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FOURTH INTERNATIONAL CONFERENCE ON THE CHEMISTRY AND BIOLOGICAL ACTIVITY OF SYNTHETIC AND NATURAL COMPOUNDS (CBC 2010). MODERN ASPECTS OF HETEROCYCLIC CHEMISTRY

S. F. Vasilevskiy, L. F. Semenova, and V. A. Agafonova

The CBC 2010 conference in commemoration of the ninety-fifth birthday of Alexey Nikolaevich Kost, Professor at Lomonosov Moscow State University, an outstanding scientist and teacher, took place on August 2-6, 2010 in St. Petersburg, Russia, in the Beloselsky-Belozersky Palace, one of the most beautiful palaces in the center of Russia's northern capital.

The conference was organized by the International Science Partnership Foundation and InterBioScreen Company, with the participation and support of the Russian Academy of Sciences, Mendeleev Russian Chemical Society, and Lomonosov Moscow State University.

The high scientific level of the conference was achieved thanks to the dedicated work of the organizing committee headed by the chairman of the Board of Directors of InterBioScreen, the chairman of the International Scientific Partnership Foundation, full member of the Russian Academy of Natural Sciences, V. G. Kartsev, and an international scientific committee comprised of the members of the Russian Academy of Sciences O. N. Chupakhin, V. N. Charushin, N. S. Zefirov, G. A. Tolstikov, V. I. Minkin, member of Russian Academy of Natural Sciences M. N. Preobrazhenskaya, the Nobel laureates Prof. E. J. Corey from the United States, Prof. R. Noyori from Japan, and Prof. J.-M. Lehn from France; and also Professors B. Stanovnik from Slovenia, H. van der Plas from the Netherlands, M. Mąkosza from Poland, and D. Spinelli from Italy. A number of prominent scientists from Russia, the Commonwealth of Independent States, the Baltic states and other foreign countries were also members of the scientific committee.

Professors van der Plas and Stanovnik spoke at the opening ceremony. They praised the excellent organisation of this conference and read out the messages of welcome from Prof. E. J. Corey of Harvard University (USA) and Prof. J.-M. Lehn of the Institute de Science and d'Ingénierie Supermoléculaires (France), who stressed the importance of an international scientific forum of this scale, with a focus on the advances in organic, heterocyclic, and medicinal chemistry.

The conference was opened with the awarding ceremony for the 2010 winners of the Medal "In memory of prof. A. N. Kost" , which was instituted in 2005 by the International Scientific Partnership Foundation, Lomonosov Moscow State University, and Mendeleev Russian Chemical Society in recognition of the outstanding contribution of Prof. Kost to the chemistry of biologically active synthetic and natural heterocyclic compounds, fine and applied medicinal chemistry, and the development of new drugs.

The Kost Memorial Medals were awarded to scientists and institutions from Russia and other countries for their significant contributions to heterocyclic chemistry. The big Medal "In memory of prof. A. N. Kost" was awarded to the Department of Chemistry and Chemical Biology, Faculty of Arts and Sciences, Harvard University (USA), in which Prof. Kost was a researcher in the laboratory of Nobel Prize winner, Prof. R. B. Woodward in 1961.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1584-1597, October, 2010.

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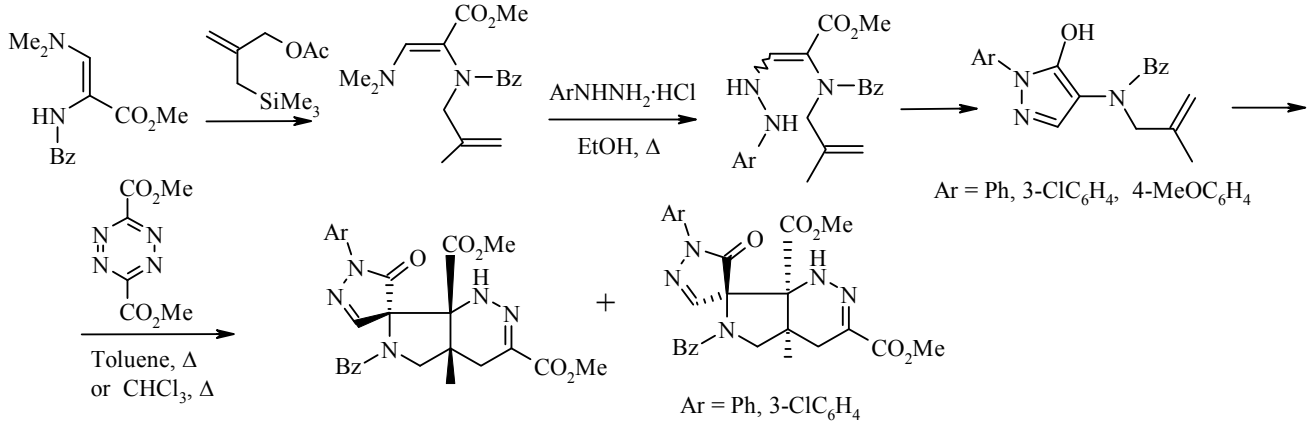
In 2010, the International Scientific Partnership Foundation instituted a new award, Gold Badge of International Scientific Partnership Foundation, of which the first winners were more than fifty outstanding chemists.

Speakers at the conference included chemists from Austria, Belgium, Cyprus, Egypt, France, Germany, Great Britain, Greece, Hungary, India, Italy, Japan, the Netherlands, Poland, Russia, Slovenia, Turkey, the United States, countries of the Commonwealth of Independent States, and others. The program included plenary lectures, oral reports, and a poster session.

