TRENDS AND CHALLENGES IN HETEROCYCLIC CHEMISTRY (REVIEW)

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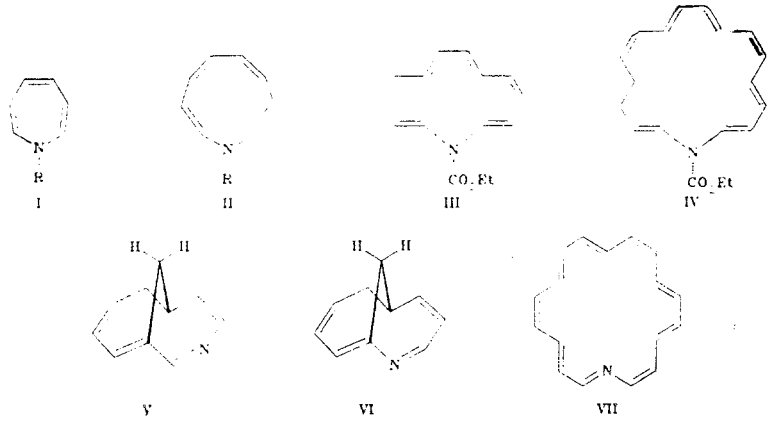
UDC 547.7/.8

This review was given as a plenary report to the Fourth All-Union Conference on the Chemistry of Nitrogen Heterocycles held in Novosibirsk in 1987, and treats the major trends and challenges in modern heterocyclic chemistry.

In the present communication, we intend, without going into detail, to provide a general picture of the development of heterocyclic chemistry, especially in relation to nitrogen heterocycles, over the past 4-5 years. However, the extent of the material does not permit even a cursory examination of all the aspects of this subject. Thus, heteroaromatic systems were taken for major consideration. Fundamental trends in applied and basic research in heterocyclic chemistry were analyzed for such systems.

Heterocyclic compounds occupy a special place in organic chemistry and, indeed, even in natural sciences. Thus, in biology, nitrogen heterocycles take part in the transfer of hereditary traits, provide for the operation of enzymatic mechanisms and the central nervous system, and support the energy transfer in organisms. In physics, heterocycles are used as laser dyes, semiconducting materials, organic metals, and liquid crystals. At least half of all drugs, pesticides, heat-resistant polymers, and photographic materials today are heterocyclic derivatives. Thus, we may state without exaggeration that we are treating an area in chemistry which significantly affects progress in science and technology.

The 1970s were probably a golden age in heterocyclic chemistry since many major achievements occurred during this period.



We should initially note the decisive breakthrough in the area of macrocyclic heterosystems not only in regard to crown ethers but also in regard to heteroaromatic compounds. The period from the end of the 1960s until the mid-1970s featured the synthesis and study of macrocycles with a pyrrolic nitrogen atom: azepins I [1] (the simplest member of this series was obtained only in 1980 [2]), azonines II [3, 4], aza[13]annulenes III, and aza[17]-annulenes IV [5, 6]. Macrocycles with a pyridine nitrogen atom, such as methanoaza[10]annulenes V and VI [7, 8] and aza[18]annulene VIII [9], were synthesized at the end of the 1970s.

The chemistry of cyclazines, which are condensed heteroanalogs of annulenes with a common pyrrolic nitrogen atom such as VIII-X [11], developed in regard to the problem of heteroaromaticity (see our previous review [10]). It became clear that the aromatic (VIII) or antiaromatic nature of annulenes (IX and X) is almost entirely a function of the peripheral π-electrons, while the heteroatoms mainly act as bridges, maintaining the macrocycle in a planar state.

M. A. Suslov Rostov State University, Rostov-on-Don 334771. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 3-23, January, 1989. Original article submitted May 26, 1988.

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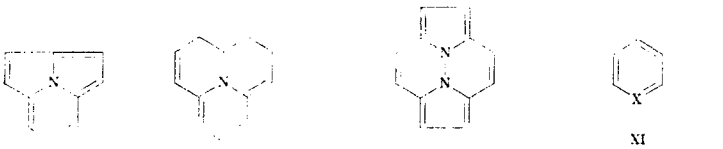


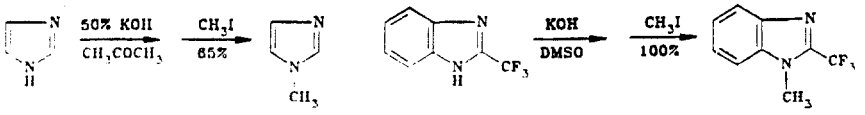
VIII IX X XI

X=P, As, Sb, Bi

Analogs of pyridine XI were synthesized with heavy heteroatoms such as phosphorus, arsenic, antimony, and bismuth [13]. The chemistry of these compounds [14] proved extremely different from pyridine chemistry. This demonstrated the special role of nitrogen as a heteroatom.

