CHRONICLES

SIXTH INTERNATIONAL CONGRESS ON THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

L. N. Yakhontov

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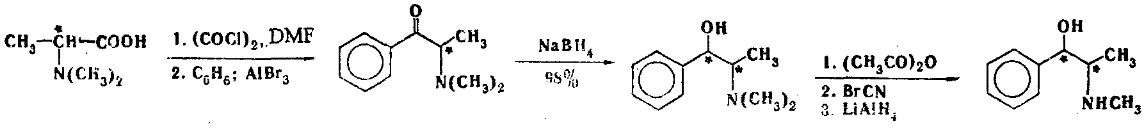
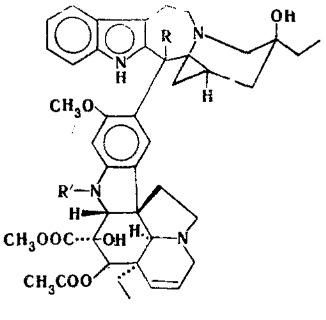
The Sixth International Congress on the Chemistry of Heterocyclic Compounds was held from July 9 to 13, 1977, in Teheran (Iran) in the College of Pharmacy of Teheran University (the president of the congress was Professor I. Lalezari). The following chemists from the USSR participated in the congress: N. K. Kochetkov (head of the delegation), G. M. Tseitlin, L. A. Yanovskaya, L. N. Yakhontov, R. M. Lagidze, I. I. Ibragimov, and O. A. Zagulyaeva. Eight plenary papers and more than 80 sectional papers in symposiums and sections were presented at the congress, and 70 bench lectures were also presented. In a plenary lecture H. Rapoport (University of California, USA) examined the possibility of stereospecific syntheses on the basis of optically active amino acids. He noted that an analysis of the literature data provides evidence for a significant degree of racemization during acetylation, benzoylation, and a number of other reactions involving the amino group attached to an asymmetric center, and he showed that aminoacylation with subsequent cyclization by the action of $POCl_3$ and mild acid hydrolysis proceeds stereospecifically.

The synthesis of L-ephedrine can be presented as an example:



Similar methods have been used for the stereospecific synthesis of polycondensed systems of the lupinine, tetrahydroprotoberberine, and other types.

J. Kutni (Columbia University, Canada) presented a paper on synthetic studies on a series of Vinca alkaloids, which have displayed effectiveness in clinics for malignant neoplasms. The studies were carried out in 1964 under a program financed by the Lily Company with a large collective of scientists (∿ 50 individuals). As a result, it became possible to synthesize not only natural alkaloids but also their less neurotoxic analogs (I), which differ with respect to the character and stereochemistry of the substituents.



I

The synthesis of the upper portion of the I molecule was carried out on the basis of tryptamine, which was subjected to condensation with substituted succinic ester and a number of subsequent transformations, including Grob fragmentation and introduction of the necessary functional groups through the corresponding ethynyl derivatives. The second portion of the molecule (vindoline) was synthesized from 6-methoxytryptamine by means of an immonium condensation.

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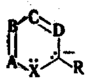
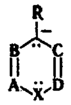
Six possible condensation variants for the fusion of the two fragments were studied. A number of intermediates in the synthesis of Vinca alkaloids that display considerable antitumorigenic activity with low toxicity are currently under more thorough investigation.

The Hungarian chemist G. Santavy (Budapest University) reported new synthetic studies devoted to benzo[a]- and indolo[2,3-a]quinolizidines involving specifically a new approach to the total synthesis of reserpine. The basis of these studies in the reaction, discovered by the author, of 3,4-dihydroisoquinolines of their β-carboline analogs with unsaturated ketones and the analogous halo or dialkylamino ketones; the reaction proceeds with ring closure to a quinolizidine system. The principal difficulty in the subsequent synthesis consists in the creation of the necessary stereochemistry at the five chiral centers in the D ring of the yohimbane system. This problem is solved in the R. B. Woodward synthesis in the initial steps and in the new synthesis is transferred to the end of the synthesis, which complicates the scheme considerably.

