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ANNIVERSARIES AND DATES

MARGERIS JUR'EVICH LIDAKS (on the occasion of his 70th birthday)

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On May 14, 1998, Professor Margeris Jur'evich Lidaks celebrated his 70th birthday and 50 years of scientific and teaching activity. M. J. Lidaks was born in Latvia, in the Bauska region, into a teacher's family. In 1946, he graduated from Riga Gymnasium I and was admitted to the chemistry department of Latvian State University. Even as a student, he worked at the Institute of Forestry Problems of the Latvian Academy of Sciences as a senior laboratory assistant (1949-1952). After finishing in his specialty of industrial engineer for the pharmaceutical industry, he worked from 1952 to 1958 at the Riga Pharmaceutical Chemical Plant as a senior chemist and then as laboratory director. At this time, he was studying in detail the technology of fine organic synthesis, and the accumulated experience was useful to him in designing new medicinal drugs.

From 1958 to the present time, M. J. Lidaks has worked at the Institute of Organic Synthesis as laboratory director. In 1964, he defended his Candidacy dissertation in the specialty of organic chemistry; in 1974, he defended his doctoral dissertation in the specialty of the chemistry of natural and physiologically active compounds. In 1991, he was awarded the degree of Dr. habil. chem.; in 1994, he was awarded the academic title of Professor; from 1978 to 1990, he has been a Corresponding Member and since 1990 a Full Member of the Academy of Sciences of Latvia.

The scientific work of M. J. Lidaks in the area of synthesis of new anticancer and antiviral compounds has been mainly directed toward investigation of the chemistry of aziridines and derivatives of quinoline, and also the possibilities for synthesis of pyrimidyl-1-, purinyl-9-α-amino acids and peptides based on them and derivatives of nucleosides and their analogs.

The earliest research of M. J. Lidaks was devoted to the study of the chemistry of ethyleneimine, which when reacted with acetaldehyde, propionic aldehyde, butyric aldehyde, and isobutyric aldehyde and ketones forms α-aziridine alkanols (N,O-hemiacetals of ethyleneimine) rather than 2-substituted oxazolidines (as was claimed in the literature). He demonstrated the uselessness of literature data on formation of derivatives of arylbis(ethyleneimino)methane when ethyleneimine is reacted with aromatic aldehydes. He established that in these reactions, N-(N^1-arylidene-β-aminoethyl)ethyleneimines are formed. He connected the unusual reactivity of ethyleneimine with the structural features of the three-membered ring: the two sp^3-hybrid orbitals of the carbon atom cannot form a $<90^\circ$ angle, so the bonds bend ("banana bonds" are formed). Under conditions when

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steric factors prevent bonding of two aziridine groups with the same carbon atom, opening of the ethyleneimine ring is more favorable. He synthesized a large number of derivatives of ethyleneimides containing radicals of substituted furancarboxylic acids, and studied their isomerization to oxazoline derivatives. The isomerization rate of ethyleneimides was explained by considering the effect of electron-donor and electron-acceptor groups. He focused special attention on the chemistry of N-aminoethyleneimine. In this series, the conjugation effect was even more pronounced. Bending of *endo* bonds facilitate their overlap with π orbitals of substituents or the unshared pair of unpaired electrons of the nitrogen atom of the amino group. In the N-aminoethyleneimine molecule, the pyramidal structure of the nitrogen is relatively stable, evidence for which comes from the slow inversion of the heteroatom of the ring. In slow inversion of the nitrogen of the N-aminoethyleneimine, no delocalization is observed for the unshared pair of the unpaired electrons of the heteroatom or formation of a planar conformation of the transition state, since this hinders the shift of electrons from the nitrogen of the amino group to the ethyleneimine ring and consequently it exerts only a small effect on the basicity of N-aminoethyleneimine.

Under the direction of M. J. Lidaks, the condensation of N-aminoethyleneimine with aliphatic aldehydes was comprehensively studied. It was established that in this case, opening of the ethyleneimine ring and formation of mixed azines is observed. By using the Venker method, it was possible to obtain a whole series of hydrazones of aldehydes with N-aminoethyleneimine. Investigations of the inversion of aziridines were successfully completed. As was established by a group of coworkers at the Latvian Institute of Organic Synthesis and the Institute of Chemical Physics of Russia, slow inversion of the nitrogen atom in aminoaziridine and related compounds at a temperature of about 20°C or higher is an unexpected phenomenon for the stereochemistry of compounds of trivalent nitrogen. The results of these investigations were registered as an invention in 1972 (S. A. Giller, R. G. Kostyanovskii, A. V. Eremeev, V. A. Pestunovich, M. J. Lidaks, O. A. Panyshin, Z. E. Samoilova, and I. I. Chervin).

