70TH BIRTHDAY OF MIKHAIL VASIL'EVICH RUBTSOV (1906-1976)

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November 19, 1976, will mark the 70th birthday of one of the outstanding scientists and organizers of pharmaceutical-chemical science and industry in our country, Mikhail Vasil'evich Rubtsov.

Professor Rubtsov worked for more than 36 yr in the All-Union Scientific-Research Pharmaceutical-Chemistry Institute, and in his last 15 yr there was the director of the institute and did a great deal of research on the development of the pharmaceutical-chemistry industry and the science of medicinals. He was one of the initiators of the coordination of scientific research in this area on a nationwide scale and did a great deal to expand contacts with foreign scientists and to raise the international prestige of Soviet pharmaceutical-chemical science.

In his scientific activities Professor Rubtsov knew how to combine thorough theoretical studies with the solution of important scientific-practical problems. The synthetic studies in the area of nitrogen-containing substances carried out in his laboratory led to the creation of new branches in the chemistry of heterocyclic compounds, to the development of methods for the synthesis of new or little-studied classes oc chemical substances (isomers and analogs of quinine alkaloids, aza- and diazabicycloalkanes, dialkylaminoalkylaminostyryl-quinolines, etc.), to the creation of practicable methods for their synthesis, and to the elucidation of the relationship between structure and biological activity.

Professor Rubtsov and O. Yu. Magidson were the first in the Soviet Union to undertake in 1935 a systematic study of sulfamide compounds; this study served as a basis for the creation in our country of the heavy-tonnage production of these important medicinal preparations. The development in the 1930's of an industrial synthesis of naganin was of great economic significance. The 15-step synthesis of this preparation, which was unusually complex for that time and was introduced in the Akrikhin plant, is used even today in its manufacture.

Another trend of the research of Professor Rubtsov involved the search for chemotherapeutic preparations in the aminoquinoline series. In the course of this research he created a practicable method for the synthesis of 6-methoxy-4-chloroquinoline from p-anisidine through 2-carbethoxy-4-hydroxy-6-methoxyquinoline and 4-hydroxy-6-methoxyquinoline and established that the specific character of the antimalarial activity is determined by the position of the amino group in the quinoline ring. In contrast to 8-aminoquinolines, which display gamotropic activity, quinoline compounds with an amino group shifted to the 4 position were found to be complete analogs of quinine with respect to their toxicity and the character of their chemotherapeutic effect, i.e., they had schizogropic activity.

Subsequent studies of 4-amino-2-styrylquinolines enabled Professor Rubtsov to find a new type of medicinal with a broad spectrum of chemotherapeutic activity. Compounds of this group displayed, in addition to considerable antimalarial activity, high effectiveness in the treatment of protozoa infections, arrested the growth of tuberculosis microbacteria in cultures higher than 1 : 500,000,000, and displayed high antivirus and antiphlogistic activity. Of this group of compounds, trikhomonatsid (a substance for the treatment of trichomoniasis) and aminoquinol (an antilambliasis preparation) have found practical application and even today are being produced by the pharmaceutical-chemical industry.

Professor Rubtsov's research in the field of alkamine esters of diphenylacetic, diphenylpropionic, and benzilic acids has made it possible to obtain original spasmolytic and cholinolytic agents and preparations with an antitussive and analgesic effect that have found practical application (aprophen, diprophen, metatsin, estotsin, etc.).

The research of Prefessor Rubtsov and co-workers on the synthesis and study of isomers and analogs of quinine alkaloids is of considerable interest. They were the first to realize the production, by a synthetic

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method, of a considerable number of isomers and analogs of hydroquinine on the basis of a general scheme through the corresponding hydroquinotoxins and hydroquininones. The study of the individual optically active stereoisomers and diastereoisomeric racemates of the synthesized compounds made it possible to establish that the position of the quinuclidylcarbinol residue in the heteroaromatic (6-methoxyquinoline or pyridine) ring is of decisive significance for their chemotherapeutic activity. The elucidation of the relationship between the structure and antimalarial activity in this series of compounds led to the synthesis of a new highly active quinine analog, (5-ethyl-2-quinuclidyl)(4-pyridyl)carbinol, the therapeutic effectiveness of which is close to that of natural quinine alkaloids. A large number of previously unknown or little-studied pyridine and piperidine derivatives were investigated during the search for efficient methods for the synthesis of quinine and quinine-like substances, and new and unusual types of transformations of these compounds were uncovered. The research in this area ended with the creation of an original method for the synthesis of the ethyl ester of racemic N-acetylhomomeroquinene.

