

## PROFESSOR MIHA TIŠLER

### A Tribute



Professor emeritus Miha Tišler reached 75 years of age in September 2001; he was born in Ljubljana on September 18th, 1926. He graduated in chemistry at the Faculty of Natural Sciences and at the Faculty of Chemistry and Chemical Engineering in Ljubljana, Slovenia (former Yugoslavia). With a scholarship from the British Council he was a postgraduate researcher in the laboratories of Lord Todd in Cambridge, England (1953-1955). There he prepared his PhD which he then defended in Ljubljana to obtain subsequently a PhD in chemistry on the basis of his thesis entitled "Syntheses in the Cycloheptatrienone Series" (1955). In Cambridge he investigated 3-hydroxytropones and, among other compounds, he prepared at that time an unusual compound, the aromatic carboxycycloheptatrienylium (carboxytropylium) bromide (**1**). His first appointment was as assistant in the Laboratory of Organic Chemistry at the University of Ljubljana and with time he gradually advanced to the position of Lecturer (Docent), Associate Professor (1961) and Full Professor (1964) as a permanent position. During 1971-1984 he served as Head of the Laboratory of Organic Chemistry and in 1995 he retired.

He was a British Council Visiting Scientist (1966), Visiting Professor at the Universities of Freiburg, Germany (1962), Trieste, Italy (1985, 1986), Brigham Young University, Provo, Utah (1986), and under an exchange program with the National Academy of Sciences, Washington, he lectured at several universities in the USA (1968, 1979). He also spent two months as Visiting Professor in Japan at the invitation of the Japan Society for Promotion of Science, Tokyo (1975), as well as in Australia (1982). He was plenary speaker at about 20 International Symposia or Congresses and at the Gordon Research Conference.

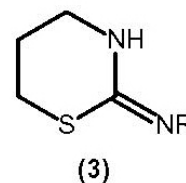
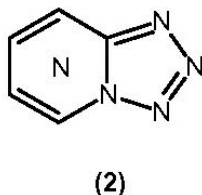
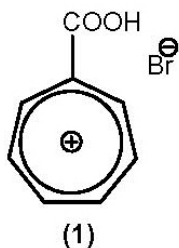
Professor Tišler is author or co-author of over 50 books, textbooks of organic and heterocyclic chemistry, monographs or review articles and over 500 published scientific papers. Of the many

organic chemists who obtained the PhD degree by accomplishing their thesis under his guidance, nine were later elected and appointed at several faculties at the universities of Ljubljana and Maribor. The Organic Chemistry laboratory in Ljubljana has become known as the school for heterocyclic chemistry in the former Yugoslavia.

His research was mainly devoted to the field of heterocyclic chemistry, syntheses of new heterocyclic systems and their transformations, development of new reagents, structural studies, tautomerism, elucidation of reaction mechanisms, *etc.* In Ljubljana, where at that time only poor research facilities were available, he started a long term research project on the chemistry of pyridazines and thiadiazoles. One of the interesting features of this research was the study of compounds where in the molecules two potentially tautomeric thioamide groups were present. At that time it was generally accepted that a thioamide group in a heterocyclic system exists as such (thiolactam form) and not in the mercapto (thiolactim) form. However, it could be proved that in the case of 2,5-"dimercapto"-1,3,4-thiadiazole or 3,6-"dithioxo"pyridazine, for example, one thioamide group existed as such and the other was in the thiolactim form.

New and interesting results were obtained from extensive investigation on azidotetrazolo isomerization. Target compounds were in the series of tetrazoloazines (**2**), and related tri- or polycyclic systems with an annelated tetrazole ring, such as azasteroids. The isomerization could be used also synthetically for the preparation of certain compounds. On the basis of much of his own data and from the literature it was possible to summarize all the general structural and other effects which control this isomerization; in particular, in tetrazoloazines with a bridgehead nitrogen atom.<sup>1</sup> Later, reactions between azidoazolopyridazine and 1,3-dicarbonyl compounds or additions to multiple bonds to give azolopyridazines substituted with a 1,2,3-triazole ring were investigated.

