FIFTH INTERNATIONAL CONGRESS ON THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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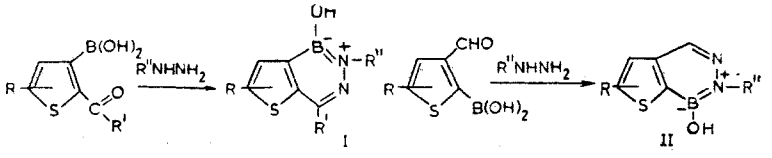
The fifth international congress on the chemistry of heterocyclic compounds was held in Lyublyana (Yugoslavia) from July 13 to 18, 1975. Approximately 600 scientists from 32 countries, including, from the USSR, 18 representatives from Moscow, Novosibirsk, Leningrad, Rostov, Riga, Yerevan, and Tbilisi. Ten plenary papers, which were primarily reviews of the author's own research, were presented at the congress.

N. Cromwell (USA) developed general methods for the synthesis of aziridine derivatives by cyclization of α-bromo-β-amino carbonyl derivatives under the influence of bases (with inversion of the configuration at the asymmetric centers) or by reaction of bromovinyl ketones with amines (under steric control in accordance with Cram's rule) and, in the case of aryl cinnamyl ketones, with O-methylhydroxylamine and subsequent cyclization.

A method based on the reaction of bromomethylchalcones with amines, in which asymmetric induction is responsible for the formation of compounds with trans-oriented 2-aryl and 3-aroyl substituents, was proposed in the azetidine series. Isomeric 2-aroylazetidines are formed by conversion of butyrolactone to α,γ-dibromobutyric acid hydrobromide, Friedel–Crafts acylation, and treatment of the resulting dibromo ketone with primary amines.

In the synthesized ketones the ring protons in the α position relative to the carbonyl group readily undergo deuterium exchange, and epimerization is also facilitated. However, in the azetidine series, in contrast to aziridines, these protons are readily replaced by alkyl groups. In acidic media cis- and trans-aziridinyl ketones readily undergo ring opening, whereas azetidine compounds are stable under these conditions. In contrast to the trans isomers and azetidine derivatives, cis-2-aryl-3-aroylaziridines undergo ring opening on catalytic hydrogenation to give aminocarbinols, whereas under the influence of lithium N-methylanilide they are rearranged through a carbonium ion to 2-amino-3-aryl-1-indenones. Other examples of isomerization or ring expansion were observed when aziridines and azetidines were treated with hydrazines, during photochemical reactions, etc. In contrast to the cis isomers, trans-1-alkyl-2-aryl-3-benzoylaziridines are characterized by considerable temperature changes in their PMR spectra, and this can be used for the solution of stereochemical problems.

S. Gronovic (Sweden) presented a paper on the aromatic boron-containing heterocycles 3,2-borazaropyridines, 2,1-borazarobenzenes, and borepines. The isomeric 4,5- and 7,6-borazarothienopyridines (I and II), for which the interatomic distances and angles are in conformity with aromatic character, were synthesized.



These substances undergo nitration, halogenation, and deuterium exchange at the 3-C atom. However, II can also be nitrated in the 4 position (in acetic anhydride). The desulfuration of I and II with nickel also led to aromatic 4- and 5-ethyl-3,2-borazaropyridines, but these compounds have lower pK_a values and dipole moments than the analogous pyridines, and are resistant to the action of electrophilic reagents in strong acids. Under conditions that restrict protonation of the ring, they are quite readily nitrated (in the 6 position) and halogenated (in the 4 position).