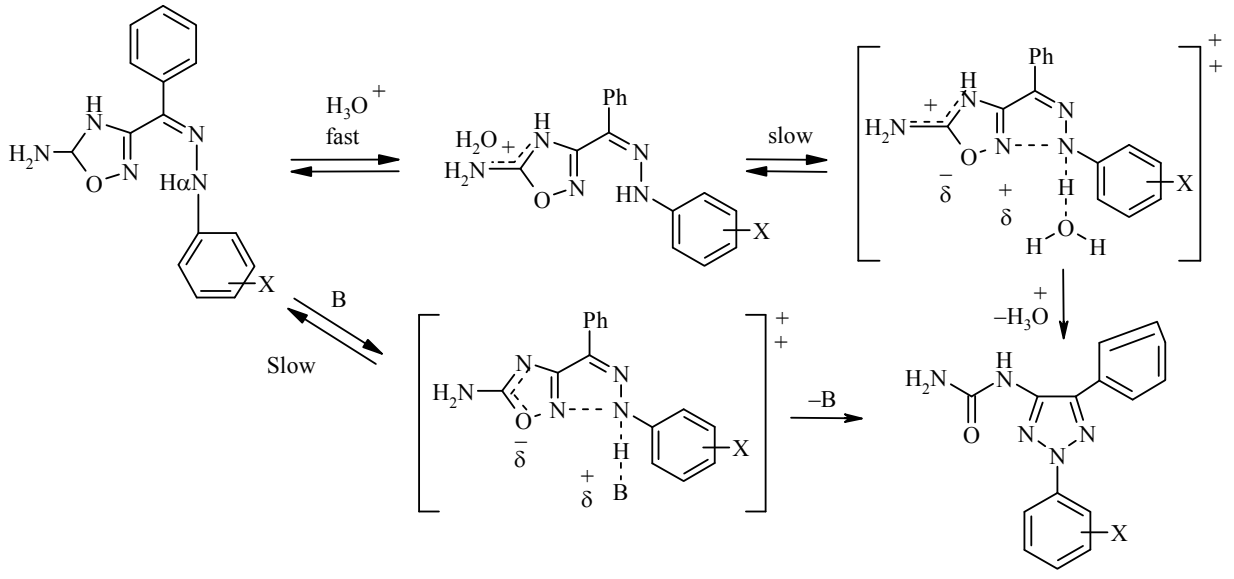
There were more than 130 participants representing 25 countries, Russian scientists from 48 leading institutes in Russia and the neighboring countries.

The first plenary lecture was given by Henk van der Plas from Wageningen University in the Netherlands, who summarized the results of his studies over many years on the transformation of cyclic systems in the synthesis of nitrogen heterocycles.

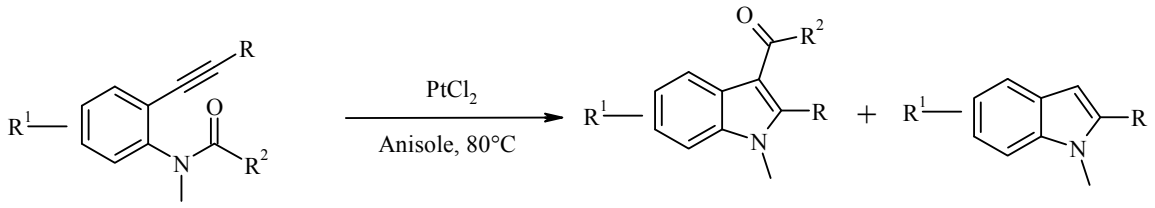
The interesting results presented by Branko Stanovnik of Ljubljana University in Slovenia deeply impressed the audience. He examined the use of the reactions of electron-deficient dimethylaminoalkenes as a helpful approach to the synthesis of a broad range of heterocycles, namely, derivatives of pyridines, indoles, pyrimidines, pyrazoles, etc. including not readily available spiro compounds such as in the following transformations:



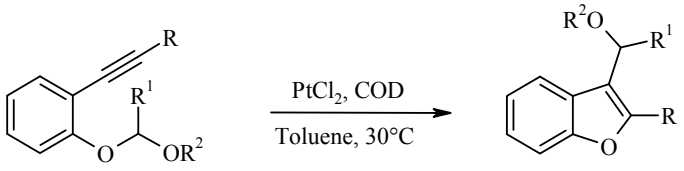
Domenico Spinelli of the University of Bologna in Italy presented numerous examples of the use of single-ring rearrangements of heterocycles in the synthesis of imidazoles, 1,2,4- and 1,2,5-oxadiazoles, and 1,2,3- and 1,2,4-triazoles, as in the following example:



Yoshinori Yamamoto representing both Tohoku University in Japan and Dalian University in China examined new approaches to the synthesis of derivatives of quinoline, isoquinoline, indole, and benzofuran. These methods were based on the use of the cyclization of arylacetylenes containing azomethine, aldoxime, azide, acetamide, and sulfamide groups in the C-2 position catalyzed by gold, platinum, silver, and indium salts as in the following example:

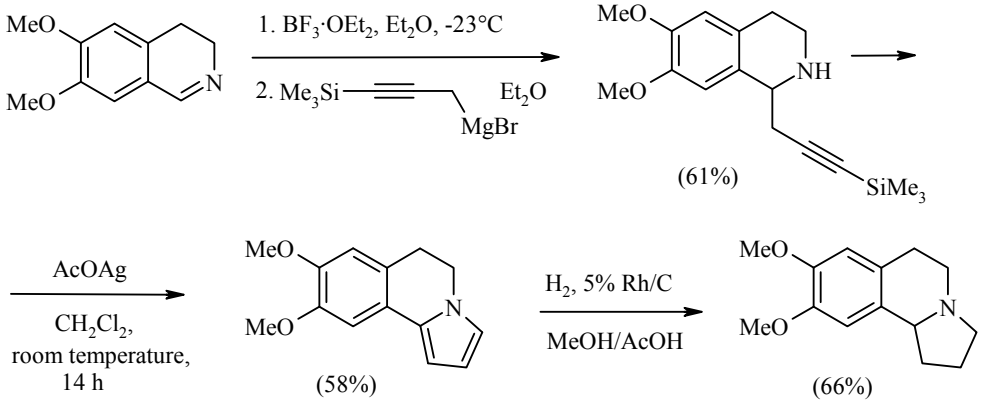


R = Alk, Ar; R^1 = 4-MeO, 5-MeO; R^2 = H, Me, Ph, Bn, CF_3



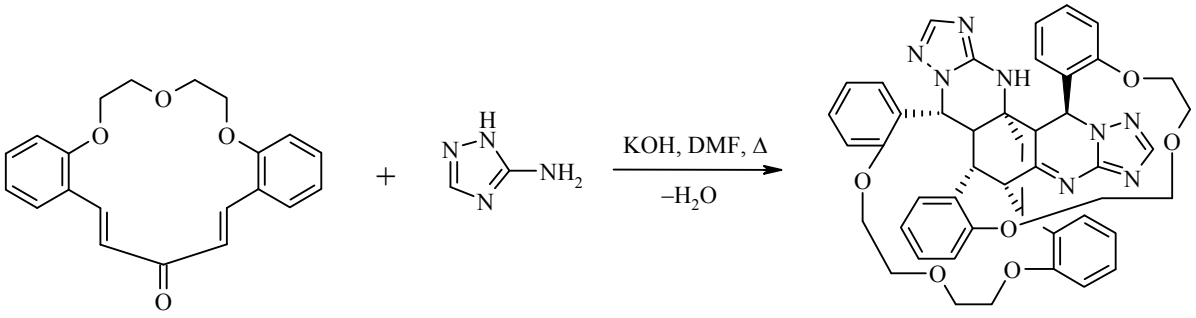
R = Alk, Ar; R^1 = H, Me; R^2 = Me, Et, Bn, TBS

The report of Hans-Joachim Knölker of the Technische Universität in Dresden, Germany, was listened to with a great interest. In the first, synthetic, part of his report, Knölker described an original approach to the synthesis of a number of natural pyrrole compounds based on the cyclization of specially selected acetylene derivatives catalyzed by silver salts, for example:

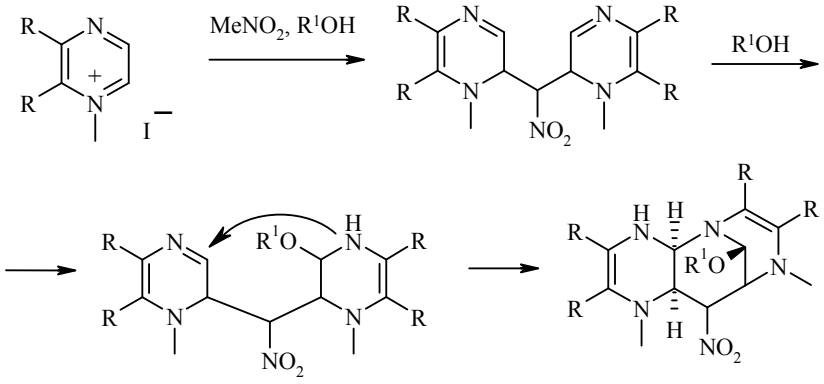


In the second, biomedicinal, part, Knölker discussed the biological screening of pyrrole products as inhibitors of muscular ATPase. A significant achievement of the scientists involved in this study was the isolation of a crystalline complex of this enzyme with the substrate and its X-ray diffraction structural analysis, which showed the site of binding of the substrate to the protein and suggested a strategy for further investigation.

In their report, "Tandem and Cascade Reactions in Heterocyclic Synthesis," Valerii N. Charushin, G. L. Rusinov, and O. N. Chupakhin and coworkers of the I. Ya. Postovskii Institute of Organic Synthesis of the Ural Branch of the Russian Academy of Sciences presented the latest results on an unusual course of such reactions, leading to polyheterocycles with a complex three-dimensional structure, for example:

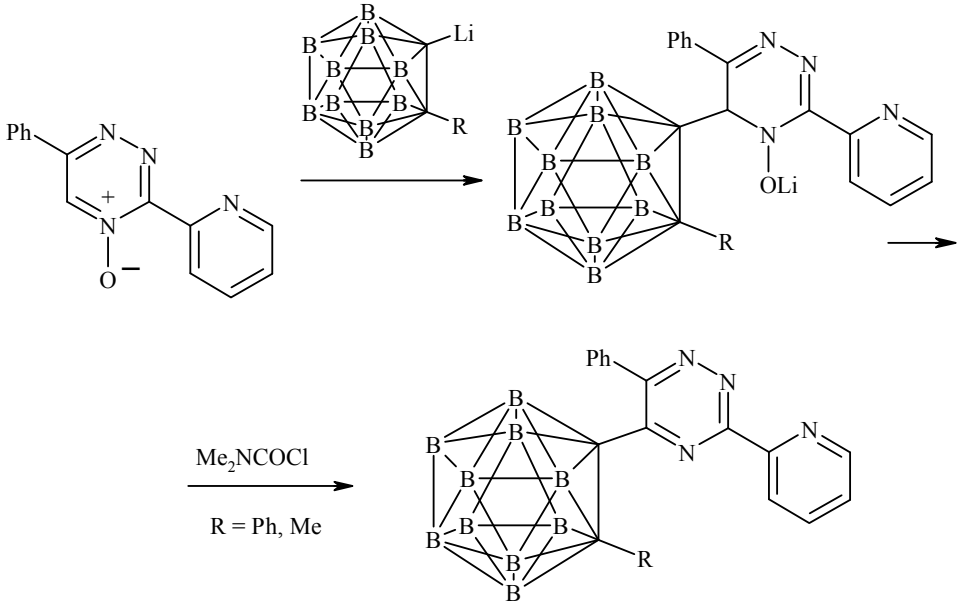


These reactions yield various polycyclic alkaloid-like compounds in high yield, for example:

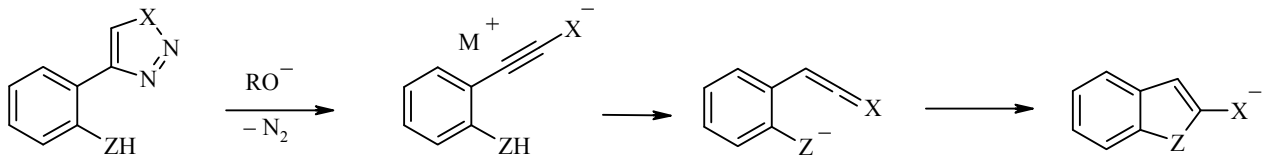


R+R = benzo; R^1 = Me, Et, Pr, Bu, C_5H_{11}, C_6H_{13}

In a separate lecture, Oleg N. Chupakhin discussed S_N^H reactions in heterocyclic chemistry, analyzed the nomenclature of nucleophilic hydrogen substitution reactions in heterocyclic compounds and presented the latest results on the synthesis of a new generation of heterocycles with potential practical applications and their possible use as adsorption materials and agents for neutron-capture therapy in the treatment of tumors, for example:

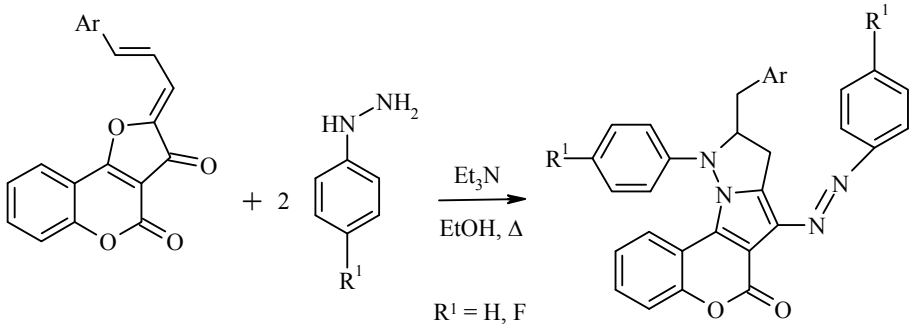


Mieczysław Mąkosza of the Institute of Organic Chemistry of the Polish Academy of Sciences reported on various aspects of the use of nucleophilic hydrogen substitution in heterocycles leading to perfluoroalkylheterocycles, while V. M. Berestovitskaya of the A. I. Herzen Russian State Pedagogical University in St. Petersburg discussed methods for the synthesis of a number of nitro derivatives of 2,3-dihydro-1,5-benzothiazepines and benzopyrans. M. L. Petrov and D. A. Androsov of the St. Petersburg State Technological Institute reported new approaches to the synthesis of benzofurans, indoles, and benzothiophenes based on the intramolecular cycloaddition of proton-containing functional groups to give thioketenes and selenoketenes:



Z = O, NH; X = S, Se; M = Li, Na, K

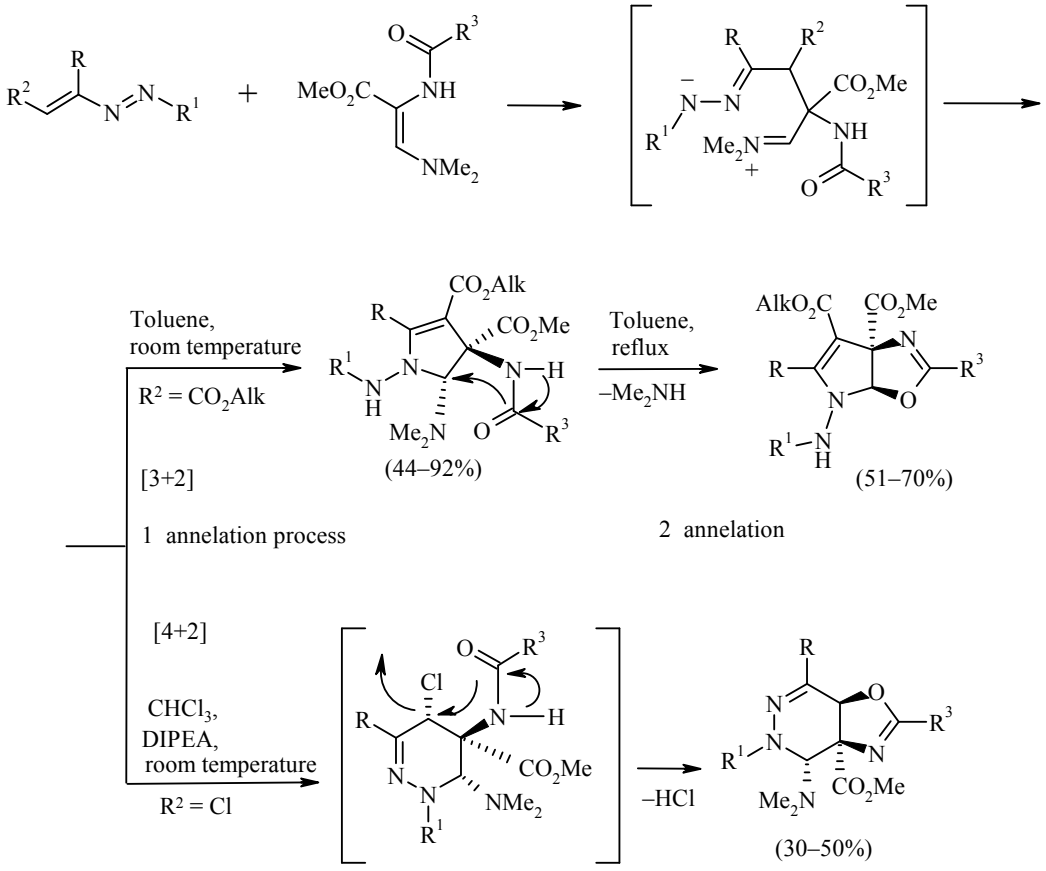
V. F. Traven and his colleagues at the Moscow D. Mendeleyev University of Chemical Technology of Russia have investigated unusual reactions of 2,3-dihydrofuro[3,2-*c*]coumarin-3-one as well as its arylidene and cinnamylidene derivatives with arylhydrazines. These authors discovered unusual transformations leading to condensed systems, for example:



N. M. Przheval'skii of the K.A. Timiryazev Russian State Agrarian University in Moscow discussed the synthesis of tryptamines by the Grandberg reaction and the use of these compounds in multicomponent reactions, while S. N. Sirakanyan of the Institute of Fine Organic Chemistry of the National Academy of Sciences of Armenia presented work on new derivatives of [1,2,4]triazolo[3,4-*a*]naphthyridines, pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines, and pyrido[3',2':4,5]furo[3,2-*d*]pyrimidines.

