SYNTHESIS OF HETEROCYCLIC MEDICINAL AGENTS AT THE INSTITUTE OF ORGANIC SYNTHESIS OF THE ACADEMY OF SCIENCES OF THE LATVIAN SSR* (REVIEW)

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UDC 547:615(047)

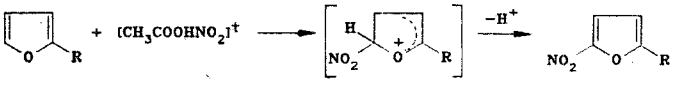
The following report reviews the contributions of the Institute of Organic Synthesis of the Academy of Sciences of the Latvian SSR in the area of the chemistry of heterocyclic compounds of medicinal value. The mechanisms of biological activity of these compounds, as well as their potential clinical applications, are discussed.

Founded in 1957 under the guidance and leadership of Academician S. A. Giller, The Institute of Organic Synthesis of the Academy of Sciences of the Latvian SSR initiated studies in the area of organic synthesis of compounds of medicinal and agricultural importance.

The academic interests of S. A. Giller were focused primarily on the synthesis and utilization of nitrogen-, oxygen-, and sulfur-containing heterocycles. He emphasized the practical importance of chemical compounds synthesized by himself and his students, and dedicated his research to the search for new physiologically active compounds. S. A. Giller was without question the founder of a new school of organic chemistry in Latvia, namely, the synthesis of physiologically active compounds.

S. A. Giller began his independent research in the area of oxygen-containing heterocycles, and, in particular, with the study of the chemistry of furan. He was to dedicate 25 years of work to the preparation of medicinally valuable compounds derived from 5-nitrofuran. His erudition in the fields of medicinal chemistry, pharmacology, and other diverse areas of medicine enabled S. A. Giller to postulate that nitrofurans consitituted a new class of antibacterial agents whose mechanism of action differed fundamentally from that of antibiotics and sulfamides [3].

In 1948 S. A. Giller and É. Yu. Gudrinets developed a method for the synthesis of 5-nitro-2-furfurylidenesemicarbazone (this compound was given the name furacillin† in the USSR); his expert discharge of its production was carried out at the Riga Chemical and Pharmaceutical Facility No. 3 [4, 5]. Giller studied the nitration of furan and its derivatives (for example, furfural) in acetic and anhydrous nitric acid in detail, and demonstrated that strong mineral acids exerted a catalytic effect on the formation of nitrofurans. S. A. Giller was the first to propose that the nitrating agent in this reaction was the nitronium ion, and that the catalytic effect of acids such as sulfuric acid was due to an increase in the concentration of the nitronium ion [6]. Subsequent investigations with K. Venter, completed after the death of S. A. Giller, indicated that other highly active intermediates, such as protonated acetyl nitrate, could also serve as nitrating agents, and that the adducts of the reaction of the starting materials with acetyl nitrate were 2-acetoxy-5-nitro-2,5-dihydrofuran and 4-acetoxy-5-nitro-4,5-dihydrofuran derivatives [7-9].



*Research advances realized at the Institute of Organic Synthesis of the Academy of Sciences of the Latvian SSR in the preparation of drugs based on derivatives of aromatic and metalloorganic compounds, peptides, and prostaglandins are reported in the collections [1, 2], which also contain more detailed information concerning drugs with heterocyclic structures.

†See note p. 9.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 5-17, January, 1985. Original article submitted August 1, 1984.

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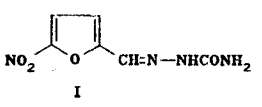
This work has shown that the nitration of furans with acetyl nitrate does not differ significantly from the nitration of other aromatic compounds. The primary difference results from the fact that the heteroatom in the furan ring increases the electron density at the α- and α'-carbon atoms, which substantially increases the nucleophilicity of the heteroaromatic ring and explains the ease of adduct formation as well as the relative stability of the adducts compared to aromatic compounds.

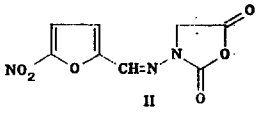
The study of the chemistry of nitrofurans formed the scientific basis for the synthetic and technological development of new medicinal agents in the nitrofuran series. Several authors under the leadership of S. A. Giller developed a safe and reliable new method for the production of 5-nitrofurfuraldiacetate, a key intermediate in the synthesis of chemotherapeutic nitrofuran derivatives [10]. The most important aspect of this method is that the nitration phase is carried out by the simultaneous and exactly proportional addition of furfural and a mixture of fuming nitric and concentrated sulfuric acids to acetic anhydride under very precise temperature control. This new technology for the production of 5-nitrofurfuraldiacetate has been adopted by the chemical and pharmaceutical industry.

