

FIFTIETH ANNIVERSARY OF THE DEPARTMENT OF ORGANIC CHEMISTRY, TECHNICAL UNIVERSITY, BUDAPEST

The first department of organic chemistry to be established in this country was in 1912 at the Technical University, Budapest. For a long time, this was the only department of organic chemistry at Hungarian Universities.

The first professor and head of the department for more than four decades (from 1913 to 1956) was Géza Zemplén, Kossuth-prize winner, member of the Hungarian Academy of Sciences. His whole life and activity completely merged with the actual history of his department at the University.

Professor Zemplén played a pioneer role in the evolution of organic chemistry in Hungary. One of his outstanding merits is the commencement of up-to-date studies and the teaching of organic chemistry in Hungary, in the second decade of this century. However, also prior to him, and among his contemporaries some prominent and excellent scientists dealt in Hungary with chemical sciences in general, such as Pál Kitaibel, Károly Than and Vince Wartha, whose names and activities achieved an international reputation.

In the development of strictly taken organic chemistry, Géza Zemplén is undoubtedly the centre point. His scientific activity and indefatigable capability for work over a period of half a century created the theoretical level and experimentative aptitude without which the Hungarian pharmaceutical industry would not attain its present excellent position.

Géza Zemplén was born in 1883 in Trencsén. He finished his university studies at the Budapest University as a member of the Eötvös College. He obtained his diploma as teacher of secondary school and also the Ph. D. in 1904. Later, he served as assistant and associate professor, respectively, at the High School (College) for Mining and Forestry at Selmecbánya.

The 3 years (1909—1912) spent in Germany, at the Berlin University, at the institute of the Nobel-prize winner Emil Fischer had the greatest effect on his scientific development. Here at first Zemplén dealt with the chemistry of enzymes in the department of Abderhalden, later joining the team of direct co-workers of Emil Fischer himself. The personality of this eminent scientist had a decisive influence on the scientific development of Zemplén.

During his activity in Berlin, Zemplén was very successful in achieving the synthesis of simple amino acids, and later, in preparing acetobromo-cellobiose. On the request of Abderhalden, he undertook the preparation of some chapters on carbohydrates and amino acids for the "Biochemisches Handlexikon". In subsequent years, Zemplén remained a permanent co-worker of both this "Handlexikon" and the vast collective work "Handbuch der biologischen Arbeitsmethoden", as well.

On returning to Hungary in 1912, he habilitated at the Budapest University, and soon after he was appointed professor of the then established department of organic chemistry at the Budapest Technical University. Even after decades, he often mentioned the bitter disappointment which he encountered on first supervising his newly created department, consisting of four almost empty rooms, without any equipments for research and education. (The Hungarian governments of that time did not give him larger grants neither for starting his institute nor for supporting its future development.) However, the extraordinary strength of will and ambition which were characteristic features of the personality of Géza Zemplén, soon found possibilities for supplying his institute with an up-to-date equipment and to start his researches there. All this was greatly facilitated by the grant obtained from the Technical University, mainly through the person of professor Lajos Ilosvay.

Soon after the organization of his department, Géza Zemplén's first independent communications were published in the field of research on enzymes and carbohydrates. The dynamic rise of these researches was however broken by World War I. During these years the attention of Zemplén was attracted by several industrial problems. The close, and even today existing connections between his department and the Chinoïn Pharmaceutical Factory established at the time, dated from this period. The appreciable financial funds obtained by investigations carried out at the request of the industry were to a considerable extent, for several decades spent by professor Zemplén on the development of equipment and on the library of his department.

After World War I, the activity of Zemplén was again centred on the field of carbohydrates. At the beginning of the second decade of this century, he studied the structure and synthesis of salicine and amygdaline glycosides.