The discovery of fundamentally new mechanisms for nucleophilic substitution had a great effect on the study of the reactivity of heterocycles (see the bibliography in the work of Minisci and Porta [15]) including the ANRORC and $S_{RN}1$ mechanisms for nucleophilic substitution and the radical-cation mechanism for electrophilic substitution. The ylide mechanism in electrophilic substitution, as well as the ipso mechanism, were widely confirmed. Radical substitution reactions found synthetic significance [16, 17].

Considerable progress was made in the N-alkylation of NH-heterocycles using phase-transfer catalysis and superbasic media such as KOH/DMSO and KOH/acetone. For example, the alkylation of imidazole has always been a problem since in ordinary media such as alkali/water and alkali/ethanol, the reaction proceeds with low yield due to the formation of quaternary salts. 2-Trifluoromethylbenzimidazole could not be alkylated under these conditions due to the low nucleophilicity of the N-anion. The use of the KOH/acetone system in the former case [18, 19] and KOH/DMSO in the latter [20] permitted the synthesis of the corresponding N-alkyl derivatives in good yield.



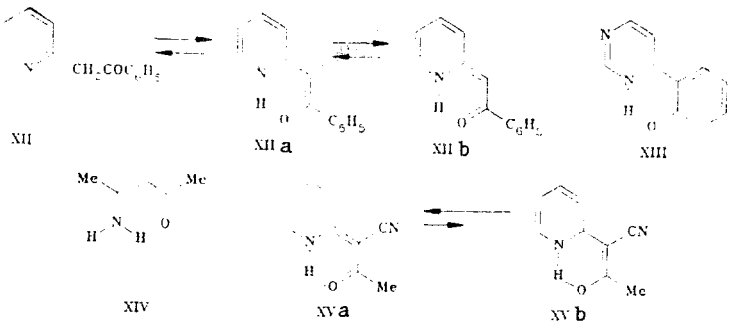
The alkylation of indole under phase-transfer catalysis conditions virtually permits us to avoid the formation of its 3-substituted derivatives, which are often undesired by-products upon carrying out the reaction under standard conditions [21, 22].

The study of gas-phase transformations, especially, of acid–base and tautomeric equilibria led to a reevaluation of a number of theoretical concepts. Pyridine in aqueous solution is known to be five orders of magnitude less basic than ammonia. In the gas phase, the basicity of pyridine is 12-13 orders of magnitude greater than that of ammonia [23]. Analogously, imidazole in water is a stronger base than benzimidazole (ΔpK_a 1.5), while benzimidazole is much more basic in the vapor phase [24]. The reason for these discrepancies is the greater solvation in water (primarily due to hydrogen bonding) for the relatively small NH_4^+ and imidazolium ions in comparison with the pyridinium and benzimidazolium ions. In the absence of solvation, the two latter ions, in which delocalization of positive charge is more efficient due to greater extension of the π-system, become more stable.

Studies in the solid phase and solution had indicated that 2-pyridone is more stable than its tautomer, 2-hydroxypyridine. Gas-phase measurements showed that the hydroxypyridine form predominates by at least one order of magnitude in the vapor phase and, thus, has greater internal stability [25].

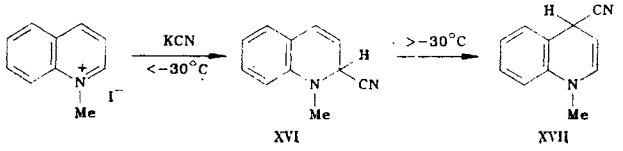
Progress in heterocyclic chemistry in the 1970s was largely a function of the development of physical research methods, especially of x-ray diffraction structural analysis, heavy nucleus NMR and EPR spectroscopy, and mass spectrometry and the development of new techniques for organic synthesis.