5-Nitrofurfuraldiacetate is used in the preparation of a wide range of nitrofuran drugs. The most important of these, as mentioned above, is furacillin, 5-nitrofurfural semicarbazone (I). Furacillin is an antibacterial agent which is effective against a variety of gram-positive and gram-negative bacteria (stephylococcus, streptococcus, dysentery bacillus, *Escherichia coli*, paratyphoid bacillus, the gaseous gangrene agent, and others). The compound is applied both externally, for the prevention and control of festering inflammatory reactions, and also internally, for the treatment of bacterial dysentery [5].

Furadonin (II) is obtained via the condensation of 5-nitrofurfuraldiacetate with aminohydantoin:



I

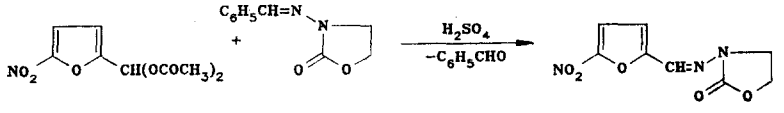


II

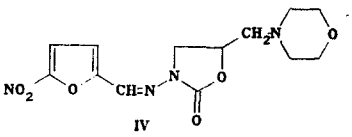
Furadonin is likewise active against gram-positive and gram-negative bacteria. The compound is effective in the treatment of urinary tract infections.

The synthesis of furazolidone, 3-(5-nitro-2-furfurylideneamino)-2-oxazolidone (III), is currently realized on a large scale [10]. The compound 3-(benzylideneamino)-2-oxazolidone, obtained according to the following scheme, is an intermediate in its production:

The transamination of 3-(benzylideneamino)-2-oxazolidone to give 3-(5-nitro-2-furfurylideneamino)-2-oxazolidone is carried out in sulfuric acid using 5-nitrofurfuryldiacetate:



III

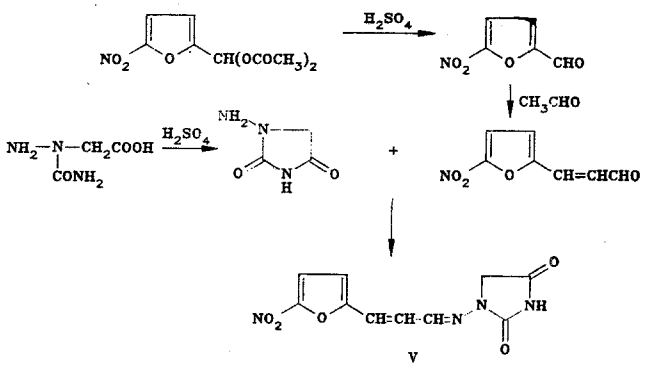


IV

Furazolidone is more active against gram-negative bacteria than either furacillin or furadonin, and it is also much less toxic. One of the most positive features of furazolidone is that microorganisms are much less likely to develop resistance to it. It is effective against a series of microbes which are resistant to both antibiotics and sulfanilamides. In addition, the compound is also active against Trichomonas [12]. As a result, furazolidone is widely used to treat dysentery, salmonella poisoning, and trichomonas infections. Furazolidone is also widely used in veterinary practice as a feed additive to suppress infections and as a biostimulant in animal husbandry.

The synthesis of furazolin, 5-morpholinomethyl-3-(5-nitro-2-furfurylideneamino)-2-oxazolidone (IV), is accomplished in an analogous manner. Furazolin is used to treat infections induced by both gram-positive and gram-negative bacteria such as staphylococcus, streptococcus, and pneumococcus, as well as in the treatment of infected cuts, erysipelas, pneumonia, meningitis, osteomyelitis, and septicemia, among others; it is also used to treat mixed infections caused by staphylococci in collaboration with either streptococci or pneumococci.

Another original antibacterial drug synthesized via the intermediacy of 5-nitrofurfuryldiacetate is furagin, 1-[3-(5-nitro-2-furyl)allylideneamino]hydantoin (V), which is widely used in medical practice; the technology for its synthesis was developed industrially. The methodology for the synthesis of furagin embraces several steps [13]. 5-Nitrofurfuryldiacetate is first hydrolyzed with sulfuric acid to give 5-nitrofurfural, which is then condensed with acetaldehyde to give β-(5-nitro-2-furyl)acrolein [14, 15]. The latter compound is finally condensed with 1-aminohydantoin to form the desired product.