A new epoch of his scientific activity begun with the investigations during the course of which he observed that sugar acetates were completely deacetylated even by catalytic amounts of sodium methylate in methanolic solution. Up to this time, in the chemistry of carbohydrates, acetates were deacetylated by an ethanolic solution of alkali hydroxides. However, on this treatment, sugars often suffered secondary changes. The Zemplén method of saponification, known today in world literature under this name, gained fundamental importance and also made the carrying out of extremely delicate deacetylations possible. This reaction became highly important actually

in the chemistry of di- and oligo-saccharides. Namely, in carbohydrate chemistry, the Wohl method of degradation of sugars is known since a long time. By this method, sugars poorer by one carbon atom can be prepared through the acetylated cyanohydrine of the sugar with a carbon chain poorer by one carbon atom. However, owing to the acid hydrolysis required in the last step of this procedure, the original Wohl method is restricted to the field of monosaccharides only because disaccharides become hydrolysed by acids. In contrast, under the conditions of the Zemplén saponification, in the presence of an amount of sodium methylate slightly exceeding one mole, the acetylated cyanohydrines convert directly into the sugar of shorter carbon chain, without any subsequent treatment with acid. Thus, degradation according to Wohl-Zemplén can also be applied in the case of disaccharides.

The next researches by professor Zemplén were aimed at establishing the site of linkage of reducing disaccharides. Of his achievements in this field, the identification of the structure of cellobiose, lactose and maltose are of the greatest importance. His investigations verified the structures obtained by Haworth on examining the completely methylated disaccharides. The Zemplén method is a preparative procedure where the structure of the decomposed disaccharides can be followed up from step to step, while with the Haworth method, the problem at that time which still remained unsolved was whether the structure of disaccharides does not become changed by methylation. These investigations for the first time gained international reputation for Géza Zemplén in organic chemistry all over the world.

The discovery of the so-called mercuric acetate method in the twenties made a marked advancement in the research work of the department. In essence, this method is based on the fact that compounds containing free hydroxyl groups are readily glycosylated by acetobromo sugars, and that the ratio to each other of the formed α - and β -glycosides actually depends on the quantity of mercuric acetate and solvent participating in the reaction. As a continuation of these investigations, Zemplén succeeded in splitting the ring of triacetyl levoglucosane with titanium tetrachloride, when 2,3,4-triacetyl chloroglucose, a product of excellent value for various syntheses was obtained.

The favourable combination of the mentioned experimental evidences was utilized by Zemplén for preparing a set of disaccharides, among others of rutinose, robinobiose, primverose, isoprimverose, melibiose and allolactose.

In the knowledge of these experimental results, Zemplén continued his researches into the structure and synthesis of natural glycosides already begun in the first years of this century. During these investigations, several problems unsolved since some decades were successfully elucidated. Of these, the synthesis of ruberythric acid and of phloridzin is to be particularly emphasized. In the case of ruberythric acid, difficulties were due to the fact that the sugar moiety of the glycoside was incorrectly established, while in the case of phloridzin,

whose structure was already known in the first years of this century, the poor reactivity of phloretin, its aglycone, gave rise to experimental difficulties.

The actual synthesis of phloridzin directed Zemplén in the field of flavonoids so widespread in nature. In this domain, Zemplén carried out a systematic work from the 1940s on, solving almost all unsettled problems of the latest decades, and nearly completely recreated the chemistry of flavonoids. Here we mention only the results of the greatest importance: the synthesis of the flavon glycosides asebotin, sacuranin and apigenin-5-D-glucoside, while in the group of isoflavon glycosides the synthesis of genistein, ononin and prunitrin.

In the last week of December 1944 the institute suffered damage from a bomb. The rooms on the second floor were partly burnt out and partly completely destroyed. Zemplén told, as was his custom, the fascist government officials quite frankly his opinion on the planned translocation of the University to Germany. Thereon he was imprisoned in the military prison of ill-repute at Margit-körút. Zemplén was liberated from this prison just on December 24, 1944, when the ring around Budapest was closed by the liberating Soviet troops, and all the fascist employees of the prison fled.