A paper by R. Schmidt (West Germany) entitled "Carbanionic heterocyclic systems" was devoted to 8π-electron heterocycles that form anions of the II or III type.



II

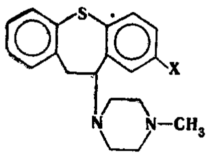


III

A, B, C, D = C—R′; N—etc.
X = O, S, N—R′ etc.

The negative charge in systems of this type is delocalized, and this is reflected in the low basicities of the starting substances and the increased reactivities of the anions. Examination of the peculiarities of the indicated anions opens up new synthetic possibilities, particularly the conversion of 1,3-oxazine derivatives to pyrrole oxides, which are also obtained by alternative synthesis by oxidative of pyrroles.

M. Protiva (Institute of Pharmacy and Biochemistry, Prague, Czechoslovakian SSR) reported the results of research accomplished by him and his co-workers beginning in 1965 devoted to the search for new psychotropic agents among dibenzo[b,f]thiepines and their analogs. A study of the principles of the relationship between the structure and activity enabled the authors to develop new preparations of the perotaiopin and oktoklotopin (IV) type, of which the former is more active by a factor of two to three and the latter is more active by a factor of four to 10 than aminazine. Oktoklotopin has passed clinical tests and has been approved for medical use.



IV

X=H Perotaiopin
X=Cl Oktoklotopin

L. Townsend (University of Utah, Salt Lake City, USA) reported the relationship between the structure and biological activity of aza-, desaza-, and aza/desazaguanines and hypoxanthines, as well as their β-D-ribofuranosides. The basis of the research was the fruitful concept of the substantial change in the reaction of compounds with enzymes when a nitrogen heteroatom is incorporated in them or removed from them. The author examined in detail the methods for the synthesis of modified nucleosides of this type and the relationship between their structure and activity with respect to RNA-ase (the most active 3-desazaguanosides and 6-thio-7-desaza compounds) and established the dependence of the biological activity on the pK_a of the substances.

C. Oae (Tsukuba University, Japan) gave a review of the reactions of heteroaromatic and aromatic amine oxides with acylating agents. K. Potts (Pennsylvania Polytechnic Institute, USA) examined new synthetic possibilities that are opened up when mesoionic heterocyclic systems are used. The development of the chemistry of heterocycles containing nitrogen and phosphorus as heteroatoms was the subject of discussion in a paper presented by J. Cadogen (Edinburgh University, Great Britain).

The topics covered in the sectional sessions and symposiums were extremely diversified Special symposiums were devoted to natural compounds, mesoionic structures, and medicinal preparations. The specific weight of bench lectures was increased significantly (up to 47%) as compared with previous congresses. As in previous congresses, a great deal of attention in the papers was directed to the development of methods for the synthesis and study of the reactivities of heteroaromatic compounds. However, papers on the syntheses and transformations of saturated heterocycles and the associated problems were represented more extensively in the sixth congress.

A great deal of attention was directed to the development of methods for the preparation of polycyclic heterocycles, particularly polyheterocyclic compounds. An interesting series of studies was presented by I. Lalezari and co-workers (Iran) on the synthesis of polyazasteroids, selenoazasteroids, etc. Heterosteroids and their synthesis was the subject of communications by other authors; for example, P. Katsulokos (Greece) discussed the preparation of thiazolo- and thiadiazolosteroids.

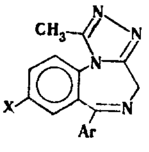
There was also a great deal of interest in the synthesis of new heterocyclic systems. The preparation of such new heterocycles as thieno[3,4-b]indoles, seleno[3,4-b]indoles, etc. (Nafis, Iran) and the synthesis of new systems on the basis of condensation of diphenyltetraaldehydes with phenylenediamine (I. Argant, Israel) were reported.