V

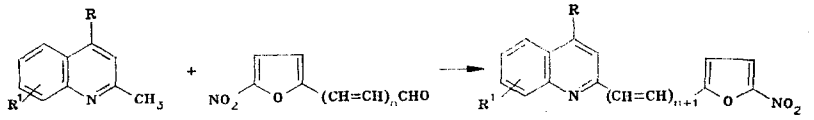
All of the above-mentioned drugs belonging to the nitrofuran series are only sparingly soluble in water; as a result, S. A. Giller and co-workers developed a water soluble derivative of furagin, namely, its potassium salt (solafur) [16].

A large variety of other novel nitrofuran derivatives have been synthesized and studied, and slowly their antimicrobial activity against gram-positive and gram-negative bacteria has been investigated. The application of these drugs against microbes which are resistant to other classes of antibiotics is of special importance; the cross resistance to these drugs has been investigated, and chemotherapeutic factors for their activity against a variety of different types of bacterial infections have been determined [7]. The influence of these nitrofuran drugs on the immunological reactions of warm-blooded organisms has also been studied, and the synergistic effects involved in the use of nitrofurans together with antibiotics or other antibacterial agents have been evaluated [18]. As a result of these investigations, those nitrofuran drugs which have successfully withstood the test of time and emerged as the best of the series are still widely used in medical and veterinary practice.

The drugs furagin and solafur possess especially valuable therapeutic properties and stand out because of their particularly effective antibacterial activity against infectious agents during surgery, in the treatment of infectious diseases of the gastrointestinal tract, and in ophthalmology and urology. They are also superior to other synthetic drugs and many antibiotics in their level of toxicity and their transport properties. These compounds are also noteworthy for their activity against many classes of bacteria, including resistant staphylococcus strains, which are resistant to antibiotics. Microorganisms develop resistance to furagin and solafur only very slowly [19].

In later years S. A. Giller together with M. Yu. Lidak and N. M. Sukhovoi began to study new types of antibacterial agents, namely nitrofurylpolyenylquinolines. The application of the antibacterial properties of derivatives of (5-nitro-2-furyl)vinyl- and (5-nitro-2-furyl)-butadienylquinoline demonstrated that compounds in this series exhibited high bacteriostatic activity. Compounds containing a chlorine atom in position 7 and either diethylaminoalkylamino- or hydroxyalkylamino groups in position 4 of the quinoline ring proved to be the most active members of this series. Various amides and hydrazides of [(5-nitro-2-furyl)vinyl]- and [(5-nitro-2-furyl)butadieneyl]-4-quinolinecarboxylic acid, as well as thiosemicarbazides in this series, were also synthesized; they exhibited high antituberculosis activity [20]. The synthesis of [(5-nitro-2-furyl)vinyl]- and [(5-nitro-2-furyl)butadienyl]quinolines was

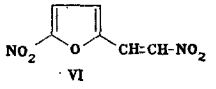
achieved by acid-catalyzed crotonic acid type condensation reactions between alkylquinolines and nitrofuran aldehydes [21].



The nucleophilic displacement reactions of chloro-substituted [(5-nitro-2-furyl)vinyl]- and [(5-nitro-2-furyl)butadienyl]quinolines with thiosemicarbazides and substituted amines have been investigated; in addition, a series of carboxyl group derivatives of quinoline-4-carboxylic acids have also been prepared. Many of these compounds have demonstrated valuable pharmaceutical properties [22].

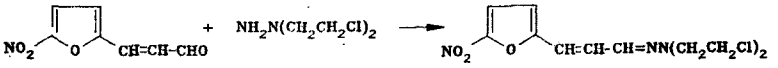
S. A. Giller pioneered the study of the chemotherapeutic properties of polymers. Acetylation of polyvinyl alcohol with β-(5-nitro-2-furyl)acrolein gave a polymer with pronounced antimicrobial activity; this work was carried out in collaboration with A. I. Meoss and L. A. Vol'f at the Leningrad Textile Institute. The antimicrobial fiber produced in this manner was named Letilan;* it found widespread use in the manufacture of a wide variety of objects used in medicine (suture and dressing materials, blood vessel prostheses, contraceptive devices, artificial heart valves, and many others) [23].

The study of 5-nitrofuran derivatives also led to the discovery of novel antifungal drugs [24]. The drug nitrofurylene [2-(5-nitro-2-furyl)-1-nitroethylene (VI)] effectively suppresses the growth od pathogenic fungi; its activity matches that of the most well-known antifungal antibiotics such as Nystatin, griesofulvin, and others. Clinical evaluations of this drug indicate that microflora do not develop resistance to its activity and that its transport properties are good [25].