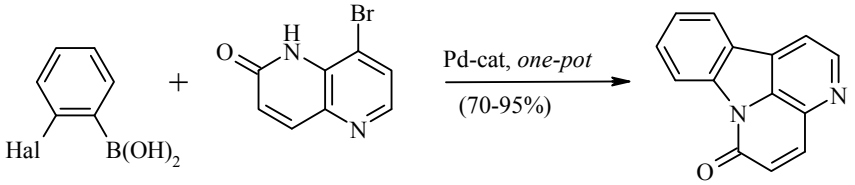
A broad range of new transformations of 4,5-difunctional oxazole derivatives discussed by V. S. Brovarets of the Institute of Bioorganic and Petroleum Chemistry of the National Academy of Sciences of Ukraine indicates pathways for the synthesis of many heterocyclic systems with potential bactericidal, antiviral, and antineoplastic activity. A. M. Demchenko of the Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine and M. O. Lozinskii of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine discussed the synthesis, transformations, and biological properties of condensed polymethyleneazoles possessing antiviral activity.

Orazio A. Attanasi of the University of Urbino in Italy discussed the stereoregular heterocyclization of 1,2-diaza-1,3-dienes, for example:

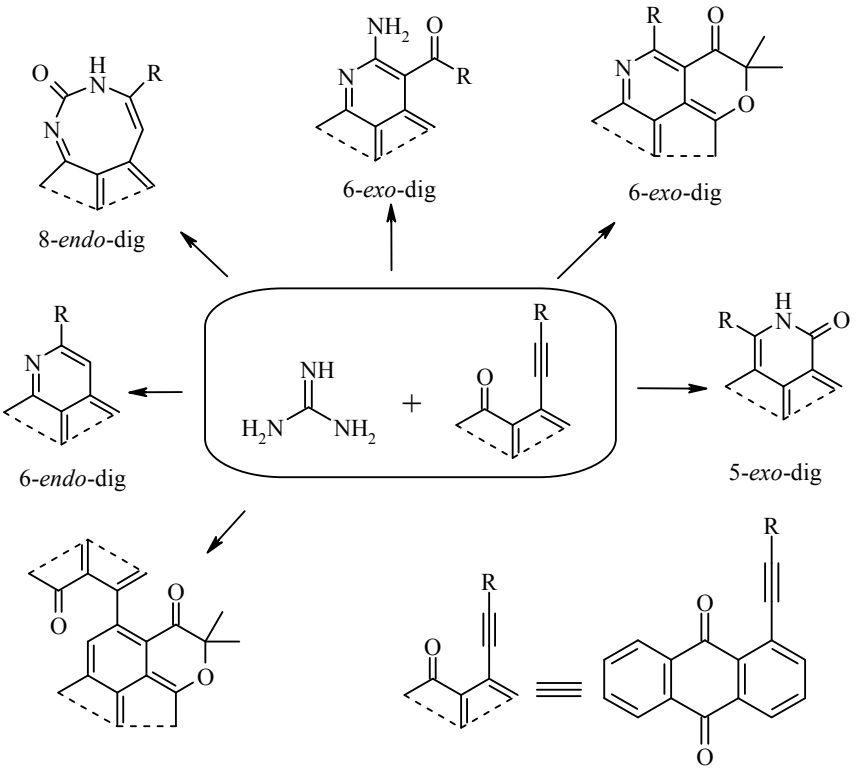


R = Me, Ph; R^1 = CO_2Me, CO_2Et, CO_2Bn, CO_2Bu-*t*, $CONH_2$, CONHPh, $CONHC_6H_4F$-*m*; R^2 = CO_2Me, CO_2Et, CO_2Bn,
DIPEA = N,N-diisopropylethylamine

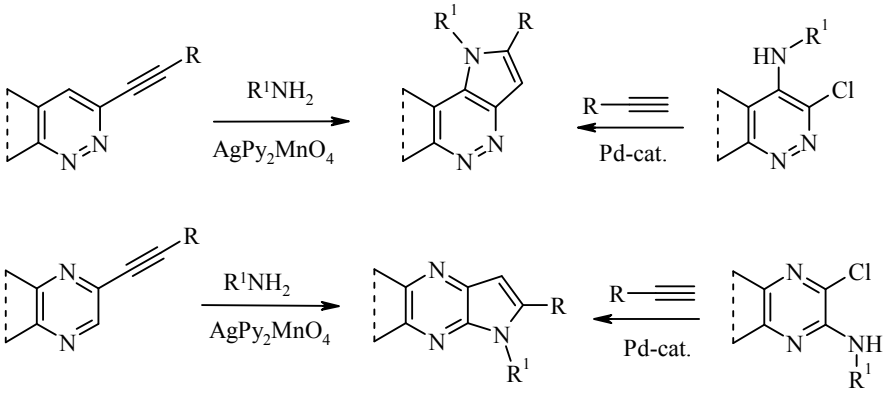
Saverio Florio of the University of Bari in Italy presented a review on "New Horizons in Aziridine Chemistry" and summarized the stereochemical aspects of the synthesis of aziridinylheterocycles, while Panayiotis Koutentis of the University of Cyprus reported a new approach for the one-step synthesis of canthine alkaloid analogs based on the palladium-catalyzed Suzuki-Miyaura reaction, for example:



Sergei F. Vasilevskiy of the Institute of Chemical Kinetics and Combustion of the Siberian Branch of the Russian Academy of Sciences in Novosibirsk discussed efficient new methods for the synthesis of annelated heterocyclic compounds by means of multichannel reactions of acetylenes and showed the feasibility of a new rearrangement with the insertion of a nitrogen atom between two acetylenic carbon atoms:



Anna V. Gulevskaya and colleagues of the Southern Federal University in Rostov-on-the-Don, Russia, presented a paper on the cyclization of mono- and dialkyl derivatives of pyrazines and pyridazines by the action of nucleophiles. These authors reported on the development of general methods for the synthesis of a broad range of heterocyclic systems, including heterocyclization catalyzed by silver and palladium complexes, for example:



R = H, $SiMe_3$, Ph, C_6H_{13}, CH_2OTHP; R^1 = H, Et, Pr, *i*-Pr, Bu, *t*-Bu, *cyclo*-C_6H_{11}

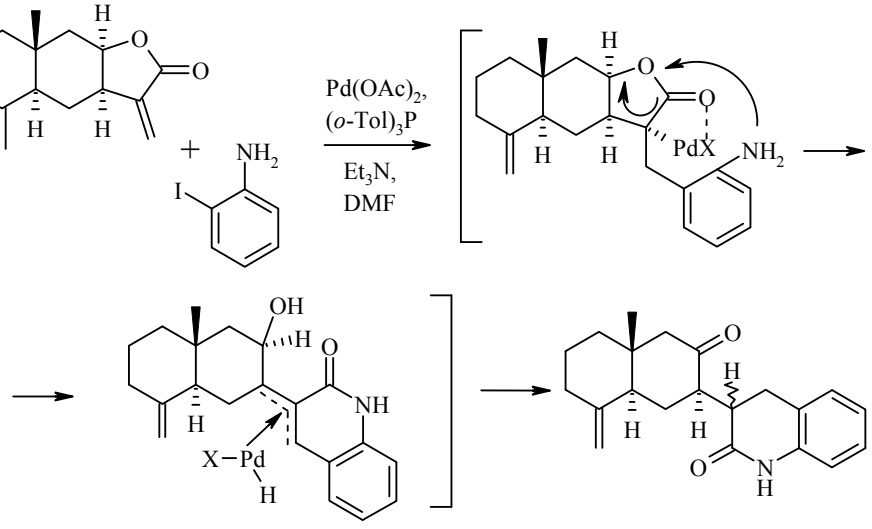
A significant number of reports given by chemists from Russia and from other countries were devoted to various aspects of the biological activity of heterocyclic compounds. The detailed report of Vladimir V. Poroikov of the V. N. Orekhovich Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences featured a summary of the use of the PASS computer program for the prediction of 3300 types of biological activity of natural products and their derivatives. Athina Geronikaki of Aristotle University, Thessaloniki, Greece, reported on the synthesis of new pyrazolooxazin-2-one COX-LOX inhibitors.

H. Bölcskei, a representive of Gedeon Richter Pls., a Hungarian pharmaceutical company, noted that the COX-2 inhibitors used in the treatment of inflammation, rheumatoid arthritis, osteoarthritis, and cancer are mostly nonsteroid compounds such as Celecoxib, Etoricoxib, Valdecoxib, and Cimicoxib, which contain pyrrole, pyrazole, or oxazole fragments with two aryl substituents. These authors carried out the synthesis of a series of diphenylpyrazoles and diphenyltriazines and discovered the considerable COX-2 inhibiting effect of some of these compounds.

The plenary report of Nikolai S. Zefirov of Lomonosov Moscow State University was devoted to an analysis of computer simulation and synthetic approaches to the synthesis of new heterocycles.

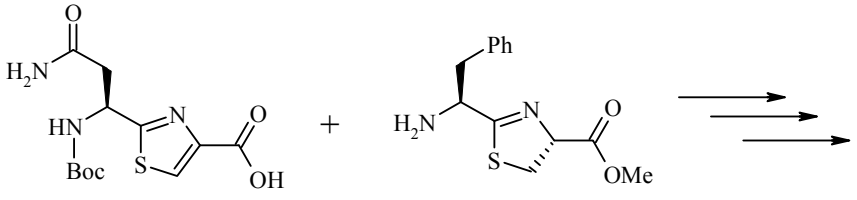
Special attention at the conference was given to lectures on the chemistry of natural products. Maria N. Preobrazhenskaya of the G. F. Gause Institute of New Antibiotics of the Russian Academy of Medical Sciences discussed various aspects of a chemical modification of macrolide antibiotics such as oligomycin and amphotericin.

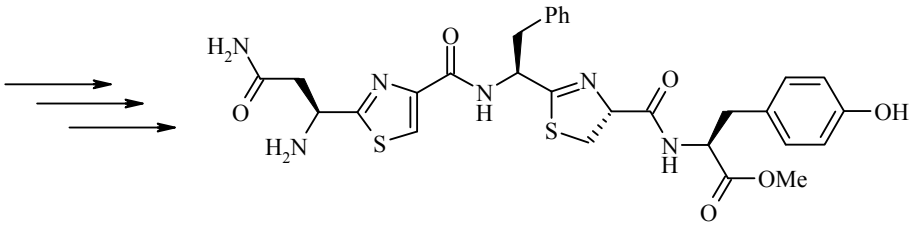
Work on new modifications of eudesmane methylene cations carried out by Elvira E. Shultz, Genrikh A. Tolstikov, and their colleagues at the N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry of the Siberian Branch of the Russian Academy of Sciences led not only to a method for the preparation of arylated lactones possessing antiulcer and antiproliferative activity but also to new rearrangements, for example:



These authors also used metal complex catalysis in the directed synthesis of morphinane alkaloids derivatives showing a pharmacological potential, and in the oxidative coupling of derivatives of labdanic acid with various alkenes.