On restoring the basement laboratory of the institute, Zemplén was able to carry out his researches only to a restricted extent. However, he did not become downhearted on seeing the destruction of his formerly flourishing department. He insisted on personally holding his lectures. He had an individual charm so attractive that even the weaker pupils attended his lectures with the utmost interest. His excellent didactic talent was proved by the number of his prominent pupils, such as Alfonz Kunz, Sándor Hoffmann, Zoltán Földi, Géza Braun, Dénes Kiss, Zoltán Csűrös, Zoltán Bruckner, Árpád Gerecs, Jenő Pacsu, Sándor Müller, Károly Tettamanti, Rezső Bognár, Loránd Farkas and László Mester, a group of scientists known not only in this country but also throughout the world.

After World War II, professor Zemplén had still ambition enough to elucidate a new domain of research, the field of sugar formazans. However, the great difficulties encountered at that time undoubtedly contributed to the decrease of his vitality. On the invitation of the Washington University, he paid a visit to the United States, but he was obliged to interrupt his work and to return to this country with the burden of an incurable severe disease. His disease made formidable progress. From 1950 on, the later professor of the department, Kossuth-prize winner Dénes Beke, at that time as associate professor took over the tasks as head of the department, till on July 24, 1956, death saved Géza Zemplén from a long and painful suffering.

The scientific activity gained for Zemplén appreciation both in this country and abroad. In 1923, he was elected corresponding member of the Hungarian Academy of Sciences, in 1927 promoted to ordinary member, and decorated in 1928 with the great golden medal of the Hungarian Academy of

Sciences. In 1931, he was honoured with the Corvin chain, and in 1948, among the first, with the golden degree of the Kossuth-prize. In addition to these, he was ordinary member of the Deutsche Akademie der Naturforscher zu Halle (Leopoldina) and corresponding member of the Schlesische Gesellschaft für Vaterländische Kultur. In 1942, the Deutsche Chemische Gesellschaft conferred on him the A. W. Hoffmann golden memorial medal.

Zemplén held a great number of lectures on the invitation of foreign universities and chemical societies. His scientific activity for over nearly five decades resulted in 213 scientific treatises, a number of technical studies, various patents and books.

After the death of professor Zemplén, the researches into the chemistry of flavonoids and isoflavonoids were continued under the guidance of Loránd Farkas at the department.

In the course of these researches, a new synthesis was evolved for the preparation of isoflavones occurring in nature. On applying this method of synthesis, daidzein, formononetin and caveubrin were prepared. Evolving a new reaction of ring isomerization, the structure-proving synthesis of tectorigenin, irigenin and caviunin, compounds known since several decades but thus far not synthesized, was carried out, and daidzin occurring in soybeans, further prunitrin the isoflavone glycoside present in a *Prunus* type were prepared (József Várady). A method was evolved for the synthetic preparation of benzal coumaranone glycosides (auron glycosides) occurring in nature (László Pallós). Besides, a new isomerization reaction was created for the preparation of a group of flavones thus far not synthesized, and of their glycosides, respectively (Ádám Major). The number of papers on the mentioned subjects from 1956 up to the present, range to over fifty.

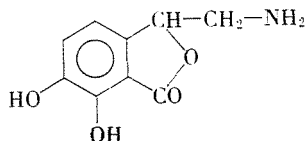
In 1951, attempts aimed at solving the problems connected with the utilization of narcotine were also placed on the working plan of the department. The leadership of this theme had been taken over by Dr. Dénes Beke, the future head of the department.

Hungary belongs, particularly in the field of poppy alkaloids, to the major alkaloid exporters of the world. Great amounts of poppy are processed by the Chemical Plant Alkaloida at Tiszavasvár. Of this raw material morphine is produced mainly. In poppies, narcotine is the compound which occurs in quantities next to those of morphine. However, owing to its unfavourable physiological properties, narcotine is unsuitable for direct use (although recently it has been recommended as a cough-relieving agent), and has been thus far treated as a useless waste.