VI

Back in 1948, in experiments designed to eliminate microflora from tumor tissue cultures, S. A. Giller along with Academician P. I. Stradyn' discovered that certain compounds in the nitrofuran series were capable of retarding the growth of tumor cells. This discovery stimulated the synthesis of nitrofuran derivatives designed specifically for cancer chemotherapy. It was found that the incorporation of an alkylating function in the nitrofuran ring was accompanied by a sharp increase in the antiblastic effect. Treatment of bis(2-chloroethyl)hydrazine with 5-nitrofurylacrolein yielded a compound with significant antitumor activity, namely Nifuron [5-nitrofurylacrolein bis(2-chloroethyl)hydrazone (VII)] [26].

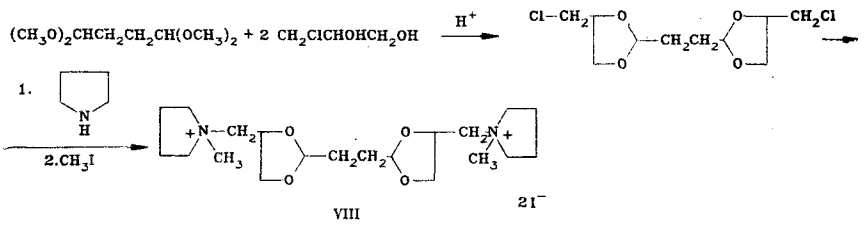


S. A. Giller's research into the ring-opening reactions of furans led to the discovery of a novel curare-like material, dioxonium (VIII), and to a method for its synthesis. Electrochemical methoxylation of furan or its derivatives, followed by hydrogenation of the double bond, provided a valuable method for the synthesis of a series of 1,4-dicarbonyl compounds which were difficult to obtain by other methods; among the compounds prepared in this manner was the bis(dimethylacetal) of succinaldehyde, the starting material for the synthesis of the drug dioxonium.

All of the steps in this process proceed smoothly; the yields of products after purification by distillation or recrystallization range from 60-85% [27, 28].

Clinical applications of dioxonium have established its potent curare-type activity, which exceeds that of D-tubocurarine by a factor of 13, that of diplacin by a factor of 70, that of ditilin by a factor of 14, and that of decamethone by a factor of 1.6. Dioxonium exhibits a selective reaction with N-choline receptors in skeletal muscles. In addition, the

*See note p. 9.



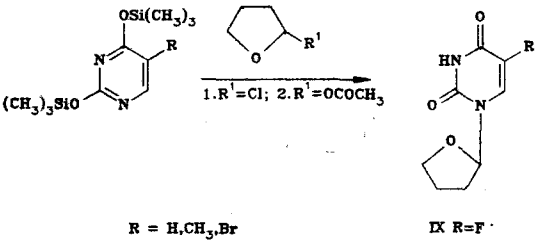
VIII

use of this drug does not produce changes in the chemodynamics or character of the electrocardiogram, it does not dilate the pupils, and therefore does not interfere with the estimation of the depth of narcosis. The drug also does not affect the antonomous ganglii and does not induce bronchial spasms. The postoperative muscular pain which accompanies the use of the typical depolarizing agents ditilin and decamethone is absent following the use of dioxonium. These advantages of dioxonium over other known muscle relaxants used in anesthesiology account for the widespread use of the drug in various types of surgical procedures, especially in cases where other muscle relaxants are contraindicated [29].

The study of the chemistry of furan and particularly tetrahydrofuran led to the discovery of a novel antitumor drug, Ftorafur,* at the Institute of Organic Synthesis (IOS) of the Academy of Sciences of the Latvian SSR. S. A. Giller proposed the synthesis of nucleic acid analogs in which the ribose or deoxyribose moiety was replaced with a simpler, noncarbohydrate fragment, namely, tetrahydrofuran. Under his leadership the synthesis of tetrahydrofuryl derivatives of pyrimidines was achieved (R. A. Zhuk); one of the first compounds to be synthesized was 1-(2-tetrahydrofuryl)-5-flurouracil (Ftorafur, IX) [30].

Several preparative methods for the synthesis of 1-(2-tetrahydrofuryl)- and 1-(2-tetrahydropyranyl)- derivatives of uracil, 6-azauracil, and cytosine were developed at the Institute. One of these methods was based on the alkylation of activated forms (mercuric or silylated derivatives) of pyrimidine bases with 2-chlorotetrahydrofuran *a* or 2-chlorotetrahydropyran [30, 31].

This reaction is carried out in an inert anhydrous solvent or in the absence of solvent, with the exclusion of moist air, at a temperature between −15 and −10°C [32]. It should be noted that the mercury-activated method of synthesis is now of secondary importance, since the silicon method offers several advantages (higher yield, the absence of traces of mercury in the desired products, and the elimination of the need to work with highly toxic mercury compounds).