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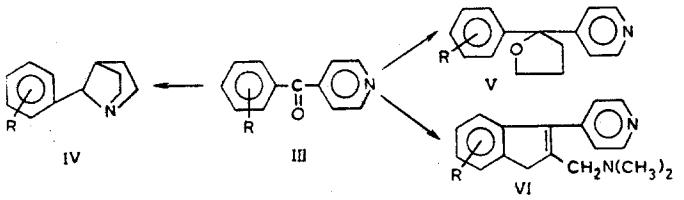
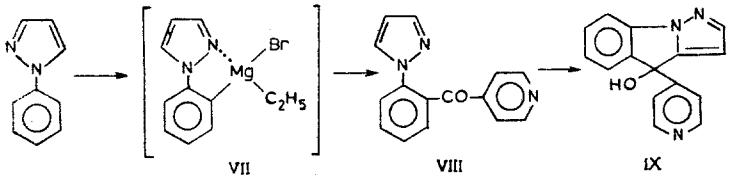
3,2-Borazaropyridines are photochemically converted, with ring contraction, to pyrazole derivatives.

A paper by A. Marxer (Switzerland) was devoted to reactions of organometallic compounds; he obtained 4-benzoylpyridines (III), which he used extensively in various syntheses – for the preparation of 2-aryl-1-azabicyclo[1.2.2]heptanes (IV), substituted 2-(4-pyridyl)-2-aryloxolanes (V), and substituted indanes (VI) – from 4-cyanopyridine and arylmagnesium bromides.

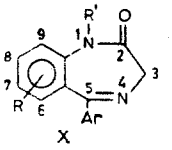


The 5 position of the pyrazole ring undergoes 39% metallation and the ortho position of the phenyl ring undergoes 10% metallation in the reaction of 1-phenylpyrazole with butyllithium; a five-membered complex (VII), which reacts with 4-cyanopyridine to give ketone VIII, is evidently formed with magnesium derivatives. Ketone VIII is capable of metallation with sodium ethoxide in the 5 position of the pyrazole ring to give IX:



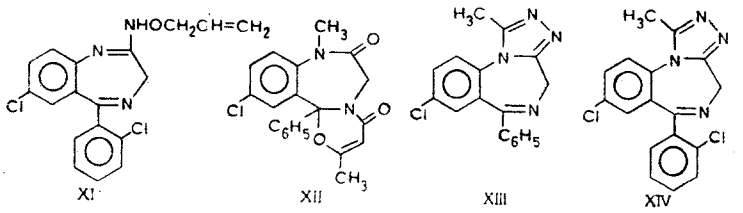
The mechanism of the chemical and photochemical rearrangements of unsaturated amines and the corresponding heterocycles was the subject of a paper presented by A. Latte (France). Problems of the chemical and photochemical heterocyclization of ethyleneamines, allylamines, enamines, and N-aryleneamines were examined. The photochemical rearrangements of olefinic amines proceed more readily with bases, and the chemical prototropic or amino-Claisen rearrangements proceed more readily with protonated amines. The reactions of N-aryleneamines, which, prior to this research, were practically unknown, are of particular interest. A. Latte examined the addition of sulfenes to enamines to give cis and trans isomers of substituted aminothietanes and the photochemical cyclizations of N-aryleneamines to hexahydrocarbazole or indoline derivatives with cis and trans configurations of the substituents in the pyrroline rings.

In a paper by R. Mofett (USA) entitled "New benzodiazepine analogs. Synthesis and effect on the central nervous system," the value of derivatives of this series as medicinal preparations with sedative and soporific action was examined, and the program of the Upjohn Company for modification of the structures of active compounds of the X type was disclosed. Hundreds of substances obtained by the following methods were tested in order to create effective medicinals:



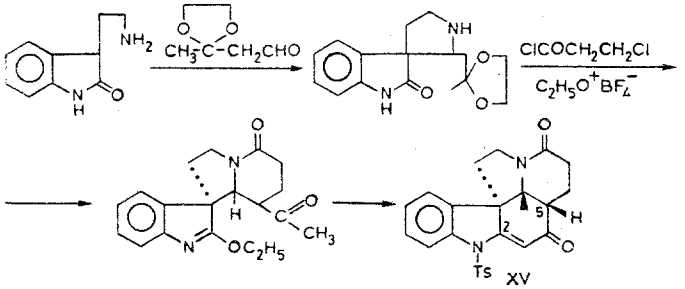
a)modification of the character of substituent R and its position in the benzene ring of the X molecule; b) changing the substituents in the 1 position; c) changing the character of the substituent in the 2 position [specifically, hydroxylamine derivatives, the most active of which was found to be uldazepam (XI), were obtained through the 2-thione; the introduction of a urea or acylhydrazine residue reduces the therapeutic effect or gives a pharmacologically inactive substance]; d) condensation of diazepine at the four free bonds with diverse heterocyclic systems.

