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ANNIVERSARIES AND DATES

On the 70th Birthday of Academician

GUNARS CHIPENS

Gunars Chipens was born on November 8, 1933 in Riga, Latvia, into the family of a musician of the Latvian theater of opera and ballet. In 1953, he graduated from the Chemistry Department of Riga Industrial Polytechnical School. Even in those years, Gunars was drawn to science; and in addition to studying at the technical school, he was a laboratory assistant at the Institute of Microbiology (Academy of Sciences of the Latvian SSR). From 1953 through 1958, he studied in the Chemistry Department of Latvian State University and was a student of the well-known Latvian biochemist, Professor Voldemar Grinshtein. During those years in the student scientific community, he was selflessly involved with synthesis of potential antitubercular drugs. From 1958 to the present, G. Chipens has worked at the Latvian Institute of Organic Synthesis.

From 1958 through 1963, G. Chipens was partly involved with the chemistry of heterocyclic compounds: the synthesis and study of the properties of acylaminoguanidines and aminotriazoles. He developed novel synthesis methods for 1-acylaminoguanidines containing aliphatic substituents in the acyl group and substituted phenyl-, 2-furyl-, and 4-pyridyl groups. He showed that solvent-free acylation of aminoguanidine hydrochloride by carboxylic acid chlorides produces the best yields. The reaction is universal for obtaining acylaminoguanidines of the aliphatic, aromatic, and heterocyclic series.

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In order to obtain some N-alkyl- and aryl-substituted 1-acylaminoguanidines, he developed a novel method for guanidation of carboxylic acid hydrazides by substituted cyanamides, and for synthesis of 1-acylamido-3-guanidines he developed a reaction between acid hydrazides and 1-alkyl-1-nitroso-3-guanidine. By reduction of 1-acylamido-3-nitroguanidines by zinc and acetic acid, he obtained 1-acylamido-3-aminoguanidines and a number of their hydrazides for the first time. Upon reduction of 1-benzyl-3-nitroguanidine and also upon hydrazinolysis of benzylguanidine, cyclization occurred with formation of 5-amino-3-phenyl-1,2,4-triazole. He studied in detail the physical and chemical properties of 1-acylaminoguanidines, and for the latter the most typical reaction is their intramolecular condensation to form a 1,2,4-triazole system.

G. Chipens recognized thermal cyclization and cyclization in aqueous alkaline solutions as the best methods for synthesis of 1,2,4-triazoles and 1-acylaminoguanidines. In the case of cyclization in aqueous alkaline solutions, upon cyclization only 5-substituted 1,4,5-triazoles are formed; in acid medium, N-substituted 5-amino-1,2,4-triazole is also formed. 5-Amino-substituted 1,2,4-triazole does not form azomethine derivatives upon reaction with aromatic aldehydes. G. Chipens showed that aminotriazoles form two series of monoacyl derivatives having an acyl radical on the ring nitrogen atom (N-acyl derivatives) or on the non-ring amine nitrogen (acylamino derivatives). N-Acyl derivatives of aminotriazoles have an amino structure. Acylamino derivatives of aminotriazoles can exist in acylamide or acylimide form. Depending on the nature of the substituents on the triazole ring, upon heating of acyl compounds the acyl radical migrates from the ring nitrogen to the nonring (amine) nitrogen or in the reverse direction.

G. Chipens synthesized compounds for the first time that contained a 5-imino-1,2,4-triazoline system. He showed that formation of salts of 1,4-dialkyl-5-imino-1,2,4-triazolines in solution is connected with their conversion to the aminotriazole form, and conversely in the crystalline state the aminotriazoline structure is retained, with the center for salt formation on the imine (ring) nitrogen. Acylation of aminotriazoles by carboxylic acid anhydrides leads to synthesis of diacyl derivatives of aminotriazoles. Reduction of N-acyl derivatives of aminotriazoles by lithium aluminum hydride, as for other N-acyl derivatives of N-acylated heterocyclic compounds of an aromatic nature, leads to reductive decomposition of the latter with formation of alcohols and the corresponding heterocyclic amines. Alkylation of alkaline solutions of acylamido derivatives in some cases leads to formation of iminotriazoline derivatives.

He determined the antitubercular activity of the synthesized derivatives of amino- and diaminoguanidine and 1,2,4-triazole. The greatest *in vitro* tuberculostatic activity was exhibited by hydrazones of 1-acylamido-3-aminoguanidines and azomethine derivatives of aminotriazoles. Unfortunately, at that time the incidence of tuberculosis was not considered to be significant, and the young scientist's research did not progress to development of effective medicinal drugs. However, such drugs are important today, with tuberculosis quite widespread again around the world, including antibiotic-resistant forms of this insidious disease.

In 1963, G. Chipens defended his candidacy dissertation in Riga on the subject "Studies of the aminotriazole and acylaminoguanidine series."

Considering the innovative thinking and organizational ability of Gunars Chipens, in 1964 Academician S. A. Hiller (founder and director of the Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR) created the Amino Acid and Peptide Laboratory under the direction of G. Chipens, suggesting to the young scientist that he follow a new direction: peptide chemistry.