Thus, for example, in the case of 2-phenacylpyridine, which exists in chloroform as 54% XII and 46% chelate form, UV, IR, PMR, and ^{13}C NMR spectroscopy did not permit an unequivocal determination of whether the chelate is enol XIIa or ketone XIIb. ^{17}O NMR spectroscopy gave an answer to this question [26]. Since oxygen in the two chelate forms has different hybridization, the chemical shifts for ^{17}O in these forms are very different as shown for model compounds XIII and XIV. The ^{17}O chemical shift for the chelate form is close to the chemical shift of the OH model, which indicates the enol form XIIa, while the chelate in the case of 2-cyanoacetonylpyridine has keto structure XVa.

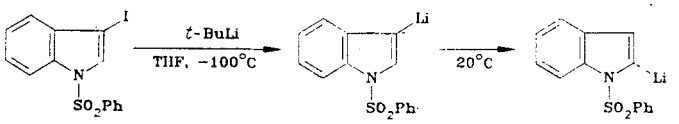


XII $\delta_{17O}=125$; XIII $\delta_{17O}=94$; XIV $\delta_{17O}=419$; XV $\delta_{17O}=356$ ppm.

The use of NMR spectroscopy in the past 15 years has permitted elucidation of the enormous role of thermodynamic factors in the control of many reactions of heterocyclic compounds. Thus, it was long considered that hard nucleophiles such as the hydroxyl ion add to the α-position of the pyridinium or quinolinium ions, while soft nucleophiles, in particular the cyanide ion, and to the γ-position. Indeed, low-temperature ^{13}C NMR spectroscopy showed that soft nucleophiles initially attack the α-position, i.e., under kinetically-controlled conditions, the course of the reaction is determined by the charge, which is greater at C-2. The α-adduct, such as XVI, only then converts to the more stable γ-adduct XVII due to the reversibility of the addition for soft nucleophiles under thermodynamic control conditions, i.e., upon an increase in temperature [27].



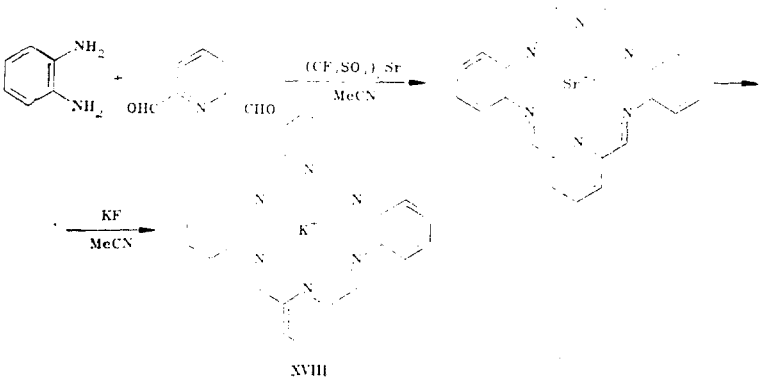
Quite a number of such examples were also found for the alkylation, electrophilic substitution, and metallation reactions. Thus, 3-lithium-1-benzenesulfonylindole formed by the action of tert-butyllithium on 1-benzenesulfonyl-3-iodoindole at −100°C is completely converted upon warming to room temperature to the 2-lithium derivative [28]:



The 1970s were years of vigorous development of new methods for heterocyclization and recyclization, which may be the quintessence of heterocyclic chemistry. For examples of major chievements by Soviet chemists, we should note the new method for pyrrole synthesis involving the reaction of ketoximes with acetylene in KOH/DMSO developed by Trofimov and coworkers [29] and the series of studies of Kost and Sagitullin on the recyclization of pyridinium salts [30].

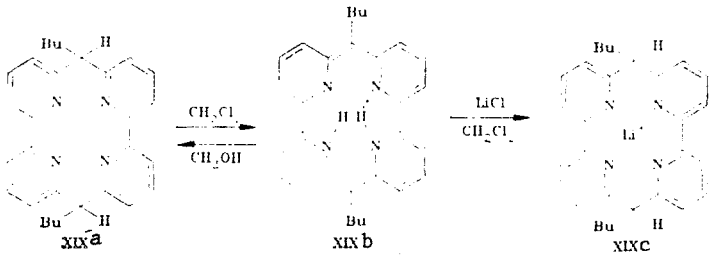
What are the major trends in the development of contemporary heterocyclic chemistry, in general, and of the chemistry of nitrogen heterocycles, in particular? We should initially note that a large portion of current developments were already begun in the 1970s. Secondly, there has been a large increase in studies, which reject a purely applied approach. We should perhaps more correctly note a pronounced tendency for the combination of applied and fundamental research and a precise formulation of fundamental problems in regard to their practical significance, although the fraction of so-called pure science remains significant.