The last section of the program proved to be the most interesting one both from a chemical point of view and with respect to the preparation of more reactive compounds. Systems condensed at the 1,2- and 4,5 positions, for which the largest number of diverse oxygen- and nitrogen-containing derivatives with five- and six-membered heterocyclic systems were studied, proved to be the most promising ones. The preparations ketazolam (XII), alprazolam (XIII), and triazolam (XIV) are of interest here. The metabolism of XIII and XIV is now being studied, and the triazole rings are apparently retained during metabolism of these substances.



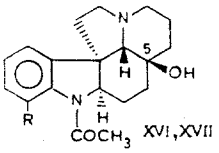
XI XII XIII XIV

Sectional papers were also devoted to research in the benzodiazepine series. Thus S. Vega and co-workers (Spain) synthesized 5-amino- and 5-hydrazino-1,4-benzodiazepines through 5-thiones; U. Golik (Israel) reported the synthesis of 2,4-benzodiazapin-1-one derivatives and their N-oxides, among which highly active substances are found; V. Gomez-Parra and co-workers (Spain) reported the synthesis of thienodiazepines and thienodiazepinotriazoles, and N. Blazevic (Yugoslavia) reported the stereochemistry of the cyclization of haloaklylamino-benzophenones to 1,4-benzodiazepine derivatives. Y Kawada and co-workers (Japan) isolated a new benzodiazepine tranquilizer – estazolam, i.e., 8-chloro-6-phenyl-4H-S-triazolo[4,3-a][1,4]benzodiazepine – compounds with hydroxyl groups in the meta and para positions of the phenyl substituent, attached to C_3 of the benzodiazepine system, and in the triazole portion of the molecule, as well as the N_4 oxide and compounds formed through cleavage of the diazepine ring at the 2,3 and 4,5 bonds.



XV

I. Ban (Japan) in a plenary paper discussed the synthesis of heterocyclic systems, particularly alkaloids of the amidospermine series. Starting from 2-hydroxytryptamine he obtained XV. An angular 5-hydroxy group was then introduced by the action of air oxygen in the presence of sodium tert-butoxide, after which successive hydrogenation with $LiAl_4$ and catalytic hydrogenation gave (±)-deoxyaspidospermine (XVI). (±)-aspidospermine (XVII) and (±)-1-acetylaspidoalbidine were similarly synthesized. Condensation in the 4 position, which makes it possible to achieve conversion to a six-ring system, was investigated.



XVI, XVII

XVI R=H, XVII R=OH

The conditions that Ban found for the periodate oxidation of indole to hydroxyindole and of tetrahydrocarbazole to the 1-keto derivative and the photochemical Hofmann–Löffler reaction, which proceeds under mild conditions, gives the products in high yields, and opens up the possibility for the construction of diverse heterocyclic systems, are of preparative interest.