R = H,CH_3,Br

IX R=F

The technology for preparing Ftorafur was further simplified by using 2,3-dihydrofuran instead of 2-chlorotetrahydrofuran; the 2,3-dihydrofuran is first treated with hydrogen chloride in the presence of a solvent, and then 2,4-bis(trimethylsilyl)-5-fluorouracil is added to the reaction mixture [33]. The IOS also developed the technology for the preparation of 2,3-dihydrofuran from 1,4-butanediol using cobalt catalysts supported on silica gel. The optimum conditions for the reaction involved carrying out the process batchwise at atmospheric pressure with removal of the 2,3-dihydrofuran by distillation [34].

The use of 2-acetyxotetrahydrofuran as the furan ring donor permitted the alkylation reaction to be carried out with very strong pyrimidine base derivatives at a temperature of 20-25°C [35]. In addition, in contrast to 2-chlorotetrahydrofuran, 2-acetoxytetrahydrofuran is stable under conditions needed for separation and isolation of the desired products, thus avoiding partial hydrolysis of the acid-sensitive 1-(2-tetrahydrofuryl)uracils.

*Flurfucil (WHO) — Translator.

Ftorafur is available in two pharmaceutical forms: as a sterile aqueous solution of the sodium salt for intravenous application, and as a capsule for oral application.

Studies of the biochemical properties of Ftorafur have shown that the compound slowly affects the *in vitro* biosynthesis of nucleic acids in tumor cells [36]. In the organism the drug is activated via metabolic conversion upon interaction with microsomal enzymes; the major metabolite of Ftorafur is 5-fluorouracil, which is further converted to 5-fluoro-2'-deoxyuridine-5'-monophosphate. In this way, therefore, it has been established that Ftorafur is a transportable form of 5-fluorouracil.

Ftorafur is used to treat tumors of the gastrointestinal tract, the mammary glands, ovaries, as well as several other types of cancer, for instance brain (craniocerebral) tumors. Ftorafur is just as effective as 5-fluorouracil in treating stomach tumors, whereas it is more effective than 5-fluorouracil in the treatment of breast tumors or intestinal cancer. In this regard, it is also important that Ftorafur only very rarely causes gastrointestinal complications, and that it does not affect blood circulation [38-40]. Ftorafur is effective when administered orally; it is rapidly absorbed from the gastrointestinal tract. Thus, after 2 h the concentration of the drug in the blood is almost the same as when an equal dose of the drug has been administered intravenously. Because of the efficacy of oral application, the drug may be used successfully in extended maintenance therapy of ambulatory patients. According to Japanese authors [41], this type of therapy increases the life span of patients who have been operated on in connection with cancer of the gastrointestinal tract, and also decreases the probability of metastasis. It has been suggested that Ftorafur be administered in suppository form in order to safeguard favorable results in the treatment of certain localized tumors. Ftorafur is also recommended for use in combination therapy. As a result of its superior therapeutic properties Ftorafur is widely used in the USSR and other countries; in Japan it has almost totally replaced 5-fluorouracil in treatment. The drug is manufactured at the Experimental Factory of the IOS of the Academy of Sciences of the Latvian SSR.

To conclude this section on the uses of oxygen-containing heterocycles in medicinal chemistry, it should be mentioned that the IOS has also developed catalytic methods for the synthesis of tetrahydrofuran from butanediol, and of sylvan (α-methylfuran) from methylfurfural. Tetrahydrofuran, as already noted, is used in the preparation of the drug dioxonium, whereas sylvan is an intermediate in the synthesis of vitamin B_1.

In evaluating the contributions of S. A. Giller to the study of chemistry of nitrogen-containing heterocycles it is necessary, first of all, to discuss his wide-ranging research into the chemistry of ethylenimine, which made possible the synthesis of a series of valuable antitumor agents.

In 1957-1959 a method was developed for the preparation of the drug thio-TEPA (X); this drug was manufactured first by the Experimental Plant of the IOS, and later by Olain Pharmaceuticals. The synthesis is based on the reaction of thiophosphoryl chloride with ethylenimine in an inert solvent in the presence of triethylamine [42].