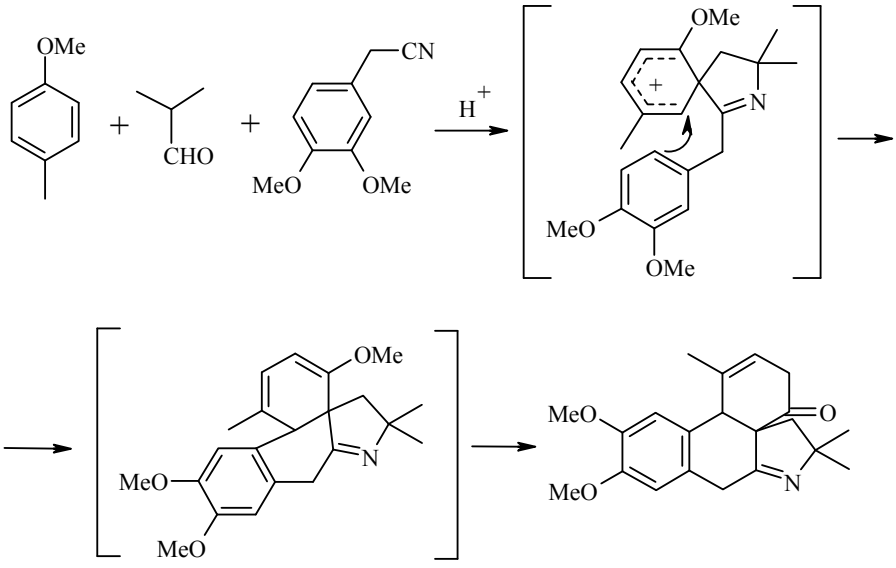
In recent years, pharmacologists and chemists working with natural products have become increasingly interested in compounds derived from sea organisms. The chemistry of marine sponges was treated in a detailed report by M. Álvarez of the Biomedical University in Barcelona, Spain, who presented the results on the synthesis of fragments of macrocyclic metabolites containing pyridine, oxazole, thiazole, and pyrrolidine rings such as



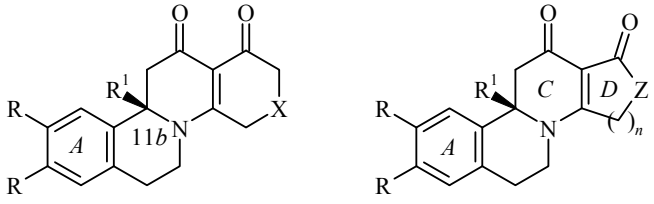


A series of marine alkaloid derivatives was synthesized and the structure-activity relationships were studied.

A. G. Mikhailovskii of the Perm school of heterocyclic chemists (the Perm State Pharmaceutical Academy) presented a report on "Cyclic 3,4-Dihydroisoquinoline Azomethines and Enamines in the Synthesis of Heterocycles." Yuri V. Shklyaev of the Institute of Technical Chemistry of the Ural Branch of the Russian Academy of Sciences and his colleagues gave a detailed report on a triple-component synthesis of partially hydrogenated nitrogen heterocycles. These authors have developed unique methods for the synthesis of new neospiran alkaloid-like systems, for example:



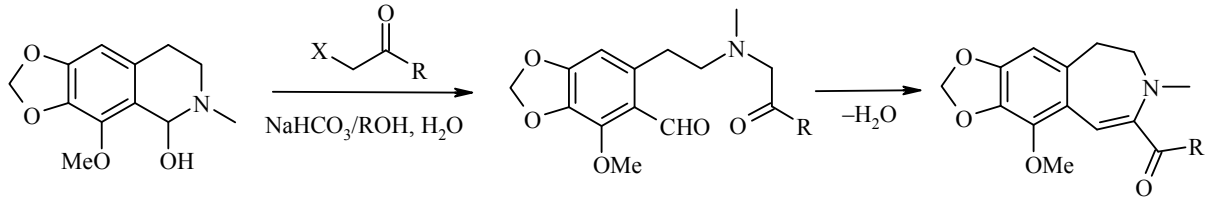
Aleksandr L. Mikhal'chuk and Olga V. Gulyakevich of the Institute of Bioorganic Chemistry of the National Academy of Sciences of Belarus discussed the transformation of azangular heterocycles:



R = H, OMe; R^1 = H, Me, Et, *i*-Pr, F; X = bond, CH_2, CHMe, CMe_2;
Z = CH_2, O, NH, S; *n* = 1–3

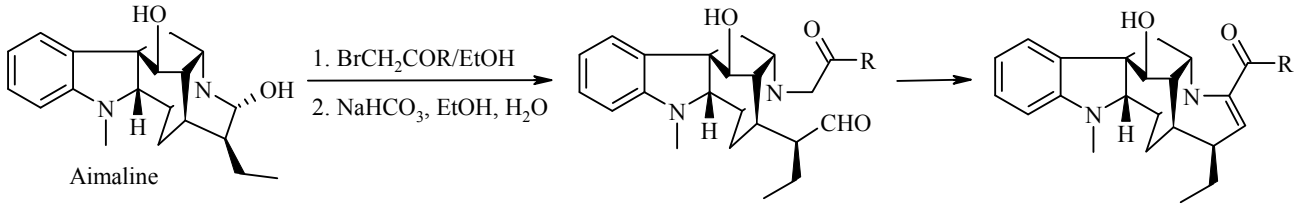
Various pathways for the functionalization of these types of compounds in the search for new pharmacological agents were shown.

