INTERNATIONAL SYMPOSIUM ON LOW-MOLECULAR-WEIGHT SULFUR-CONTAINING NATURAL COMPOUNDS

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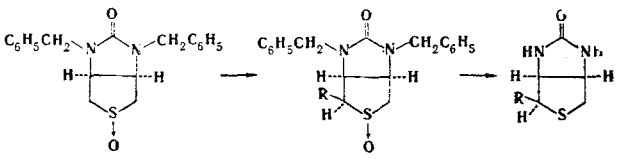
The Second International Symposium on Low-Molecular-Weight Natural Compounds Containing Sulfur was held from July 6 to 10, 1976, in the small town of Jablonna (near Warsaw). The symposium was organized by the Polish Academy of Sciences and the chemistry department of Warsaw University with the support of the chemistry section of IUPAC. Approximately 40 Polish scientists and 40 scientists from other countries participated in the work of the symposium. Nine plenary papers and 13 sectional papers were presented. The plenary papers included both general reviews of several problems and reviews of the research of individual authors in narrower areas.

The first plenary paper was presented by Professor A. Kjaer (Denmark) and consisted of a review of the state of the research on low-molecular-weight sulfur compounds that play an important role in the vital activity of plant and animal cells. The author gave a brief characterization of sulfides, thioglucosides, amino acids, and terpenoids, as well their sources, transformations, and possible biological significance.

Sulfur-containing antibiotics were the subject of a long paper by Professor N. N. Lomakina (USSR). The enormous significance of sulfur-containing antibiotics – penicillins and cephalosporins – for public health and the importance of research aimed at the preparation of semisynthetic penicillins and cephalosporins by chemical modification of their molecules were emphasized in the paper. This approach has been used to obtain extremely effective preparations, some of the properties of which surpass those of natural compounds (resistance to the action of enzymes, breadth of the antibacterial spectrum, duration of activity, etc.). Antibiotics with a peptide structure containing cysteine and its analogs have not found application in medicine but may be used in other areas, particularly in the food industry and in plant growing. Also examined were antibiotics of the quinoxaline group that have peptide character and contain sulfur in the N-methyl-L-cysteine residue (echinomycins, quinomycins, triostins, etc.), as well as the antibiotics lincomycin and celesticetin, which contain the groupings of thioglycosides of 6-aminodidesoxyoctose, and data on the biogenesis of sulfur-containing antibiotics by microorganisms were presented.

A communication by A. Marcoue (France) was devoted to some aspects of the chemistry of biotin and its analogs. In the course of the last few years the chemistry of biotin has again undergone substantial development owing to the significance of this compound as a coenzyme of carboxylase, which catalyzes some fundamental metabolic processes. The authors reported a new stereospecific synthesis of biotin based on the stereoselective alkylation of the corresponding sulfoxide I and subsequent reduction of alkylation product II:



I II

R = t-BuOOC(CH2)4

This synthetic pathway makes it possible to obtain biotin analogs. The author was the first to synthesize selenobiotin. Data on the mechanism of the participation of biotin and of some of its analogs in some exchange reactions are presented in the paper.

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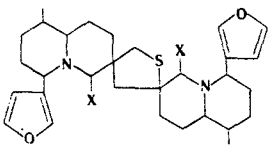
R. T. Lalond (USA) presented a paper on some properties of sulfur-containing C_{15}-C_{30} alkaloids of water lilies in which principal attention was directed to thiaspiran alkaloids of the III type:



III

The spectral properties of these systems as applied to the establishment of the structures of the thiaspirans, the configurations at the nodal atoms, and the stereochemistry of the fusion in the quinolizidine fragment were discussed briefly. Data on ways to approach the synthesis of simplified analogs of the thiaspirans and on their antibiotic activity were also presented.

Professor Oae (Japan) presented a review paper on his research on the oxidation of some biologically active systems and their simplified analogs that include a disulfide grouping.

Two long papers devoted to the chemical properties and metabolism of S-adenosylmethionine and similar sulfur-containing natural compounds were presented by the Italian scientists F. Salvatore. V. Zappina, and F. Zimino. They accomplished the synthesis of some structural analogs of S-adenosylmethionine – the key intermediate in some metabolic processes in various cells – and investigated their ability to undergo transmethylation, which makes it possible to identify the site of bonding of a sulfonium compound with enzymes that participate in the transfer of a methyl group. The complex regulatory role of these compounds in metabolism was discussed.