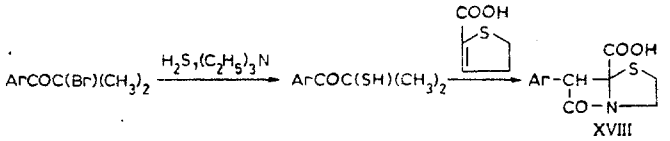
A paper by J. Clark (Great Britain), in which the literature on numerous examples of opening of the pyrimidine ring during nucleophilic attack, reduction, pyrrolysis, photochemical transformations, etc., is analyzed in detail and the types of reactions that occur in this case are correlated, as are the principal pathways of cleavage of the pyrimidine rings with respect to the sites of cleavate of the bonds (when the 1,2, 1,2, and 3,4; 3,4, 1,2, and 2,3; and 4,5, 4,5, and 1,6 bonds are cleaved), was devoted to ring opening, tautomerism, and ionization of pyrimidines and related compounds. According to the speaker's own data, nucleophilic substitution of chlorine in 2-chloro-4-dialkylamino-5-nitropyrimidine proceeds without ring opening, whereas the ring in the isomeric 4-dialkylamino-5-nitro-6-chloropyrimidine is readily opened under the influence of acidic and alkaline catalysts to give 2-nitro-3-amino-3-dialkylaminoacrylonitriles. 4-Alkylamino-5-nitro-6-pyrimidones react similarly. 4-Dialkylamino-6-chloro-5-formylpyrimidines also readily undergo ring opening, but they are simultaneously deformylated to give a cyanoacetamidine. The same opening of the pyrimidine ring also occurs in imidazo- and pyrimidopyrimidines. In the case of 4-alkylarylamino-5-formyl-6-chloropyrimidines the process is accompanied by disproportionation, and 4-methyl-5-nitro-6-acylamino-2,3-dihydroimidazo[1,2-a]-pyrimidines are recyclized to form pyrazole derivatives.

K. Hafner (Federal Republic of Germany) reported new conjugated π-electron systems with nonbenzenoid character: azafulvenes, aza- and polyazaazulenes, azapentalenes, cyclopentapyridazines, etc. The starting compound was pentafulvene, which by successive 2-formylation and condensation with dimethylguanidine is converted to 5,7-diazaazulene and on condensation with dimethylaminoacrolein gives 5-azaazulene. The 5-azaazulenes are stable compounds, whereas their 6-aza analogs are unstable. The 5-aza isomers are protonated, are reduced to perhydro derivatives, form N-oxides, and, in contrast to azulenes, undergo cycloaddition with acetylenedicarboxylic acid esters. The author stated that the changes arising from the introduction of a nitrogen atom in nonbenzenoid aromatic systems are determined primarily by the position of the nitrogen atom.

M. Mihailovic (Yugoslavia) presented a paper entitled "Formation of cyclic ethers from alcohols during intramolecular substitution and addition processes." He examined the methods for the construction of tetrahydrofurans: 1) from saturated compounds (1,4-diols and their mono- and disulfo esters, halohydrins, hydroxy esters, etc.) or by oxidative cyclization of alcohols with activation of the δ-carbon in them with lead tetraacetate, heavy metals, etc.; 2) from unsaturated alcohols by addition reactions with the aid of lead tetraacetate, mineral acids, halogens (sometimes in combination with silver oxide), N-bromosuccinimide, peracids, etc. The reactions based on diols and their mesyl derivatives proceed stereospecifically: cis derivatives are obtained from the meso and erythro compounds, and trans derivatives are obtained from the threo compounds. The oxidative cyclization of saturated alcohols is a nonstereospecific process. Homolytic processes occur during the cyclization of unsaturated alcohols under the influence of oxidizing agents (through the epoxides) or by photochemical means, and the direction of attack depends on the character of the substituents and the stereochemistry is kinetically controlled.

A special symposium, in which 25 papers devoted to the total synthesis of penicillins, cephalosporins, and their analogs by means of various methods for the construction of the β-lactam ring were presented, was devoted to the problem of these and other β-lactams.

A review paper by A. Bose (USA) was devoted to synthetic (including stereospecific) methods for the preparation of β-lactams and their analogs and homologs by special reactions of penams, cephams, and other B-lactam derivatives. In the opinion of the author, one of the convenient methods that lead to the primary formation of cis compounds is the reaction of azidoacetyl chlorides with imino compounds. Condensed β-lactam systems are formed when thiazolines and thiazinines are used, and the ratios of the cis and trans isomers depend on the reaction conditions. A convenient variant of the synthesis of uncondensed β-lactams is the conversion of N-arylbenzoylthioamides to S-alkyl derivatives and subsequent reaction with substituted acetyl halides. Biologically active cis-substituted β-lactams can be obtained after desulfuration with nickel. β-Lactams condensed with azacycloalkanes and having rings of various size – heptams, octams, nonams, and decams – were synthesized via an analogous scheme. Penicillin and cephalosporin analogs (XVIII) were synthesized.