The condensation of C-aminomethylethyleneimine with aldehydes and ketones was studied in detail. Novel heterocyclic compounds were obtained: derivatives of 2-substituted 1,3-diazobicyclo[3.1.0]hexane (a condensed system of two heterocycles: ethyleneimine and imidazolidine). These compounds have an exo-R^1 conformation. In hydrochloric acid medium, degradation of the ring occurs with formation of the original ketone and 3-chloro-1,2-diaminopropane (the reaction is reversible). In alkaline medium, the corresponding derivative of 2-substituted 1,3-diazobicyclo[3.1.0]hexane is again formed.

In the aziridine series, an effective drug for treatment of erythremia was synthesized: imifos, containing an aziridine and a thiazolidine group.

Under the direction of M. J. Lidaks, unsaturated β-ethyleneimino alcohols and high-molecular compounds containing ethyleneimine rings were synthesized. A number of compounds displayed anti-tumor activity.

Novel alkylating anti-tumor drugs were developed, bis-2-chloroethylhydrazones of aldehydes of the nitrofuran series, and convenient preparative methods for obtaining them were proposed (the anti-tumor drug nifuron belongs to this series of compounds).

The synthesis of β-(5-nitro-2-furyl)vinylbutadienylquinolines was studied comprehensively and their chemical and biological properties were investigated. It was established that these compounds have antibacterial activity (the drug Quinifuryl belongs to this series of compounds).

With the goal of designing new anti-cancer and antiviral drugs, under the direction of M. J. Lidaks starting in 1964 extensive research has been done on synthesis and study of the properties of components of nucleic acids and their analogs. Early work in this direction involved synthesis of aliphatic and acyclic analogs of nucleosides of 5-fluorouracil. Jointly with Academician S. A. Giller and R. A. Zhuk, research was continued on development of a new direction in nucleoside chemistry: the chemistry of aliphatic and acyclic analogs of nucleosides. Novel aliphatic analogs of nucleosides were synthesized in which alkoxy-, alkyl-, hydroxyalkoxyalkyl-, or dihydroxyalkyl groups and also tetrahydrofuryl and tetrahydropyranyl rings were added to the purine or pyrimidine ring instead of hydrocarbon groups; derivatives of amino alcohols were synthesized, 9-[β-hydroxyalkyl)amino]ethylpurine, the corresponding analogs of nucleosides of amino hydrocarbons. With the goal of obtaining aliphatic analogs of nucleosides, regiospecific methods of $N_{(1)}$ alkylation were developed in the series of pyrimidine derivatives and $N_{(9)}$ alkylation in the series of pyrine derivatives. Phase transfer catalysis was used to solve this problem. Methods were devised for regioselective synthesis of $N_{(9)}$-, $N_{(7)}$-, and $N_{(3)}$-substituted purine nucleosides by varying the structure of the catalysts and the reaction conditions. In this series, an original low-toxicity (7-10 times less toxic than 5-fluorouracil) anti-tumor drug was developed: ftorafur, a latent form of fluorouracil (1-(tetrahydro-2-furyl)-5-fluorouracil), for treatment of gastrointestinal cancer, breast cancer, and other types of tumors (S. A. Giller, R. A. Zhuk, and M. J. Lidaks). Pharmacokinetic studies suggest that breaking of the pseudoglucoside C–N bond occurs in the ftorafur molecule when treated

with hepatic microsomal oxidase and the active component 5-fluorouracil is released. This is responsible for the sustained action of 5-fluorouracil on affected tissues. The Grindex company is producing and exporting ftorafur to Japan and Russia.

High anti-tumor activity is characteristic of the fluorouracil derivative 1-(2,5-di-O-acetyl-β-D-glucafuranosyl-6,3-lactone)-5-fluorouracil, whose toxicity is less than for fluorouracil, and whose therapeutic index is significantly higher. A water-soluble form of this compound has been developed.

The (9-hydroxyalkoxy)guanine series has high antiviral activity. Goal-directed synthesis of nucleosides which can be utilized for transformation of nucleosides used in medicine was also pursued, with variation of the hydrocarbon components (for example, N-β-D-glucofuranourosides of pyrimidine and purine).

With the objective of obtaining new models for biopolymers (hybrids of nucleic acids and peptides), synthesis methods were developed for analogs of nucleotides in which the phosphorus groups are replaced by amino acid residues or by peptide fragments. Oligocondensation and polycondensation of these compounds was also investigated. Back in the period from 1965 to 1975, they demonstrated the reaction of polymers containing pyridinyl- and purinylamino acid residues with polynucleotides and nucleic acids; in contrast to natural biopolymers, these are more stable toward nucleases and carboxypeptidases. Twenty years later, in 1994, extensive studies of such polymers began abroad with the objective of designing high-activity antisense oligonucleotides which are stable relative to enzyme hydrolysis.

With the objective of obtaining peptides containing residues of pyrimidyl- and purinylamino acids, under the direction of M. J. Lidaks a series of studies were carried out on synthesis of uracilyl-, thyminyl-, adeninyl-, and guaninylamino acids and their derivatives. Thus, methods were developed for synthesis of enantiomers of ω-(9-purinyl)-α-amino acids and peptides containing residues of optically active purinylamino acids. Considerable attention was focused on synthesis of peptides containing residues of the major amino acids.

