considering the ever-increasing globalization and competition of the world market.

However, in our view, cooperation, establishment of a certain favorable status from the international scientific community, and the backing of local developments by one's own state in small nations can secure a more uniform international distribution of scientific labor (including the field of organic chemistry). Models for privatization of the applied sector of the Institute while preserving the academic component responsible for the development of fundamental organic chemistry, including the chemistry of heterocycles, are under discussion. The trends of recent times make it possible to hope for successful future growth of the Institute of Organic Synthesis and preservation of all the chemical traditions that have been inherent in Latvia for more than 25 years.

The younger generation represents the security for the future, and the conditions for working in an institute provided with a modern equipment base have now been created for it. Investigations in pharmaceuticals and biomedicine (gene technologies, the synthesis of new drugs) have been included by the Cabinet of Ministers of the Latvian Republic among the state priority directions for science in 2006-2009.

The Principal Books and Scientific Collections of the Institute

1. *Aspects of the Use of Pentosan-Containing Raw Material* [in Russian], Izd. Akad. Nauk Latv. SSR (1958), 521 pp.
2, G. Vanags (editor), *Cyclic β-Diketones* [in Russian], Izd. Akad. Nauk Latv.SSR, Riga (1961), 374 pp.
3. J. P. Stradyn, *Polarography of Organic Nitro Compounds* [in Russian], Izd. Akad. Nauk Latv. SSR, Riga (1961), 165 pp.
4. M. V. Shimanskaya and V. A. Slavinskaya, *Analytical Determination of Furfural* [in Russian], Izd. Akad. Nauk Latv. SSR, Riga (1961), 184 pp.
5. L. N. Alekseeva, *Antibacterial Preparations – Derivatives of 5-Nitrofuran* [in Russian], Izd. Akad. Nauk Latv. SSR, Riga (1963), 219 pp.
6. L. V. Kruzmetra, *Nitrofuran Preparations in the Fight with Staphylococcus Infection* [in Russian], Izd. Akad. Nauk Latv. SSR, Riga (1964), 119 pp.
7. E. Lukevics and M. G. Voronkov, *Hydrosilylation, Hydrogermylation, and Hydrostannylation* [in Russian], Izd. Akad. Nauk Latv. SSR, Riga (1964), 370 pp.
8. S. N. Borisov, M. G. Voronkov, and E. Lukevics, *Elementoorganic Compounds of Silicon* Elementoorganic Compounds [in Russian], Khimiya, Leningrad (1966), 541 pp.
9. E. Ya. Lukevits and M. G. Voronkov, *Organic Insertion Reactions of Group IV Elements*, Consultants Bureau, N. Y. (1966), 413 pp.
10, S. N. Borisov, M. G. Voronkov, and E. Ya. Lukevics, *Organosilicon Derivatives of Phosphorus and Sulfur* [in Russian], Khimiya, Leningrad (1968), 292 pp.
11. S. N. Borisov, M. G. Voronkov, and E. Ya. Lukevits, Organosilicon Heteropolymers and Heterocompounds, N. Y., Plenum Press, 1970, 543 pp.
12. V. Egerts, Y. Stradinš, and M. Shimanska, Analysis of 5-Nitrofuran Derivatives, London, Ann Arbor Science Publ. (1970), 167 pp.
13. A. Ya. Fogel, *Protection of Inventions in the Field of Chemistry* [in Russian], Zinatne, Riga (1970), 360 pp.
14. S. N. Borisov, M. G. Voronkov, and E. Ya. Lukevits, *Organosilicon Derivatives of Phosphorus and Sulfur*, Plenum Press, N. Y., London (1971), 333 pp.
15. S. A. Hiller and M. V. Shimanska (editors), *Heterogeneous Catalysis in the Production and Transformations of Heterocyclic Compounds* [in Russian], Zinatne, Riga (1971), 259 pp.
16. E. Ya. Gren, *Regulatory Mechanisms of Replication of RNA-Containing Bacteriophages* [in Russian], Zinatne, Riga (1974), 231pp.
17. J. F. Freimanis, *Chemistry of Enamino Ketones, Enamino Imines, and Enamino Thiones* [in Russian], Zinatne, Riga (1974), 274 pp.
18. S. G. Mairanovskii, J. P. Stradins, and V. D. Bezuglyi, *Polarography in Organic Chemistry* [in Russian], Khimiya, Leningrad (1975), 352 pp.
19. M. G. Voronkov, G. I. Zelchan, and E. Ya. Lukevitz, *Silizium und Leben: Biochemie,Toxikologie und Pharmakologie der Verbindungen des Siliziums* [in German], Akad. Verlag, Berlin (1975), 370 pp.
20. *Catalytic Synthesis and Transformations of Heterocyclic Compounds: Heterogeneous Catalysis* [in Russian], Zinatne, Riga (1976), 247 pp.
21. O. J. Neiland, J. P. Stradin, E. A. Silinsh, D. L. Balode, S. P. Valtere, V. P. Kadysh, S. V. Kalnin', V. E. Kampar, I. B. Mazheika, L. F. Taure, *Structure and Tautomeric Transformations of β-Dicarbonyl Compounds* [in Russian], Zinatne, Riga (1977), 448 pp.
22. J. P. Stradin and S. G. Mairanovskii (editors), *Polarography. Problems and Perspectives* [in Russian], Zinatne, Riga (1977), 412 pp.