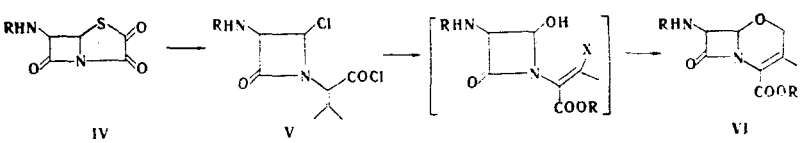
A review by U. Schmidt (Austrilia) was devoted to the synthesis and interconversions of mercaptoamino and dehydroamino acids that are components of natural peptides and metabolites. A scheme was proposed for the transformations, and a biologically similar model for the reactions that occur was developed.

The chemistry of glucosinolates – derivatives of sugars that have sulfur-containing functional groupings was examined in a communication by M. Benn (Canada). Various pathways for the transformations of the $-SC(R)=NOSO_3^-$ grouping under the influence of various reagents without involvement of the carbohydrate fragment were discussed. The possible metabolic pathways of compounds of this sort were examined.

M. Mikolajczik and J. Luczak presented a communication on the oxidation by dimethyl sulfoxide (DMSO) of some fragments of nucleic acids containing a thiocarbonyl group. They also presented the results of the synthesis and oxidation of thiodiribonucleotides with DMSO.

Studies devoted to the modification of antibiotics containing a system of condensed β-lactam and sulfur-containing heterocycles, i.e., penicillins and cephalosporins, were of great interest. The increase in the interest in these transformations is due to the attempts to find structures that have higher antibiotic activity and also to the study of the possible transformations of these compounds in organisms. Extensive research has been devoted to methods for the incorporation of substituents in both the β-lactam and thiazolidine or thiazine ring of penicillins and cephalosporins, respectively. In a number of cases antibiotics that have definite selectivity and activity that surpass the selectivity and activity observed in the native products have been obtained by these methods. A correlation of a considerable number of studies in this area has recently been published by Hungarian researchers [J. C. Jaszberenyi, Progr. Med. Chem, 12, 395 (1975)].

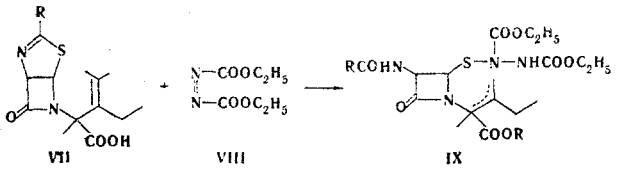
The trend of modification of penicillins and cephalosporins, which consists in replacement of the sulfur atom in the thiazolidine or thiazine ring, respectively, by other heteroatoms (for example, N, O, or P), is interesting. These studies were correlated in a paper by S. Wolf (Canada). The method for the synthesis of these compounds consists in opening of the thiazolidine ring of penicillin-structure (IV) with simultaneous elimination of the sulfur atom and subsequent transformations of β-lactem V, which are accomplished by closing of the condensed (with it) heteroring containing a heteroatom other than sulfur, particularly an oxygen atom:



IV V VI

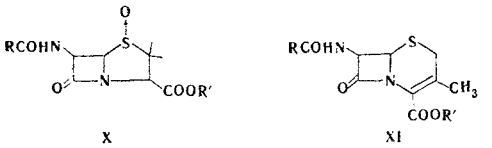
The resulting oxygen analog (VI) of cephalosporin has the same activity as the natural product but is considerably less toxic.

Another method for the modification of penicillins was set forth by G. Franceschi (Italy). It consists in cleavage of thiazoline-β-lactam structure VII by azo compound VIII and subsequent closing of the resulting thiohydrazoazetidinones IX to a cephalosporin structure:



VII VIII IX

A different method for the conversion of a penicillin structure to the cephalosporin structure was proposed by Polish scientists (J. Mikolajczik, M. Domoradcki, J. Kazimirczak, and J. Gislak), who investigated the effect of protic acids, uronium and thiuronium salts, and amino acids, picric acid salts, and pyridine derivatives on the rearrangement of penicillin-1-oxides X to the corresponding 3-desacetoxy-Δ^3-cephalosporins XI:



X XI

A communication by I. Jaszberenyi, E. Gunda, and R. Bognar (Hungary), who studied the possibility of the conversion of the penicillin structure to the cephalosporin structure as a function of the oxidation state of the sulfur atom in the thiazolidine portion of the molecule, was devoted to similar studies. These studies were summarized in part in the above-mentioned review of these authors.

In conclusion it should be stated that it is impossible in a brief communication to report on all of the papers presented, despite the fact that all of them without exception were sufficiently interesting and timely. One should also note the high scientific and organizational level at which the symposium was conducted and its undoubted value for the mutual exchange of information among the scientists of various countries engaged in research in this area.

Additional information can be obtained somewhat later, since all of the plenary papers will be published in the Journal of Pure and Applied Chemistry.