XVIII

Also of interest were communications regarding the asymmetric synthesis of β-lactams through β amino esters developed by Bulgarian chemists (E. Simova, S. Khristoskova, and B. Kurtev), a method, created by the Squibb Company (P. Voitkovsky and co-workers, USA), for the preparation of β-thionolactams, new reagents for the synthesis of functional derivatives of β-lactams and their immonium salts (L. Gosez et al., Belgium), β-lactam derivatives that are potential antagonists of L-asparagine synthetase (E. Moriconi et al., USA), and research on modified cephalosporins with a modified "head portion" of the molecule by introduction of electron-acceptor and electron-donor substituents in the 3 position [H. Peter et al. and R. R. Scartacini et. al (Switzerland), R. Geim et al. (France), and B. Christensen et al. (USA)], etc.

Four sections, in which 180 papers were presented, were in session simultaneously with the symposium mentioned above. In addition, ~60 communications were presented in the so-called "poster sessions," in which no papers were read, but tables and diagrams, through which the authors gave explanations to all who were interested, were displayed (material from ~30 papers was demonstrated in the auditorium in 1 h). This format made it possible to discuss a considerable number of additional studies without overburdening the already extremely saturated sectional sessions.

Most of the sectional papers were devoted to the search for new synthetic methods for the preparation of heterocyclic compounds.

Three major trends appeared distinctly among the papers within the synthetic plan. The first trend involved the study of various methods for closing heterocyclic (primarily nitrogen- and sulfur-containing) systems. Here one should note the paper by G. Fritz and co-workers (Switzerland) on a new synthesis of pyridines from acrylonitrile dimer (α-methyleneglutaronitrile), which is converted to 3-chloromethyl-2-chloroglutarimide and then to 2,6-dichloropyridine with chloromethyl or formyl groups in the 3 position. E. Breuer et al. (Israel) reported the synthesis of condensed trans-aziridine systems in reactions of cyclic nitrones with phosphorus ylids. P. Dubs (Switzerland) reported new syntheses of macrocyclic pyridine-containing systems (muscopyridine isomers) and the preparation of thiazines from acylated α-mercapto ketones and ammonium acetate. One should note the paper by R. Promel (Belgium) on the preparation of tetrazolo- and ditetrazolopyrazines and tetraazathianthrenes from industrially accessible 2,3-dichloropyrazine, the paper by G. Newcomb and co-workers (USA) on the synthesis of pyridine-containing macrocyclic compounds that have a crown effect, and the paper by F. Boberg (Federal Republich of Germany) on the preparation of pyrroles from α-nitro olefins. A series of papers [by G. Gringel (Austria), B. Zwanenburg (the Netherlands), K. Akiba (Japan), K. Groe (Federal Republic of Germany), C. Bradsher (USA), G. Desimoni (Italy), etc.] were devoted to the synthesis of heterocylic systems on the basis of cycloaddition reactions and to the study of the mechanisms of these processes.

The second trend involves the interconversions of heterocycles – ring opening and the closing of new heterocyclic systems. Of the works in this area, one should note the research of the G. van der Plas school (Holland) on the mechanism of the conversion of pyrimidine derivatives to compounds of the pyridine series (labeled carbon and nitrogen atoms were used), as well as the research of L. Townsend (USA) on the thermal conversion of azidopyrimidines to substituted triazoles. R. Abramovitch (USA) showed that the thermolysis of 2-azidopyridine N-oxide in an aprotic solvent gives 2-cyano-1-hydroxypyrrole in 90% yield. 2-Cyanopyrrole and 3-methoxy-2-pyrrolone are formed in the presence of nucleophilic solvents. 2-Azidopyrazine N-oxides undergo rearrangement to give the corresponding N-hydroxyimidazoles, and pyridazine compounds are converted to substituted dicyanoethylenes.