23. A. K. Belousova, N. I. Blokhin, V. I. Borisov, G. F. Gauze, S. A. Giller *Chemotherapy of Malignant Tumors* [in Russian], Meditsina, Moscow (1977), 318 pp.
24. M. G. Voronkov, G. I. Zelchan, and E. J. Lukevics, *Silicon and Life* [in Russian], Zinatne, Riga (1978), 562 pp.
25. E. Lukevics (editor), *Advances in the Chemistry of Furan* [in Russian], Zinatne, Riga (1978), 291 pp.
26. J. Freimanis, *Progress and Some Prospects in Charge-Transfer-Complex Chemistry*, 1978, Wroclaw Technical Univ., Wroclaw, 1978, 79 pp.
27. G. I. Chipens, L. K. Polevaya, N. I. Veretennikova, and A. Yu. Krikis, *Structure and Functions of Low-Molecular Peptides* [in Russian], Zinatne, Riga (1980), 327 pp.
28. R. Kh. Freidlina and A. Skorova (editors), *Organic Sulfur Chemistry*, Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, Frankfurt (1981), 230 pp.
29. A. A. Anderson, *Gas Chromatography of Amino Compounds* [in Russian], Zinatne, Riga (1982), 369 pp.
30. A. A. Zidermane, *Fluoropyrimidines in the Chemotherapy of Malignant Tumors* [in Russian], Zinatne, Riga (1982), 174 pp.
31. G. V. Nikiforovich, S. G. Galaktionov, and G. I. Chipens, *Conformations of Peptide Bioregulators* [in Russian], Meditsina, Moscow (1983), 190 pp.
32. A. B. Rozenblit and V. E. Golender, *Logico-Combinatorial Methods in the Design of Drugs* [in Russian], Zinatne, Riga (1983), 338 pp.
33. V. E. Golender and A. B. Rozenblit, *Logical and Combinatorial Algorithms for Drugs,* Research Studies Press Ltd., Letchworth; John Wiley Sons Inc., N. Y., etc. (1983), 289 pp.
34. A. A. Anderson, *Liquid Chromatography of Amino Compounds* [in Russian], Zinatne, Riga (1984), 291 pp.
35. V. E. Klusa, *Peptides – Regulators of Brain Functions* [in Russian], Zinatne, Riga (1984), 179 pp.
36. K. D. Pletsityi and M. Yu. Lisak, *Vitamin A and Synthetic Retinoids in Immunology and Oncology* [in Russian], Zinatne, Riga (1984), 126 pp.
37. E. Lukevics and Z. Zelmene, *Biological Activity of Compounds of Silicon. Literature Index* 1976-1982, Riga (1984) 301 pp.
38. J. F. Freimanis, *Organic Compounds with Intramolecular Charge Transfer* [in Russian], Zinatne, Riga (1985), 185 pp.
39. E. Lukevics and A. E. Zablotskaya, *Silyl Method of Synthesis of Nucleosides* [in Russian], Zinatne, Riga (1985), 438 pp.
40. M. V. Shimanskaya, Zh. G. Yuskovets, V. V. Stonkus, V. A. Slavinskaya, D. R. Kreile, and A. A. Avots, *Contact Reactions of Furan Compounds* [in Russian], Zinatne, Riga (1985), 301 pp.
41. E. Lukevics (editor), *Organosilicon Derivatives of Amino Alcohols. Physicochemical Investigations* [in Russian] (1987), 231 pp.
42. G. I. Chipens, V. A. Slavinskaya, A. K. Strautinya, D. E, Sile, D. R. Kreile, and O. Yu. Krikis, *Modified Amino Acids and Peptides Based on them* [in Russian], Zinatne, Riga (1987), 278 pp.
43. V. D. Shatz and O. V. Sakhartova, *High-Performance Liquid Chromatography. Fundamental Theories. Methodology. Application in Drug Chemistry* [in Russian], Zinatne, Riga (1988), 390 pp.
44. Yu. Sh. Goldberg, *Selected Chapters of Phase-Transfer Catalysis* [in Russian], (1989), 554 pp.
45. E. Lukevics, O. Pudova, and R. Sturkovich, *Molecular Structure of Organosilicon Compounds*, Ellis Horwood Ltd., Chichester (1989), 359 pp.
46. E. J. Lukevics T. K. Gar, L. M. Ignatovich, and V. F. Mironov, *Biological Activity of Germanium Compounds* [in Russian], Zinatne, Riga (1990), 191 pp.
47. M. V. Shimanska, L. Ya. Leitis, R. A. Skolmeistere, I. F. Iovel, and L. O. Golender, *Vanadium Catalysts for the Oxidation of Heterocyclic Compounds* [in Russian], Zinatne, Riga (1990), 256 pp.