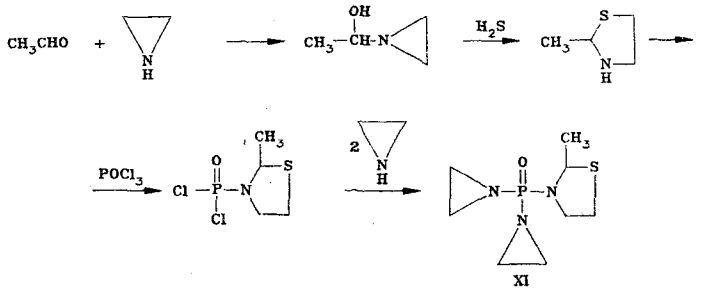
X

The synthesis and study of more than 200 ethylenimine derivatives led to the discovery of a new substance for the treatment of erythremia, namely Imifos* [diethyleneamide of 2-methylthiazolidine-3-phosphoric acid (XI)], [43]. This compound is prepared via the reaction of 2-methylthiazolidine with phosphorus oxychloride and subsequent replacement of the two remaining chlorine atoms with ethylenimine. 2-Methylthiazolidine is obtained by treating the product of the reaction between acetaldehyde and ethylenimine with hydrogen sulfide.

Thiophosphamidium (thio-TEPA) is used in the treatment of malignant ovarian tumors after nonradical surgery and metastasis; it is also used in the treatment of inoperable recidivism or metastasis of uterine and cervical cancer which do not respond to radiation therapy. The use of this drug reduces the number of cases of recidivism and metastasis following radical mastectomies; when used in complex therapy for the treatment of breast cancer thiophospham-

*See note p. 9.

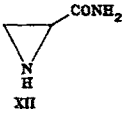
ide also increases the percentage of nonrecidivism [44, 45]. It is also possible to use thiophosphamide in the treatment of chronic lympholeucosis, myeloleucosis, lymphogranulomatosis, reticular sarcoma, and lymphosarcomatosis.



XI

Imifos is used mainly in the treatment of erythremia, particularly in patients in advanced stages of the disease [46]. At this time, 20 years after the discovery of Imifos, it may be said that the drug has successfully passed the test of time and that it is the best chemotherapeutic agent available for erythremia therapy.

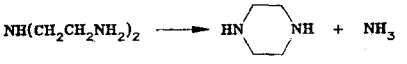
In the search for novel antitumor agents derived from ethylenimine, several derivatives of aziridinecarboxylic acid were synthesized [47]. These compounds exert a profound antitumor activity which does not depend upon alkylation of purine and pyrimidine bases of nucleic acids; this fact is attested to by their low toxicity. The amide of aziridinecarboxylic acid was selected for more intensive clinical evaluation. In addition to its antitumor activity



XII

this compound also this compound also possesses immunostimulatory reactivity.

One other study in the research of novel drugs based on nitrogen-containing heterocycles deserves mention, and that is the discovery of new methods for the synthesis of piperazine from diethylenetriamine, a side product in the manufacture of ethylenediamine. The basis of the above-mentioned preparation of piperazine involves the catalytic deamination of diethylenetriamine. The process occurs under pressure in a protic solvent with a liquid phase over a stationary catalyst bed [48].

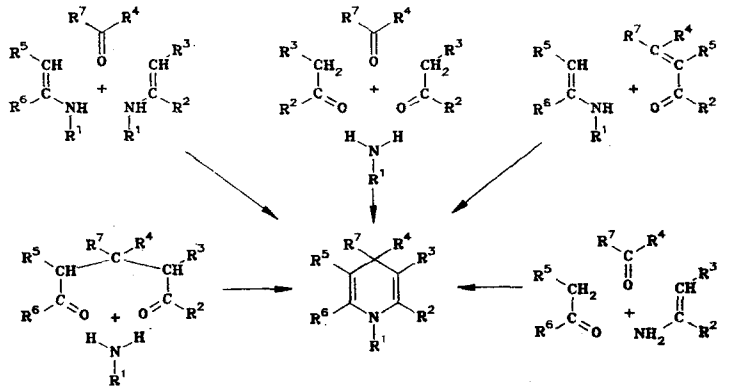


The process technology was developed and an apparatus was constructed and tested so that the piperazine could be obtained via this new stream-type method; this method has been used in the production of multiton quantities of piperazine, an intermediate in the synthesis of a series of antihelminthic agents based on piperazine salts.

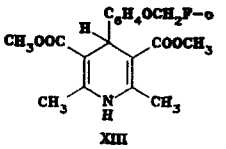
Various mono- and polycyclic dihydropyridines have been synthesized and studied at the Institute since its inception; this work was carried out at first under the leadership of Academician G. Ya. Banag, and, after his death, under the guidance of G. Ya. Dubur. S. A. Giller prepared these compounds specifically for evaluation as potential medicinal agents and drugs for farming and agriculture.

The research conducted at the Institute into the synthesis of dihydropyridines is illustrated in the scheme at the top of the following page.