The third trend includes various transformations of compounds without changes in the heterocyclic ring. Diverse nucleophilic substitution processes constitute a weighty portion of such transformations. T. Higishino (Japan) found that quinazoline and a number of other azines react in dimethyl sulfoxide (DMSO) with aromatic aldehydes and cyanide ions to give aryl(4-quinazolyl)carbinol, aryl 4-quinazolyl ketone, and 4,4'-diquinazolyl. Interesting nucleophilic substitution reactions were observed by H. Feuer and co-workers (USA) in the case of isopropylpyridines substituted at the tertiary carbon of the side chain. The problems of nucleophilic substitution of halogens in naphthyridines were examined in a paper by V. Chuba (Poland) and a different pathway for processes involving the replacement of amino and methylsulfanil groups in azines under the influence of "soft" and "hard" nucleophilic reagents was examined in a communication by G. Broadbent (USA).

Among the papers devoted to the fundamental problems of the chemistry of heterocycles, one should note the communication by M. Reinecke (USA) whe obtained data on the possibility of the existence of five-membered hetarynes, which are intermediates in the thermolysis of heterocyclic anhydrides. An interesting paper by K. Potts (USA) dealt with nonclassical heterocycles with tetravalent sulfur and an angular nitrogen atom – 3-phenylthiazolo[3,4-b]indazole-1-carboxylic acid esters.

A number of papers were devoted to the problems of the photochemistry of heterocycles. G. Strait (France) reported the photochemical conversion of pyridine N-oxides to 2-formylpyrroles (this transformation was discovered and studied by O. Buchardt in Denmark) and the unexpected effect on this process of the addition of copper salts, which raise the yields considerably. The photochemical reactions of halopyridines in liquid ammonia, which give amino compounds in the case of bromo derivatives and dehalogenated compounds in the case of the chloro derivatives, were the subject of a study by G. van der Plas (Holland). The photosyntheses of new heterocyclic systems were examined in a paper by J. Bradshaw (USA), and the reductive photocyclizations of benzofurans and their analogs were examined in a paper by A. Lablache-Combier (France).

A great deal of attention in the congress was directed to the problems of stereochemistry, conformational analysis, and stereospecific synthesis. I. Takeugi and co-workers (Japan) examined the stereodynamics of the two nitrogen centers in bicyclic hydrazines and bicyclic urethanes by means of C^{13} NMR spectroscopy. J. Fischer and co-workers (Hungary) made a PMR spectroscopic study of the cis-trans isomerism and conformation of eight-membered heterocycles in dibenzo[d,g][1,3]dioxacines and dibenzo[d,g][1,3,6]dioxathiocines. P. Klaus (Austria) discussed the stereospecific rearrangement of thian- and 1,3-dithian-1N-arylimides to give 2-(o-aminophenyl)thians of 1,3-dithians with migration of a phenyl residue from the equatorial position to the axial positions and vice versa. I. Pozharliev (Bulgaria) devoted his paper to the conformational analysis of phenyl-substituted 2-oxotetrahydrooxazines and 2-oxo- and 2,4-dioxohexahydropyrimidines, and M. Gaimova

(Bulgaria) discussed the stereoselective synthesis of 3,4-dihydro-1(2H)-isoquinolones in the reactions of homophthalic anhydrides with azomethines. The interesting problem of the use of the tetraphenylborate anion as a shift reagent in the PMR spectra of heterocyclic onium cations was examined in a paper by H. Schimenz (Federal Republic of Germany).