48. G. I. Chipens, V. A. Slavinskaya, A. K. Strautinya, D. E, Sile, E. Kh. Korchagova, and O. M. Galkin, *Structure and Action of Inhibitors of Zinc-Containing Enzymes – Kininase II and Encephelinase* [in Russian], Zinatne, Riga (1990), 238 pp.
49. G. I. Chipens, N. I. Veretennikova, R. E. Vegner, L. E. Gnilomedova, and G. F. Rozental, *Structural Principles of the Action of Peptide and Protein Immunoregulators* [in Russian], Zinatne, Riga (1990), 326 pp.
50. V. Kluša (Ed.-in-Chief), *Central and Peripheral Peptidergic Regulation*, Institute of Organic Synthesis, Riga (1991), 159 pp.
51. *Ftorafur, An Antitumor Drug*, Riga (1979), 358 pp.
52. *Ftorafur. Proceedings of the International Symposium*, Zinatne, Riga (1985), 292 pp.
53. E. Lukevics and A. Zablocka, *Nucleoside Synthesis. Organisilicon Methods,* Ellis Horword, Chichester (1991), 496 pp.
54. E. Lukevics and L. Ignatovich, *Heterocycles on the World Market of Drugs* [in Russian], Inst. Org. Sinteza, Riga (1992), 40 pp.
55. V. B. Pukhnarevich, E. Lukevics, L. I. Kopylova, and M. G. Voronkov, *Prospects for Hydrosilylation* [in Russian], Riga (1992), 383 pp.
56. J. Freimanis, *Studies in Prostanoid Chemistry* [in Latvian], OSI, Riga, (1992), 72 pp..
57. J. Freimanis, *Organoclays and Some their Applications: a Milestone Review*, OSI, Riga (2000), 96 pp.

Some Publications on the Problems and Development of the IOS

1. S. A. Hiller, *Design of Drugs,* in: *Science and Mankind, 1968, International Year Book – Accessible and Accurate on the Essentials of World Science* [in Russian], Moscow (1968), pp. 368-383.
2. S. A. Hiller, "From the history of the establishment and development of scientific activity at the Institute of Organic Synthesis*," Izv. Akad. Nauk LatvSSR*, No. 3, 80-87 (1971).
3. *Order of Labor Red Banner Institute of Organic Synthesis, 1957-1969* [in Russian], Zinatne, Riga (1970), 159 pp.
4. *Order of Red Banner Institute of Organic Synthesis, 1957-1969* [in Russian], Zinatne, Riga (1972) 152 pp.
5. *Chronological and Systematic Index of Works: Institute of Organic Synthesis, 1957-1976* [in Russian], Zinatne, Riga (1977), 176 pp.
7. *Academy of Sciences of the Latvian SSR, Institute of Organic Synthesis. Basic and Applied Research.* [in Russian] (1980), 107 pp.
8. J. Stradins (editor), *S. A. Hiller, Life and Scientific Activity* [in Russian], Zinatne, Riga (1982), 391 pp.
9. J. Stradins (editor), *Gustavs Vanags dzīvē un darbā (Life and work of Gustavs Vanags)* [in Latvian], Zinatne, Riga (1969), 408 pp.
10. *Order of Labor Red Banner Institute of Organic Synthesis, 1957-1981,* Zinatne, Riga (1982), 238 pp.
11. J. Stradins, "History of the Creation of Ftorafur," *Experimental and Clinical Pharmacotherapy,* No. 12, 5-10 (1983).
12. *Institute of Organic Synthesis, Bibliography (Index of Literature),* published annually from 1984 to 2004.
13. *Akadēmiķis Solomons Hillers.* Biobibliogrāfija, Rīga (1967), 129 pp.
14. *Latvijas Zinātņu akadēmijas akadēmiķis Gunārs Čipēns*. Biobibliogrāfija, Rīga: Latvijas akadēmiskā bibliotēka (LAB) (1993). 195 pp.
15. *Latvijas Zinātņu akadēmijas akadēmiķis Gunārs Duburs.* Biobibliogrāfija, Rīga: LAB (1994), 218 pp.
16. *Latvijas Zinātņu akadēmijas akadēmiķis Jānis Freimanis.* Biobibliogrāfija, Rīga: LAB (1995), 200 pp.
17. *Latvijas Zinātņu akadēmijas akadēmiķis Elmārs Grēns.* Biobibliogrāfija, Rīga: LAB, 1995, 119 pp.