The high electron- and hydrogen-donating ability of dihydropyridine derivatives served as a basis for a study of their antioxidant properties. It was established that they do indeed constitute a new class of C–H antioxidants. These compounds regulate diverse types of peroxide oxidation processes. The efficacy of dihydropyridines has been demonstrated in model studies of the peroxide-induced oxidations of unsaturated compounds [49]. This effect explains the dihydropyridine-mediated stabilization of Vitamin A in oily solutions.



Fluorine-containing 4-aryl-1,4-dihydropyridines display a very high hypotensive activity. The most promising compound in this series is Foridon* (XII).



XIII

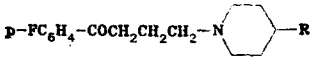
Foridon possesses the same activity in this regard as the known drug SKF-24260, but is ten times less toxic in acute cases. In acute, subacute, and chronic experiments it is less toxic than two other known drugs in the dihydropyridine series, namely, nifenidine and nicardipine [50].

β-Alkoxyethyl esters of 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acids are distinguished by their pronounced vasodilator, hypotensive, and adrenal blocking activity. Several of these esters are not inferior to the known drug carbocromen in their ability to influence the rate of coronary blood flow [2, p. 186].

In the course of research on N-substituted derivatives of 2,6-dimethyl-3,5-bis(carboalkoxy)-1,4-dihydropyridine, several active coronary dilatory agents with very low toxicity were discovered. The best of these essentially surpass papaverine (in their activity); in addition, several of these compounds have pharmacological indices of activity 1.5 times greater than that of the known drug nifedipine [2, p. 187].

Derivatives of 2,6-dimethyl-3,5-dicarbonyl-1,4-dihydropyridine retard the growth of complex tumors. Some of these compounds exhibit a very pronounced antimetastatic activity, and yet, possess little toxicity [2, p. 181].

Butyrophenone derivatives containing heterocyclic residues were synthesized, and the effect of their structures on their neuroleptic properties was studied.

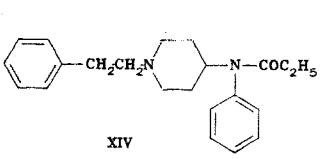


Compounds in which the R substituent was a binuclear heterocycle were particularly well studied. On the basis of an analysis of the dependence of neuroleptic activity of these compounds on their molecular structure a hypothesis was proposed concerning the structural elements of the butyrophenone moiety essential for binding with dopamine receptors [2, p. 183].

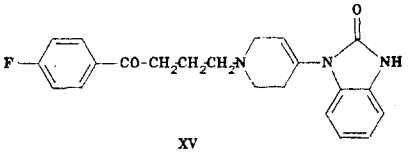
Original methods were developed for the preparation of the drugs benperidol, droperidol, and fentanyl [51, 52]. Fentanyl {N-(β-phenylethyl)-4-[(N-propionyl)anilido]piperidine} (XIV) is currently widely used as an analgesic component in neuroleptic analgesia as a supplementary analgesic at the end of surgery performed under local anesthetic; it is also used to eliminate the pain due to myocardial infarction, stenocardia, strenuous manipulative therapy, or postoperative pain. It is also used to reduce the pain, and as a prophylactic, for traumatic shock. The joint administration of droperidol {1-[3-(p-fluorobenzoyl)propyl]-4-(2-oxo-

*See note p. 9.

benzimidazolinyl)-1,2,3,6-tetrahydropyridine} (XV) and fentanyl confers a strong neuroleptic and analgesic effect, induces drowsiness and muscle relaxation, prevents shock, and demonstrates an antiemetic effect. Patients pass out easily from the condition of neuroleptic analgesia [53].



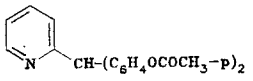
XIV



XV

A surface contact reaction for the vapor-phase oxidation of methylpyridines to pyridinealdehydes using atmospheric oxygen on vanadium-molybdenum catalysts was developed at the Institute of Organic Synthesis and carried out at the Experimental Plant of the IOS of the Academy of Sciences of the Latvian SSR. 4-Pyridinecarbaldehyde is prepared in this way; its oxime is an intermediate in the synthesis of the drugs trimedoxime bromide (XVI) and Efosine* (XVII), which react with cholinesterase and are inhibited by organophosphorus compounds [54-56].

2-Pyridineoximeethanesulfonic acid, prepared from 2-pyridinecarbaldehyde, is used in the synthesis of bisacodyl — bis(4-acetoxyphenyl)(2-pyridyl)methane (XVIII) — a contemporary laxative widely used in medicine [57].