Within a short time, he had mastered a new and complicated field, the synthesis of peptide and protein bioregulators, and was training scientists. 25 dissertations were defended in competition for the academic degree of Candidate of Chemical Sciences under the direction of G. Chipens, and he was an advisor for a number of doctoral dissertations. In the heart of an institute mainly involved with classical organic synthesis, he created a center for bioorganic chemistry (for synthesis and study of the properties of peptide biologically active substances) that also became famous in the scientific world.

A major direction for the scientific work of Gunars Chipens became the investigation of the structural and functional organization and mechanism of action of peptide and protein bioregulators. In analyzing the "structure – function" relations for many peptides, he arrived at the conclusion that there were common structural fragments of a certain amino acid sequence mainly determining the biological activity of peptides (extending the area of application of "signature theory"). It was only 10-15 years after G. Chipens' research that the general concepts of active centers in peptide and protein molecules (pharmacophores) were developed, which to this day are widely used in designing biologically active peptides.

In 1973 in Riga, G. Chipens defended his dissertation in competition for the academic degree of Doctor of Chemical Sciences on the subject "Synthesis and study of the structural and functional organization of some peptide hormones and kinins."

In 1975, after the death of the founder of the Institute of Organic Synthesis, Academician S. A. Hiller (and on the recommendation of Solomon Aronovich, who himself was already seriously ill), G. Chipens filled the post of Director of this institute for a term of almost 7 years (1975-1982). As director of the institute, he was democratic and listened to the views of his colleagues. After he was relieved of the responsibilities of director, G. Chipens remained at the institute as head of the Peptide and Protein Bioregulator Department. Dozens of researchers worked under his guidance: chemists, biologists, conformational computation experts. G. Chipens cooperated closely with scientists from other scientific centers, especially with the M. M. Shemyakin Institute of Bioorganic Chemistry (Academy of Sciences of the USSR) in Moscow, with Academician Yu. A. Ovchinnikov, Academician V. T. Ivanov, and others.

Despite how busy he was with his scientific organizational work, Chipens continued basic research, over the course of which he demonstrated the major role played by cyclopeptides in synthesis of biologically active peptide drugs. Under his guidance, targeted synthesis of cyclic analogs of biologically active linear peptides was accomplished for the first time; he advanced original ideas about possibilities for mutations of nucleotides and amino acid sequences in the genetic system of cells, about the role of the signal molecule of the membrane receptor protein, etc. G. Chipens was always generating bold new ideas, many of which were echoed and recognized in expert circles.

In connection with the reduction in funding for science in the last decade, G. Chipens turned to theoretical approaches in the field of molecular biology and genetics. He postulated the existence of a previously unknown second genetic code, and he attempted to investigate the problem of how genes and introns arise.

G. Chipens in due course did considerable teaching, lectured on the chemistry and biology of peptides at Riga Polytechnical Institute and Latvian State University, and also at the University of Brussels. In 1977, he was conferred with the title of professor, and in 1982 he was elected as an Academician of the Academy of Sciences of the Latvian SSR (he became a Corresponding Member of the Academy in 1975).

Along with investigation of the structural and functional organization of peptides, G. Chipens has been involved with development of technology for peptide drug production and its commercialization. The experimental plant of the Institute of Organic Synthesis (now the *GRINDEX* company) manufactured angiotensin, pentagastrin, tyroliberin, deaminooxytocin, oxytocin (the *GRINDEX* company also produces the latter drug today). He developed a novel technology for synthesis of the antihypertensive drug enalapril and some modified amino acids.

G. Chipens was coinventor on 63 inventor's certificates and several patents for synthesis and investigation of novel drugs.

G. Chipens is the author of 7 monographs, more than 500 scientific papers, and 330 abstracts of scientific reports. In the period 1986-1990, according to Garfield's Science Citation Index, G. Chipens was No. 4 in citations among the 700 most widely cited Latvian scientists.

G. I. Chipens was a member of the Presidium of the Academy of Sciences of the Latvian SSR, and was president of the All-Union Science Council on "Chemistry and Technology of Organosulfur Compounds" of the State Committee on Science and Technology of the USSR. He has been a member of 5 science councils and

commissions of the Academy of Sciences of the USSR, and the supervisor of the comprehensive program on Peptide and Protein Bioregulators. For some time G. Chipens was also a member of the Editorial Board of the journal Khimiya Geterotsiklicheskikh Soedinenii [Chemistry of Heterocyclic Compounds] and participated in the work of the journal.

For his scientific achievements, G. Chipens has been awarded State Prizes of the Latvian SSR (1976) and the USSR (1981), the Gustav Vanag Prize (1992), and also medals dedicated to the memories of outstanding scientists, in particular the P. K. Anokhin medal (1986), the S. A. Hiller medal (1990), the D. H. Grindel' medal (2001), and others. In 2002, G. Chipens was honored with the title Scientist Emeritus.

We wish our colleague and friend good health, new and brilliant ideas, and a chance to bring them to life.

J. Stradins
President of Latvian Academy of Sciences.