The methods for the synthesis of quinuclidine and other 1-azabicycloalkanes developed by Professor Rubtsov and his school, with which all modern advances in this field of the chemistry of heterocyclic compounds are intimately associated, are of great significance. Broad possibilities for further studies were uncovered by the development of practicable methods for the preparation of key substances – quinuclidine-2-carboxylic acid, 3-quinuclidone, as well as various 2-, 3-, and 4-monosubstituted quinuclidines and quinuclidine derivatives with various substituents in the 2,3, 2,5, 2,6, etc., positions. As an example, one may cite the classical synthesis of quinuclidine-2-carboxylic acid by Professor Rubtsov and M. I. Dorokhova.

Professor Rubtsov and his co-workers made systematic studies of a series of other 1-aza- and 1,2-diaza-bicyclic systems and, in particular, of a series of isomeric (with respect to quinuclidine) 1-azabicyclo[3.2.1]-octanes. 3,9-Biazabicyclo[3.3.1]nonanes and other analogous saturated heterocyclic systems were studied. In the course of these studies new medicinal preparations – ganglion blockers (temekhin, dicolin, and dimekolin), a parasympatomimetic (aceclidine), a hypotensive and tranquilizer (oxylidine), a myelo relaxant (kvalidil), etc. – which have been incorporated in the medicinal industry, were created.

The research of Professor Rubtsov and co-workers on the creation and incorporation in industry of an original and technologically simple method for the preparation of isonicotinic acid, which ensured the rapid development in our country of heavy-tonnage production of a series of antituberculous preparations (isoniazid), ftivazid, metazid, saluzid, etc.), was of great practical value. This method has been used by industry for more than two decades. Further studies of the complex utilization of the β-picoline fraction made it possible to develop and incorporate in industry, in addition to the preparation of isonicotinic acid and its derivatives from γ-picoline, the conversion of β-picoline to nicotinic acid and subsequently to medicinal preparations – niketha-mide (a substance with a cardiovascular effect) and nikodin (a substance for the treatment of diseases of the bile tracts) and the production from 2,6-lutidine of the ganglion blockers dicolin and dimekolin, as well as the antisclerotic preparation parmidin (anginin).

The theoretical studies of Professor Rubtsov and his school led to the development of a number of new reactions in the chemistry of heterocyclic compounds. Included among these were the unusual transformations of β-arylaminoacrylic esters, which made it possible to create an original scheme for the preparation of N-aryl-3-pyridone-4-carboxylic acids by reaction of arylamines with hydroxymethyleneacetic ester, subsequent conversion of the resulting arylaminomethyleneacetic esters by heating to N-bis(carbethoxyvinyl) arylamine, and their cyclization with splitting out of water.

The closing of a pyrrolopiperidine system by Hofmann cleavage of 3-(β-dimethylaminoethyl)-1-acetyl-piperidine methylchloride led to the discovery of a new method for the construction of 1-azabicyclic compounds. New bicyclic dihydropyranopyridine systems were obtained by saponification of 3-(β-hydroxyethyl)-4-(γ,γ,γ-trichloro-β-hydroxypropyl)pyridine with alcoholic alkali and by condensation of 3-(β-acetoxyethyl)-4-methyl-pyridine with dihydroxymalonic ester and subsequent saponification and decarboxylation. The closing of a pyrroline ring in the reaction of α- (and γ) -chloro-β-chloro(hydroxy,methoxy)ethylpyridine and pyrimidines with primary and secondary amines opened up the possibility for extensive research in the aza- and diazaindole series.

The development of practicable methods for the synthesis of diverse azabicyclic systems and the study of the reactions of these compounds made it possible to subsequently ascertain the peculiarities of the quinuclidine nitrogen atom as compared with the nitrogen atoms of other isomeric and homologous 1-azabicycloalkanes, as well as those with nitrogen atoms of aliphatic and monocyclic compounds, and to determine the characteristic chemical and biological properties of quinuclidine derivatives.

Methods developed by Professor Rubtsov and co-workers for the incorporation of vinyl groups in piperidine and quinuclidine rings, for the study of allyl, acetylene-allene, Beckmann, and pinacole rearrangements in a number of azabicyclic systems and Hofmann cleavage of unsymmetrical 1-azabicyclic quaternary bases are of considerable theoretical interest.

The search for new synthetic methods, the use of novel methods of investigation, and high experimental mastery and a creative approach to the solution of problems were always characteristic of Professor Rubtsov. As a result of many years of research by Professor Rubtsov and his co-workers more than 200 scientific papers were published, and 12 original effective medicinal preparations were created and incorporated in medical practice.

Professor Rubtsov was not only a great scientist, organizer, and talented researcher, he was also an excellent teacher and a sensitive and sympathetic human being.

LIST OF THE MOST IMPORTANT SCIENTIFIC RESEARCH OF M. V. RUBTSOV

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