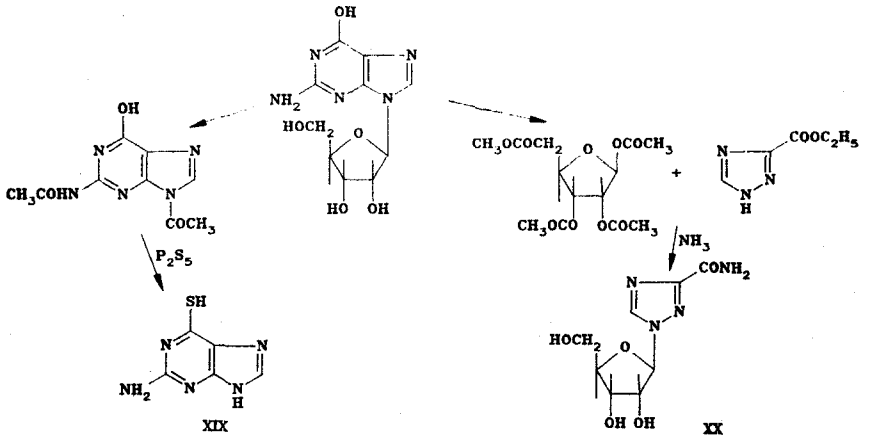
XVIII

The reduction of 3-pyridinecarbaldehyde gives 3-pyridinecarbinol, whose salts are utilized as drugs acting on the central nervous system [58].

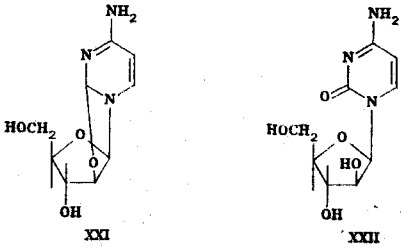
Recently, the IOS has been extensively exploring the preparation of new therapeutic agents derived from purine and pyrimidine bases of the nucleic acids, and also drugs based on analogs of nucleosides and nucleotides. Studies with Ftorafur demonstrated how promising this type of research was in the development of novel antitumor agents. During the latter stages of his career S. A. Giller formulated a theoretical framework for the preparation of antitumor agents based on oligonucleotide analogs. According to his hypotheses, compounds which possess conformations similar to those of the naturally occurring nucleic acids and which are complementary to the sequence essential for operation (of the nucleic acid) should be capable of shielding the derepression segment of the biopolymer chain and thus of blocking the function of the derepression genome [59, 60]. Several years later similar studies of new classes of antitumor agents began to appear at other academic institutions of the USSR, and also in other countries; many diverse classes of simplified structural analogs of nucleotides and nucleic acids have been synthesized and investigated.

The IOS, in collaboration with the Scientific-Production Organization "Biochemical Reagents," developed a complex scheme for the utilization of natural nucleosides in the preparation of novel antitumor and antiviral drugs, derivatives and analogs of nucleosides and of the nitrogen bases of nucleic acids [61]. For instance, guanosine is currently used in the preparation of the antileucosis drug thioguanine (XIX) and also in the synthesis of an antiviral agent, ribavirin (virazol, XX), which also displays antitumor activity. For this purpose, guanosine is cleaved using a solution of acetic anhydride in glacial acetic acid; the tetraacetylribose and diacetylguanine formed as a result are used in the corresponding syntheses of ribavirin and thioguanine, respectively [62]. G. I. Chipens and V. Ya. Grinshtein in 1964 developed a method for the synthesis of the ethyl ester of 1,2,4-triazole-3-carboxylic acid [63]. Laboratory syntheses were worked out for both drugs, and samples were made available for both clinical use (thioguanine) and research (ribavirin). This research was conducted in collaboration with the Oncologic Scientific Center of the Academy of Medical Sciences of the USSR. A second nucleoside, cytidine, has been used in the synthesis of the antileucosis drugs cyclocytidine (XXI) and cytosinearabinoside (XXII), which are undergoing clinical trials in conjunction with complex drug therapy in the treatment of leucoses [64].

*Limitations of time and resources have prevented a rigorous verification of the compounds mentioned in this article. Where the equivalent English for a common name could not be found we have given a rough transliteration of the Russian name — Publisher.



Several studies have demonstrated that the use of complex drug therapy involving cytidine, thioguanine, prednisolone, and other drugs gives much better results and prolongs patient survival more than single drug therapy [65].



The IOS, in collaboration with the Institute of Organometallic Chemistry of the Academy of Sciences of the USSR, developed a method for the fluorination of uracil using elemental fluorine [66]; this method constitutes a technologically feasible and relatively inexpensive way to prepare 5-fluorouracil. A commercial method for the synthesis of uracil was also developed.

The future research plans of the Institute call for further exploration and studies in the chemistry of heterocyclic compounds and analogs of naturally occurring nucleosides for the purpose of obtaining valuable new medicinal agents.

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