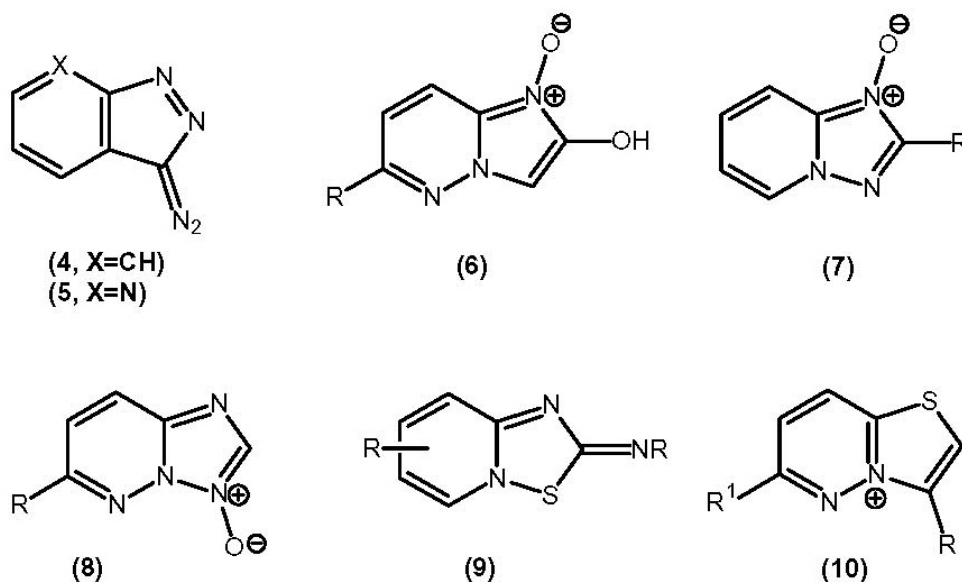
Another interesting potentially tautomeric system was the substituted 1,3-thiazine (**3**). Studies with the aid of UV and IR spectroscopy, at that time the only available spectrometers in Ljubljana, were published in a short communication in *Tetrahedron Letters*. The proposed structure was for many years controversial, but it was later confirmed by American, and after 32 years by Japanese, investigators.



Heterocyclic diazo compounds, contrarily to the corresponding diazonium salts, were practically unknown. Their synthesis was developed and it was possible to obtain for the first time an X-ray structure of 3-diazo-3*H*-indazole (**4**). Heterocyclic diazo compounds such as 3-diazo-3*H*-indazole (**4**) or 3-diazopyrazolo[3,4-*b*]pyridine (**5**) were reactive synthons and they could be also

transformed with trimethylsilyl azide into heterocyclic azides. Their utility in organic synthesis was presented in a review article.<sup>2</sup>

Many years of research were devoted to investigations of azoloazines and azaindolizines, *i.e.* bicyclic 10  $\pi$ -electron aromatic systems with bridgehead nitrogen atom which are, for example, isoelectronic with indole. A review article on structure and reactivity correlation of bicyclic 10  $\pi$ -electron systems with bridgehead nitrogen atom was published in 1980.<sup>3</sup> Many new synthetic approaches towards bicyclic, tricyclic or polycyclic heterocyclic systems containing the azaindolizine unit (the six-membered ring being a pyridine, pyridazine, pyrazine or pyrimidine ring) were developed and their reactivity was investigated, such as the site of protonation and quaternization, hemolytic phenylation, *etc.* In addition to the preparation of a great number of new compounds of various heterocyclic systems, an interesting example was the preparation of imidazo[1,2-*b*]pyridazine 1-oxide (**6**), *s*-triazolo[1,5-*a*]pyridine 1-oxides (**7**) or *s*-triazolo[1,5-*b*]pyridazine 3-oxides (**8**), where the *N*-oxide function resides in the five-membered ring. Moreover, some sulfur analogs, for example 1,2,4-thiadiazolo[2,3-*a*]pyridines (**9**), pyridazinium compounds (**10**), isothiazolo[5,4-*b*]pyridine (**11**) and their tricyclic counterparts could be prepared. A review article on sulfur containing heterocycles from thioamide precursors was published.<sup>4</sup> Studies on nucleophilic substitution revealed another peculiarity, *i.e.* *tele* substitution. 5-Halogenated derivatives of azolopyrazines with bridgehead nitrogen atom reacted with nucleophiles to give the *tele* substituted 8-derivatives in addition to the normal substitution products.