Nucleoside bases were also modified by aminoalkyl groups. N^1-Aminoalkyluracils were obtained by reaction of polyethylenediamines with uracilyl-1-alkyl halides with formation of the corresponding uracilylalkylpolymethylenediamines. N,N^1-Bis(1-uracilyl)propionylpolymethylenediamines were obtained analogously based on uracilyl-1-propionate reacted with polymethylenediamines. As a result of cyclization of 5-substituted halo derivatives of uracilylalkylamines, the novel 5,7-dioxyimidazo[1,2-*e*]pyrimidines and pyrimido[1,6]pyrimidines were obtained.

Under the direction of M. J. Lidaks, investigations were carried out on modification of nucleosides, including synthesis of 5-, 8-, and 2,8-disubstituted purine nucleosides and their acyclic analogs, and their properties were studied. Methods were developed for modification of the 8 position in purine nucleosides and their bases by biogenic polyamines. Some of the nucleosides obtained and their associates with amino acids and amino alcohols are effective interferon inductors and immunomodulators. They continued to study the biological properties of 8-substituted purine nucleosides, derivatives of purine nucleoside 8-acetic and 8-propionic acids.

The scientific activity of M. J. Lidaks is a shining example of successful combination of basic research in chemistry with development and design of medicinal drugs. In addition to original drugs (ftorafur and imifos), under the direction of M. J. Lidaks the technology for obtaining medicinal drugs has been developed: thio-TEPA, cyclophosphane, acyclovir, Tubazid, thioguanine, cytosine arabinoside (tsitozan [name not verified — Translator]); a commercial method has been proposed for obtaining ethyleneimine.

M. J. Lidaks is the author of 400 publications, 90 inventor's certificates and patents, and 5 monographs (including: N. G. Blokhina, M. J. Lidaks, B. T. Garibdzhanyan, and A. B. Syrkin, The Anti-Tumor Drug Ftorafur [in Russian], Meditsina, Moscow (1979), 179 pp.).

M. J. Lidaks was deputy director for scientific research at the Latvian Institute of Organic Synthesis (1964-1971). Since he is a considerate person and an excellent psychologist, he was able to quite successfully work together with the director of the Institute, his teacher Academician S. A. Giller. The Institute flourished during the years in which they worked together. Academician S. A. Giller highly valued the extensive knowledge of M. J. Lidaks and his brilliant ideas, and deeply respected him as a human being. M. J. Lidaks was the chairman of the chemical and biological sciences division of the Latvian Academy of Sciences, a member of the editorial board of the international journal *Khimiya Geterotsiklicheskikh Soedinenii* [Chemistry of Heterocyclic Compounds] (since 1969), editor-in-chief of the journal *Éksperimental'naya i Klinicheskaya Farmakoterapiya* [Experimental and Clinical Pharmacotherapy] (1976-1992), a member of the editorial board of the journal *Izvestiya Akademii Nauk Latvii. Seriya B* [Bulletin of the Academy of Sciences of Latvia, Series B] (since 1996), a member of the editorial board of the journal *Voprosy Virusologii* [Topics in Virology] (since 1996). M. J. Lidaks is a member of the Expert Council of the Latvian Institute of Organic Synthesis.

The results of his basic research in the field of chemistry and development of new medicinal drugs have been highly esteemed: M. J. Lidaks has been awarded the title of Merit Scientist (1976), the State Prize (1965), an Honorary Certificate from the Cabinet of Ministers of the Latvian Republic (1995), the G. Vanags Prize for Chemistry (1990), the D. H. Grindel Medal (1995), and an Honorary Certificate from the Latvian Academy of Sciences (1998).

M. J. Lidaks has made an inestimable contribution to the professional training of young scientists. Under his direction, 10 doctoral dissertations have been defended; he is a consultant for 2 dissertations in competition for the academic degree of Dr. habil. chem. Students of M. J. Lidaks include Academician I. Ya. Kalvin'sh, Doctor R. A. Zhuk, Yu. Maurin'sh, Ya. Yu. Polis, É. S. Lavrinovich, and others.

M. J. Lidaks is an exceptionally friendly and cordial person. He is turned to for expert advice on drug production chemistry and technology and on medicine, and always provides very exhaustive answers to interesting questions.

Dear Margeris Jur'evich! On the occasion of your birthday, we sincerely thank you for your achievements in organic chemistry, for the medicinal drugs you have designed, for your organizational efforts in science, and for your training of young specialists! We especially recognize you for your expert guidance in chemistry and medicine. We wish you good health and many new brilliant ideas and great achievements in science! May you be destined to see the flowering of Latvia and its science!

The editorial board of the journal Khimiya Geterotsiklicheskikh Soedinenii [Chemistry of Heterocyclic Compounds] congratulates M. J. Lidaks on his birthday, and wishes him long years of creative work and new successes for the good of science and public health.