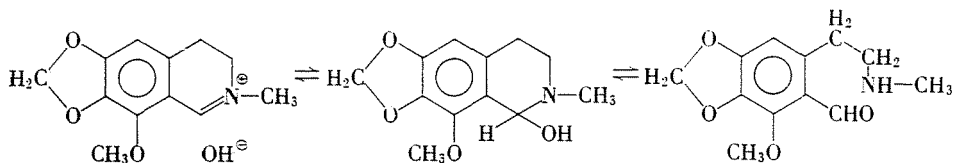
For the conversion of narcotine into valuable compounds, the only promising way appeared to be the splitting of the narcotine molecule into portions which could be directly (as cotarnine) or on further conversion, applied as drugs.

The first results (on the optimum conditions of the oxidative and reductive splitting of narcotine and of the purification of the products obtained) were reported by the department in 1953, at the Conference of Organic Chemistry at Debrecen (Dénes Beke, Kálmán Harsányi, Mrs. István Martos, Gábor Pongor and Csaba Szántay).

Starting from opianic acid, one of the products of the oxidative splitting of narcotine, the synthesis of a number of substances could be carried out. Among others, vanilline, isovanilline and protocatechic aldehyde were prepared from opianic acid. These compounds proved to be suitable for pharmaceutical use alone, on the one hand, and served as initial substances for the synthesis of valuable intermediates, on the other hand. Subjecting opianic acid to adequate conversions, a compound of an entirely new type: 1-amino-1-(6,7-dihydroxy-3-phthalyl) methane with very interesting pharmacological effects was prepared.



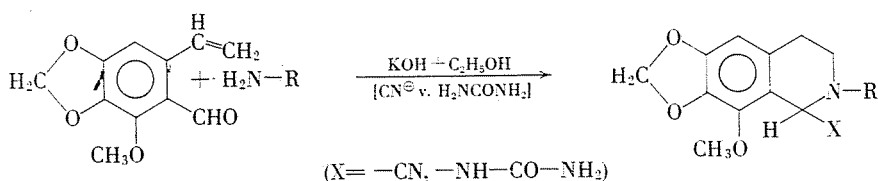
Investigations connected with cotarnine, another product of the oxidative splitting of narcotine, directed the attention of the research workers of the department to an extremely interesting problem of the greatest importance from both a theoretical and a practical aspect. Namely, cotarnine is a typical representative of heterocyclic pseudobasic aminocarbinols which offer possibilities for complicated tautomerisms and for manifold convertabilities. Earlier, the conditions of tautomerism of cotarnine were characterized by the formulae:



During the investigations of cotarnine, it was found that the major part of the present data of literature must be supervised in respect to the reliability of the experiments and to the validity of conclusions theoretically deduced from the experimental data. Subsequent researches were then extended, in addition to cotarnine, also to two further natural alkaloids: berberin and sanguinarin, together with a set of various synthetic model compounds, mainly analogues of cotarnine. By this extension, it was attempted to draw conclusions

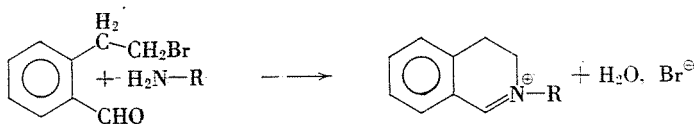
of a more general validity and to find the correct interpretation of the chemical behaviour of this group of compounds.

On preparing analogues of cotarnine, the first direction to be followed was to produce the derivatives substituted on the nitrogen atom, instead of the methyl group, by various alkyl, aralkyl and aryl groups, just from cotarnone which can be obtained by the exhaustive methylation and thermic decomposition of cotarnine itself. It was found that cotarnone, on boiling with primary amines in an alkaline ethanolic solution, reacts under formation of 1,2,3,4-tetrahydro-isoquinoline derivatives substituted in position 1 by an ethoxy group or, in the presence of alkyl cyanide and urea, of derivatives substituted by a cyano and ureido group, respectively:



In this way, it was possible to carry out a new ring closure reaction of isoquinolines (Dénes Beke, Kálmán Harsányi, Dezső Korbonits, Pál Kolonits and Mrs. Elek Markovits).