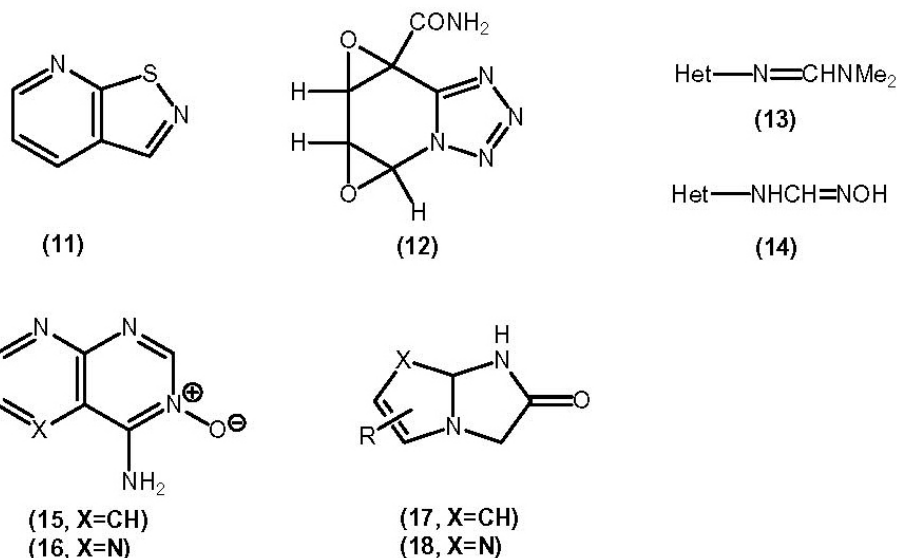
With electron withdrawing substituents at position 8, tetrazolo[1,5-*a*]pyridines underwent ring opening of the six-membered ring in alkaline solution. If, however, hydrogen peroxide was present with the aim of converting a cyano group into the carboxamido group, an unusual bicyclic diepoxide (**12**) was obtained and the structure was solved in collaboration with Dr. Milan R. Uskoković from the Chemical Research Department of Hoffmann-La Roche. There

was also some collaboration with WHO and the National Cancer Institute of National Institute of Health, Bethesda, Maryland.

An enormous synthetic potential was opened up with the introduction of *N,N*-dimethylaminoformamide (or acetamide) dialkyl acetals for the construction of new heterocyclic rings. The formamidines themselves (**13**) or hydroxyiminomethyleneamino derivatives (**14**) derived from them could be widely used for annelation reactions, for the formation of [2+2] cycloadducts with phenyl isocyanate, *etc.* Unsaturated *N,N*-dimethylamidine synthons, prepared from enamino amides, thioamides or esters and even activated methylene groups of pyridines, proved to be reactive with these acetals. The utility of heterocyclic amidines and hydroxyamidines as synthons for bi- and polycyclic heterocycles has been reviewed.<sup>5</sup>

Other heterocyclic systems that were investigated in detail were the synthetic derivatives of 4-aminopyrido[2,3-*d*]pyrimidine- (**15**) and 4-aminopteridine 3-oxide (**16**). Here, the pyrimidine part undergoes transformations and ring opening either at the C2- N3 or the N3-C4 bond; an "in-out" nitrogen translocation and subsequent cyclizations may, for example, give 1,2,4-oxadiazolopyridines. The many aspects of these transformations have been reviewed.<sup>6</sup>

A new entrance into the domain of heterocyclic compounds was provided by a study of heterocyclic amino acids. They proved to be good synthons for the formation of, for example, 1,2,4-triazines, some azaindolizines or quinolizines resulting from the reaction between heterocyclic amino acids and dicarbonyl compounds, and condensed 5/5 membered bicycles with a bridgehead nitrogen atom, such as pyrrolo- (**17**) or imidazo[1,2-*a*]imidazoles (**18**).