Great interest was displayed to the report of Viktor G. Kartsev and A. A. Zubenko on a new rearrangement found in natural and synthetic hemiaminals. The authors described new recyclization reactions recently discovered in their laboratory for cotarnines, leading to 3-benzazepine systems:



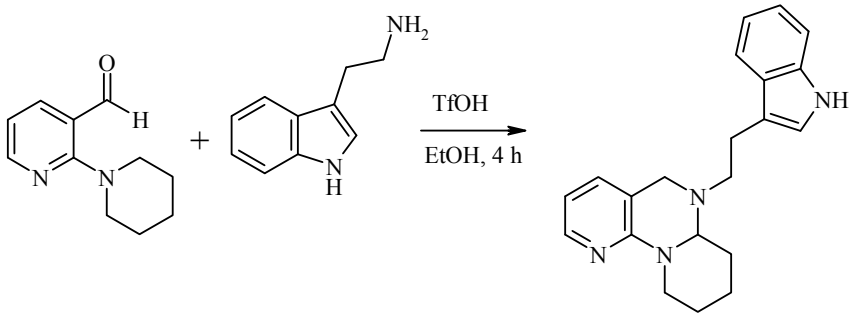
R = Alk, Ar, Het; X = Cl, Br

The authors extended this type of rearrangement to a whole series of natural products and showed the general nature of this reaction, permitting the synthesis of rare and difficult-to-obtain alkaloid systems, for example:

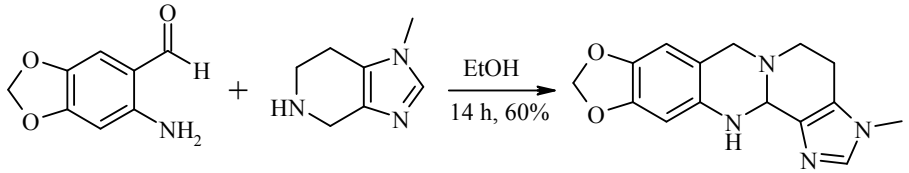


Aimaline

The reports of A. Serov and A. Sukhotin of Lobachevsky State University, Nizhni Novgorod on their joint research with Viktor G. Kartsev were devoted on the use of new types of T-reactions in the construction of rare analogs of alkaloids and other natural systems such as



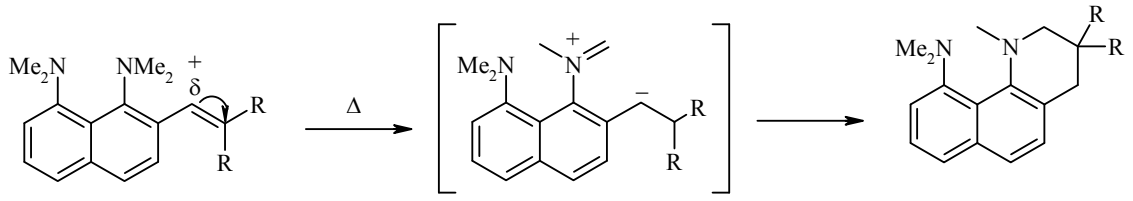
Another type of T-reactions studied by these authors is the intramolecular heterocyclization of aromatic *o*-amino aldehydes accompanied by a 1,6-hydride shift. The use of this type of T-reactions for natural products also permits the synthesis of rare mimetics of alkaloid systems such as villagorgin, xylopinin, and alamaridin, for example:



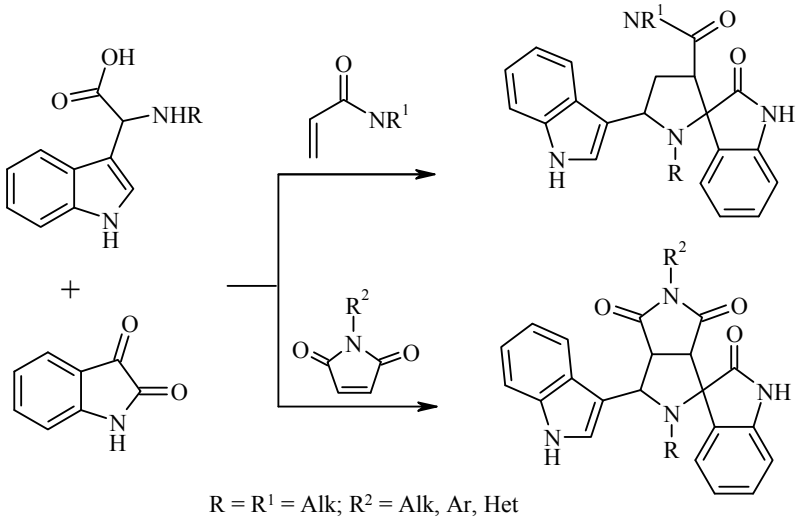
N-Me-Spinaceamine

K. A. Krasnov of the Institute of Toxicology of the Federal Medicobiological Agency of the Russian Federation in St. Petersburg discussed diastereoselective T-reactions of derivatives of barbituric acid, including cases related to its T-adducts with alkaloid cytisine.

Aleksandr F. Pozharskii of the Southern Federal University in Rostov-on-the-Don, Russia devoted his report to an analysis of heterocyclization using proton sponges. On a number of cases, he showed that T-reactions specific for proton sponges take place, for example:



InterBioScreen reported on a number of studies by V.G. Kartsev, A. B. Serov, and A. V. Sukhotin on the modification of indole systems. One aspect of this work concerned 1,3-dipolar addition to indolylglycines, leading to indole-containing spiro systems, which are analogs of the violacein family of alkaloids, for example:



$R = R^1 = Alk$; $R^2 = Alk, Ar, Het$

Another aspect of this research concerned the development of methods for the synthesis of spiroindolonopiperazines with potential antiulcer activity, analogs of ICI-158535 and ICI-171071, and horsfiline, rincofilin, and mitrafilin alkaloids.

It is important to say that many students of Professor Kost and chemists whose lives were in some way touched by his attended the conference. Their recollections of his extraordinary abilities as a teacher imparted particular shade of nostalgy to the scientific presentations. The well-organized cultural program with many excursions around St. Petersburg and its environs made this conference unforgettable.

The reports given at the conference, as always, were published in a perfectly done 504-page book *Modern Aspects of Chemistry of Heterocycles*.

A meeting of members of the Editorial Board of *Khimiya Geterotsiklicheskikh Soedinenii (Chemistry of Heterocyclic Compounds)* with many of the contributors to this journal took place during the conference.

According to the opinion of leading chemists from Russia and other countries, the series of international conferences under the title *The Chemistry and Biological Activity of Synthetic and Natural Compounds* has become one of the most prestigious and representative of scientific forums held in Russia.

The next conference marking the centenary of Professor Kost is planned to be held in 2015 at one of the cities of the Golden Ring northeast of Moscow.