A high percentage of the papers presented at the congress was devoted to the search for new physiologically active compounds and the synthesis and modification of natural biologically active substances. Methods for the synthesis of modified nucleosides were examined in a series of communication. A. Deino and co-workers (France) presented a paper on a general method for the preparation of the difficult-to-obtain 1-D-ribofuranosylpurines from 4-carbethoxy-5-aminoimidazoles, and R. Schmidt and co-workers (Federal Republic of Germany) reported a method for the preparation of allopurinol riboside and the furanosides of other pyrazole derivatives, which consists in the reaction of a protected ribose (or other furanose) with hydrazine and subsequent construction of a heterocyclic system. This method makes it possible to obtain nucleosides selectively with a β-glycofuranoside residue in one step from hydrazinoribose. The synthesis of C-nucleosides of a number of sym-trazolo[3,4-a]pyrimidines and their transformations, which led to the preparation of the aza analog of the antibiotic formicin, were the subject of a communication by the Yugoslavian scientists G. Kobe, M. Japel, et al., who are doing research to find antivirus agents. U. Pundit and co-workers (the Netherlands) reported an interesting possibility for the modification of pyrimidine nucleosides, having demonstrated that the products of the addition of dihalocarbenes to 1,3-dibenzyluracils are capable, with ring expansion, of undergoing conversion to 1,3-diazepine derivatives.

I. Monkowicz (USA) presented a paper on the synthesis and pharmacological study, as analgetics and narcotic antagonists with prolonged activity, of nitrogen-"weighted" 9-hydroxybenzomorphan derivatives and C-oxomorphinans, and A. Kreuzberger (Berlin) presented a paper on the high antiphlogistic activity of 1-(3,4,5-trimethoxybenzoyl)-benzotriazole. Considerable interest was generated by a paper by T. Kametani (Japan) on the total synthesis of the alkaloid mappicine, research by the French scientists G. Finet and co-workers on the total synthesis of analogs of the alkaloid emetine in a series of C_1-alkylated bisnoremetines, and the research of S. Sarel and E. Dieckmann (Israel) on transition from tropine systems to scopolamine systems by oxidation of N-carbethoxynortropine with lead tetraacetate in the presence of iodine to the 3,6-dioxide and reduction of the latter to the $\Delta^{6,7}$-dehydro derivative of tropine with lithium aluminum hydride.

Soviet scientists presented seven papers at the congress. V. P. Mamaev discussed his research, accomplished jointly with O. P. Shkurko, on the transmission of electronic effects of substituents in the pyrimidine ring, and S. A. Vartanyan discussed new methods for the synthesis of aldehydes of six-membered oxygen-, sulfur-, and nitrogen-containing heterocycles by dehydration of 4-hydroxy-4-alkoxymethyl derivatives of piperidine, tetrahydropyran, and tetrahydrothiopyran, and also by formylation of the corresponding 4-oxo derivatives in the 3 position by the Claisen reaction. A paper by L. N. Yakhontov was devoted to the peculiarities of the conformation of quinuclidine compounds that are associated with the rigidly fixed structure of the quinuclidine ring and the character of the symmetry of the molecules. A. F. Bekhli presented a paper on the synthesis of 2,3-dihydrobenzo[h][1,6]naphthyridine-4(1H)-ones and the preparation of new heterocyclic systems with a naphthyridine ring. L. I. Belen'kii presented a paper on the stability of thiophenium ions and some transformations of 2,5-bis(alkylmercapto)thiophenes under the influence of protic acids, which lead to elimination of the alkylmercapto groups and conversion of the 2,5 isomers to the 2,4 derivatives. V. M. Shostakovskii reported the reaction of furan derivatives with carbenes. M. V. Mavrov reported the syntheses of acetylenic derivatives of piperazine from 4-(2-hydroxyethylamino)-1,2-butadienyl bromide or bis(4-bromo-2,3-butadienyl) alkylamines. A paper by R. M. Lagidze devoted to the aralkyl analogs of tetrahydronorgamane was presented in the "poster session" of the congress.

The director of the Soviet delegation, Corresponding Member of the Academy of Sciences of the USSR V. P. Mamaev, presided at one of the plenary sessions.

The next (sixth) congress on the chemistry of heterocycles is scheduled to be held in 1977 in Teheran (Iran) with Professor I. Lalezari as president of the organizing committee.