However, other routes were required for the preparation of further analogues. Thus, in order to obtain derivatives not substituted in the ring, the following route proved to be successful:

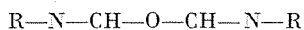


while analogues carrying an *o*- or *p*-nitrophenyl substituent on the nitrogen atom could be prepared by the oxidation of the corresponding tertiary amines by *N*-bromosuccinic imide (Dénes Beke, Marietta Beke-Bárczai and Ede Eckhart).

In the possession of the required model compounds, extensive investigations were undertaken to solve the problems of tautomerism. On elucidating problems of this type, chemical reactions can only quite rarely be used because, when a labile equilibrium exists between the various isomers, it is possible to obtain from every form such a derivative which should only form from one of the forms, in question. Namely, when the form which is desired to react with the reagent in question is actually present (even in minute concen-

trations), slowly the entire amount converts, due to the continuous recovery of the equilibrium. When, however, the reaction which is expected from only one of the possible isomers fails to occur, this may be taken as an unequivocal evidence for the absence of the isomer in question.

In the case of the bases which can be liberated from heterocyclic quaternary ammonium salts, the aminocarbinols as cyclic compounds of the aldehyde-ammonia type are capable of reacting with all reagents actively reacting with amino aldehydes as well. However, also such reactions of amino carbinols are known which are not disclosed by amino aldehydes. E.g. by dilute acids they can be reconverted into the initial quaternary ammonium salts, while by alcohols they are converted very easily into alkyl ethers. The failure of these latter reactions undoubtedly proves that the bases in question are of an aminoaldehyde structure, while reversedly, the occurrence of the reactions does not unequivocally verify the aminocarbino structure. The reactions mentioned are also given by the "dimolecular" ethers of the type:



The above-mentioned investigations were greatly facilitated by the fact that on the basis of their behaviour against the Karl Fischer reagent, it was possible to distinguish aminocarbinols from "dimolecular" ethers and amino aldehydes.

Physical methods alone are unsatisfactory for the elucidation of structural problems. Infrared spectra in many cases yield quite unequivocal informations in respect to the structure of *solid* bases. On establishing whether an absorption band characteristic of the oxo group or of the hydroxyl group appears in the spectra, it is possible to decide the aminocarbino or amino aldehyde nature of the compound examined. However, a tautomeric equilibrium occurs only in solutions where the sensitivity of the infrared or ultraviolet spectrum is unsatisfactory for the detection of the presence of a form present in minute concentration (which concentration, however, cannot be neglected from the aspect of chemical reactivity) in the case when the equilibrium strongly shifts in favour of one of the forms.

From these it follows that in order to approach the "triple tautomerism" problem in question, the combined consideration and weighing of the results of investigations obtained by various physical and chemical methods is necessary.

In the case of cotarnine, the presence of the amino aldehyde form could not be detected by infrared or ultraviolet spectra established in solid form and in solutions of various pH values, either (Sándor Holly, László Láng, György Varsányi, of the Department of Physical Chemistry). The results of the polaro-

graphic investigations (Károly Győrbiró, of the Department of Inorganic Chemistry) were in full accordance with the spectroscopical data.

The fair accordance of the values calculated on the basis of the determined degrees of dissociation and the measured conductances of cotarnine with those obtained on the basis of spectrophotometric measurements similarly proved that the undissociated portion cannot consist of appreciable amounts of the amino aldehyde form (Dénes Beke, Csaba Szántay, László Tőke).

The comparative kinetical investigation of the reaction of cotarnine and some aromatic aldehydes with hydrogen cyanide showed that between cotarnine and the aldehydes essential differences exist in the kinetical and thermodynamical parameters of the reaction, and further also in respect to catalysis. These marked differences completely exclude the presumption that cotarnine may participate in the reaction in the amino aldehyde form. Even if this form would be present in negligible concentration, below the limit of detectability by spectroscopy, it cannot play any perceptible role in the chemical process.