Many crystal and molecular structures of new heterocyclic compounds were determined by Professors Ljubo Golič and Ivan Leban (University of Ljubljana). A fruitful collaboration with research possibilities was provided in the form of an exchange programme with the participation of Professors Jerald S. Bradshaw (BYU University Provo, Utah), Ronald J. Pugmire and David M. Grant (University of Utah, Salt Lake City), Gordon B. Barlin and Desmond J. Brown (John

Curtin School of Medical Research, Canberra, Australia). Last but not least one should mention and acknowledge that Professor Tišler had great pleasure in a long-standing friendship, collaboration and support from Professors Jerald S. Bradshaw and Alan R. Katritzky (University of Florida, Gainesville), dating from the time when the latter was professor at the University of East Anglia in Norwich. He has also many friends at universities and institutes throughout the world.

Professor Tišler was Dean of the Faculty of Natural Sciences and Technology (1973-1976) and he was the first elected rector at the University of Ljubljana in the independent Slovenia (1991-1995). He served as Vice-President, President and Past- President of the International Society of Heterocyclic Chemistry (1973-1980).

He is member of the ACS, MRSC, International Standing Committee of the International Association "Ius Primi Viri" in Rome, Italy, and member of the Governing Council of the European Science Foundation (Strasbourg). He was also a member of the Permanent Committee of the European Rectors Conference and the State Council of Republic of Slovenia (1992-1997). He served as the National Representative in Organic Chemistry Division, Commission on Physical Organic Chemistry of IUPAC (1986- 1997). He was elected to membership of the Slovenian Academy of Sciences and Arts (1970), Serbian Academy of Sciences and Arts (1978), Croatian Academy of Sciences and Arts (1979), New York Academy of Sciences (1980) and Academia Scientiarum et Artium Europaea, Salzburg (1995). He was decorated as Knight of the Order of St. Gregorius the Great (1995).

He received the Award for Science from Slovenia (1977), Plaque from the International Society of Heterocyclic Chemistry (1979), Honorary Medal and Diploma of the Slovak Technical University, Bratislava (1981), Diploma of the Tohoku University, Sendai (1975) and Hoshi University, Tokio (1986); he received documents of recognition from the Faculty of Pharmacy (1982) and Faculty of Natural Sciences and Technology, University of Ljubljana (1989) and the award Ambassador of the Republic of Slovenia (1995). He is an Inaugurated Honorary Member of the Florida Center for Heterocyclic Compounds, Gainesville, Florida. In 2000 he received the Honorary Degree (Doctor *honoris causa*) of the University of Ljubljana.

He served or is still serving at the Editorial or Advisory Board of the following scientific journals: Journal of Heterocyclic Chemistry, Heterocycles, Advances in Heterocyclic Chemistry, Heterocyclic Communications, Organic Preparations and Procedures International, Duga (Turkish Journal of Chemistry), Croatica Chemica Acta, Acta Chimica Slovenica (formerly Vestnik Slovenskega kemijskega društva).

Professor Tišler (alone or with colleagues) organized several National or International Symposia or Congresses: 5. International Congress of Heterocyclic Chemistry (1975), 5th International Symposium on the Chemistry of organic Sulfur Compounds (1978), 3rd Yugoslav Symposium of Organic Chemistry (1983) and TRISOC Symposium (symposium of the universities of Graz, Trieste and Ljubljana)(1985).

Professor Tišler is happily married and his wife Vida was Professor of Organic Chemical Technology at the same University. Their daughter Tanja is a holder of a PhD in biology and is

working at the National Chemical Institute on water pollution problems.

Since his retirement he has remained active in preparing some review articles (on pyridazines, which was first published in 1968, and thereafter in 1979, 1990, 2000, on heterocyclic quinones in 1989, and on heterocyclic amino acids (1995), all in *Advances in Heterocyclic Chemistry*). Recently he published two books, *Molecules and their Messages*, and *Reminiscences and Reflections*, both in the Slovene language.

Professor Tišler has always been an excellent supervisor to his students and friendly and helpful to his associates and acquaintances. I, as one of them, have been extremely fortunate in having him first as a supervisor during my PhD studies then later becoming one of his coworkers and colleagues; the result has been fruitful collaboration and friendship for over four decades.

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