With respect to methods for the construction of heterocyclic systems, various reactions involving cycloaddition, intramolecular cyclization (for example, the conversion of hetaryl-1, 3-butadienes to 4,5-dihydrobenzo[b]heterocycles by pyrolysis in vacuo, as reported by V. Weber, USA), and intramolecular coupling [for example, the preparation of dithiophene analogs of phenanthrene from cis-1,2-(o-bromothienyl)ethanes by halogen-lithium exchange and subsequent treatment with copper chloride, as reported by S. Gronowicz, Switzerland] have been most widely used. Enamines and enol ethers (in the synthesis of substituted pyridines by the reaction of tert-butylamines with enamines, as reported by M. Komatsu, Japan) and immonium salts in the synthesis of heterocycles have been frequently used.

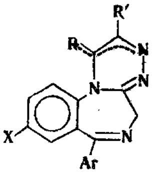
A great deal of attention in the congress was directed to the study of the mechanisms of various transformations and to the development of new general methods of synthesis.

As in previous congresses, applied research — the search for new medicinals, monomers for the polymer industry, photoreagents, insecticides, fungicides, etc. — figured prominently.

Among the sectional papers devoted to the search for new medicinals, one should note the paper by R. Moffet (Upjohn, USA). The author made a systematic study involving the search for psychotropic agents among benzodiazepines, which were the subject of an interesting review plenary paper presented by the same author at the Fifth International Congress on the Chemistry of Heterocyclic Compounds in Ljubljana. At the Sixth Congress R. Moffet reported some new results of research on three-ring benzodiazepines of the V and VI type.



V

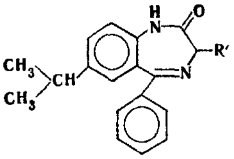


VI

X = Cl, Br; Ar = C_6H_5, o-Cl—C_4H_5, 2-Py

The synthesis of compounds of this type was accomplished from hydrazinobenzodiazepines through the corresponding hydrazones. Compound VI (where R = R' = H, X = Cl, and Ar = o-Cl—C_4H_5), which is twice as active as the well-known Librium, proved to be the most interesting substance. Several hydrazones, which have a more specific action than known preparations, also displayed activity.

M. Zinic (Zagreb University, Yugoslavia) reported some unexpected results; he and his co-workers from the Italian San Giovanni Company searched for new psychotropic preparations in the benzodiazepine series and observed high antiphlogistic activity of compounds with the general formula VII.



VII

R' = methyl, isopropyl, phenyl, and 3-indolylmethyl

It was found that the S form of the compound is more active than the R form.

N. K. Kochetkov discussed the fluorescent labeling of nucleotides based on the reaction of aminopurines and aminopyrimidines with chloroacetaldehyde and related compounds. L. N. Yakhontov set forth the peculiarities of the construction and chemical properties of 1,4-diazabicyclo[2.2.2]octanes, which are 4-aza analogs of quinuclidine compounds. R. M. Lagidze reported the synthesis of macrocyclic arylalkylbisquaternary ammonium salts and bis-(sulfonamido)arylalkyl sulfides. In addition, the following four bench lectures were presented: the synthesis of oxiranes from isoprenoid ethers by L. A. Yanovskaya, the synthesis of furans and pyrroles from dichloro ketones by I. I. Ibragimov, the hydrolysis of heterocyclic compounds in acidic and alkaline media by G. M. Tseitlin, and the tautomerism of substituted pyrimidylmethanes by O. A. Zagulyaeva.

Like the previous congresses, the Sixth International Congress on the Chemistry of Heterocyclic Compounds was a demonstration of the constantly increasing interest in the theoretical and practical problems in the chemistry of heterocycles and the advances and prospects in research in this field of organic chemistry.

The Seventh International Congress on the Chemistry of Heterocyclic Compounds will be held in Florida (USA) in 1979.