18. *Latvijas Zinātņu akadēmijas akadēmiķis Edmunds Lukevics.* Biobibliogrāfija, Rīga: LAB (1997), 293 pp.
19. *Latvijas Zinātņu akadēmijas akadēmiķis Edmunds Lukevics.* Biobibliogrāfija, Rīga: LAB (2001), 383 pp.
20. *Latvijas Zinātņu akadēmijas akadēmiķis profesore Vija Zaiga Kluša.* Biobibliogrāfija, Riga, LAB (2005), 231 pp.
21. *Latvijas Zinātņu akadēmijas akadēmiķis Jānis Stradiņš.* Biobibliogrāfija, Rīga: LAB (1993), 304 pp.
22. *Latvijas Zinātņu akadēmijas akadēmiķis Jānis Stradiņš*. Biobibliogrāfija, II, Rīga: LAB (2004) 464 pp.
23. *Order of Labor Red Banner Institute of Organic Synthesis, 1957-1987, Zinatne, Riga (*1987), 408 pp.
24. J. Stradyn and M. Shimanskaya, "Academy of Sciences of the Latvian SSR and the formation of the Chemical Scientific-Production Complex in Olaine"*, Izv. Akad. Nauk LatvSSR,* No. 11, 36-44 (1988).
25. Ya. Stradinsh, "Gustavs Vanags and the development of organic chemistry in Latvia," *Khim. Geterotsikl. Soedin.,* 711-717 (1992).
26. Ya. P. Stradyn', "New name reactions in the chemistry of heterocyclic compounds," *Khim. Geterotsikl. Soedin.,* 1412-1424 (1981).
27. G. Čipēns and A. Skorova, "Basic results of the work of the Scientific Council at the State Committee for Science and technology "Chemistry and Technology of Sulfur Organic Compounds" in 1960-1980" [in Russian], *Izv. Akad. Nauk LatvSSR,* No. 12, 107-114 (1981).
28. "To the memory of Solomon Aronovich Hiller," *Khim. Geterotsikl. Soedin.,*3-26 (1976) (with a full bibliography of the scientific works by S. A. Hiller).
29. Ya. Stradin', A. Anderson, and L. Leite, "Life and scientific activity of Professor V. M. Shimanskaya (1922-1995)," *Khim. Geterotsikl. Soedin*., 1704-1709 (1995); *Chem. Heterocycl. Comp.*, **31**, 1484-1488 (1995).
30. Ya. Stradinš, R.Valters, and B. Ādamsone, "Margeris Līdaka (1928-2003), a Latvian chemist: in memoriam," *Proceedings of the Latvian Academy of Sciences*, Sect. B, **57**, No. 5, 197-198 (2003).
31. J. Stradins (editor), *No Grindeļa līdz mūsdienām* (*From Grindel to the Present*), [in Latvian], Riga, Nordik 1996, 360 pp. (Together with features of historical–chemical nature the activity of the Institute of Organic Synthesis in 1957-1987 is discussed in detail, founders of the institute S. A. Hiller, G. Vanags, M. B. Shimanska, prehistory and the way to the establishment of the firm Grindeks).
32. *Latvian Institute of Organic Synthesis. Administrative structure and research activities*, Riga (1994), 63 pp.
33. *Latvian Institute of Organic Synthesis. Administrative structure and research activities,* Riga (1997), 78 pp.
34. J. Stradins (editor), *Gustavs Vanags un organiskā ķīmija Latvijā (Gustavs Vanags and Organic Chemistry in Latvia)* [in Latvian], Riga, PIC (2005), 212 pp.
35. J. Stradins, "Landmarks of Biography and Research Activities of Academician S. A. Hiller", *Khim. Geterotsikl. Soedin.*, 21-30 (2005); *Chem. Heterocycl. Comp.*, **41**, 16-23 (2005).
36. J. Stradins, "By the sources of the "Journal Chemistry of Heterocyclic Compounds", *Khim. Geterotsikl. Soedin.*, 15-20 (2005); *Chem. Heterocycl. Comp.*, **41**, 11-15 (2005).