Therefore, it was attempted to shift the complicated acid-base equilibrium by various structural changes carried out on the cotarnine molecule, in a direction that the concentration of all molecule types participating in the equilibrium should be raised over the limit of detectability. On applying the afore-mentioned chemical and physical methods on the derivatives, the conclusion was drawn that it is possible to classify the representatives thus far known of bases liberated from quaternary ammonium salts as follows:

1. Strong bases. These are aminocarbinols in the solid state and in apolar solvents, while they dissociate to a major extent to mesomeric cations and hydroxyl ions in polar solvents. The existence of the amino aldehyde form could not be supported by evidence.

2. Moderately strong bases. These are aminocarbinols in solid state, while in an aqueous solution they are in equilibrium both with their own ions and with the ethers formed with themselves. Thus far, the existence of the amino aldehyde form could not be detected in this group, either.

3. Aminocarbinols not dissociating to cations and hydroxyl ions. These can be converted into the isomeric amino aldehydes. It is possible to prepare both forms separately or at least to detect their presence. Under adequate experimental conditions, both forms are in dynamical equilibrium with each other.

4. Compounds disclosing no basic properties at all (insoluble in diluted aqueous acids). These solely exist in the amino aldehyde form. Their aminocarbinol forms may only exist intermediately, directly at the moment of their liberation from the quaternary salt.

The overwhelming majority of the examined compounds belong to groups 1 and 2, i.e. they are of cyclic structure.

Thus, in principle, the existence of the "triple tautomerism" could not be excluded, though too far its presence could not be proved actually. In contrast to the generally accepted opinion, however, it cannot generally or often occur, solely in rare and exceptional cases.

The existence of "triple tautomerism" has been presumed not only in the bases themselves but also in their various derivatives. Thus, the researches carried out in the department were extended to the investigation of the structure of these derivatives as well. In the course of these investigations it was proved that the derivatives formed on the effect of nucleophilic reagents (such as hydroxylamine, aniline etc.) are, in contrast to the statements also to be found in quite recent literature of cyclic structure, and cannot be derived from the amino aldehyde form.

The elucidation of the theoretical problems facilitated the development of new synthetic methods which, on the one hand, yielded so far unknown ring systems (imidazo-isoquinoline, pyrimido-isoquinoline) and, on the other hand, made possible to prepare in a very advantageous way a number of well-known quinolizine ring systems of great practical importance (Dénes Beke, Csaba Szántay, László Tóke).

In the department, the Research Group for Alkaloid Chemistry was established in 1960 under the personal guidance of professor Dénes Beke, head of the department. This group combined the research workers of the department dealing with investigations of alkaloid chemistry into a uniformly organized team. After the unexpected sudden death of professor Dénes Beke on March 21, 1962, the leadership of the alkaloid theme was taken over by his nearest co-worker, Csaba Szántay, candidate of chemical sciences.

The third group of themes of the department, under the leadership of Károly Lempert, associate professor, set himself the aim of studying the compounds with a 1,3-diazole, 1,3-diazine and 1,3-diazepine skeleton, from the aspects both of organic and of pharmaceutic chemistry. These investigations included primarily the study of the oxo, thioxo and imino derivatives of the mentioned types of compounds, and they led to the discovery of several new reactions of importance from the aspect of theoretical and preparative organic chemistry, further to the preparation of some compounds with a valuable pharmaceutical activity. Thus, the base-catalyzed rearrangement reaction of 3-substituted glycoyamidines (and analogous compounds), and the dealkylation and transalkylation reactions, respectively, of 2-substituted glycoyamidines on the effect of ammonia and amines were detected, and the mechanism of these reactions was elucidated by isotope investigations. Further, it was found that the reaction conditions exert a marked guiding effect on the base-catalyzed condensation of benzil and guanidines. The causes of this guiding effect were successfully cleared up. On the other hand, in co-operation with the Pharmacological Institute of the Medical University, Budapest,

a glycoyamidine derivative was prepared which proved to be efficient in preventing the development of various narcomanies (alcoholism, morphinism), and, respectively, in exerting a favourable influence on tapering-off cures applied in chronic narcomany.

The international reputation of the Department of Organic Chemistry of the Technical University, Budapest was founded by the late professors Géza Zemplén and Dénes Beke of the Department.

The present staff of the Department set themselves the aim at further preserving the attained high level of international reputation.