Work on macrocyclic compounds undoubtedly occupies first place relative to the amount and clarity of the results obtained. The past work with porphyrins, phthalocyanines, and crown ethers had already shown the great future for macrocycles. These compounds are the basis for obtaining catalysts, photoconductors, photosensitizers, biological models for heme and chlorophyll, conducting materials, photochemical memory devices, devices for molecular electronics, analytical reagents, and selective extragents. Increasing use is being found for azacrown ethers and combined nitrogen–oxygen macrocycles, which have a number of advantages over simple crown ethers due to their compressed geometry. Thus, azamacrocycle XVIII, which is readily obtained from o-phenylenediamine and 2,6-pyridinedialdehyde, forms are more stable complex with the potassium ion than 18-crown-6 [31].



XVIII

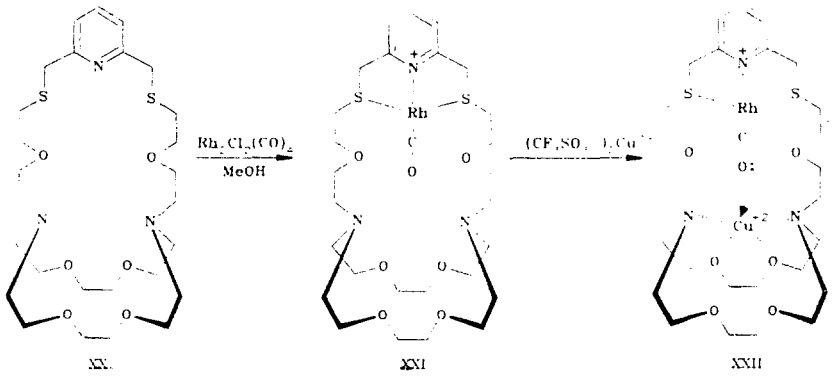
Azacrown ether XIX, which consists of two 2,2'-dipyridine fragments, has a set of interesting properties, which may be used for an elegant determination of the lithium ion [32].



XIXa — XIXb — XIXc

Colorless — Red — Colorless

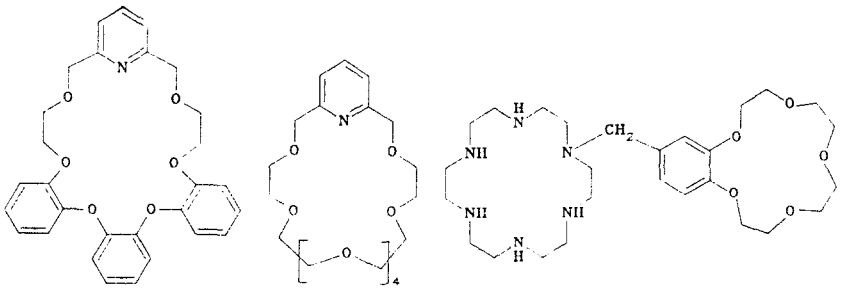
Greater effort is being spent on the development of cascade or coreceptor ligands on the basis of macrocyclic systems, which usually contain two different complexing units, namely, a soft Lewis site and a hard site. A characteristic example may be found in XX, in which the soft site is located in the region of a pyridine nitrogen surrounded by two sulfur atoms and a hard site in the cryptand fragment [33]. If a soft reagent such as rhodium carbonyl acts on this ligand, complex XXI at the soft site is formed with orientation of the carbonyl group within the ring. Upon the subsequent action of a cupric salt on the complex obtained, the Cu^{2+} ion is coordinated with the cryptand part of the molecule to give XXII. The cupric ion is located near the carbonyl oxygen and activates the carbonyl group relative to nucleophilic addition due to coordination with this group as found in enzyme systems. The addition of two identical ions to the two sites is possible. These ions may differ strongly in the complex formed due to their different environments, for example in reduction potential.



XX — XXI — XXII

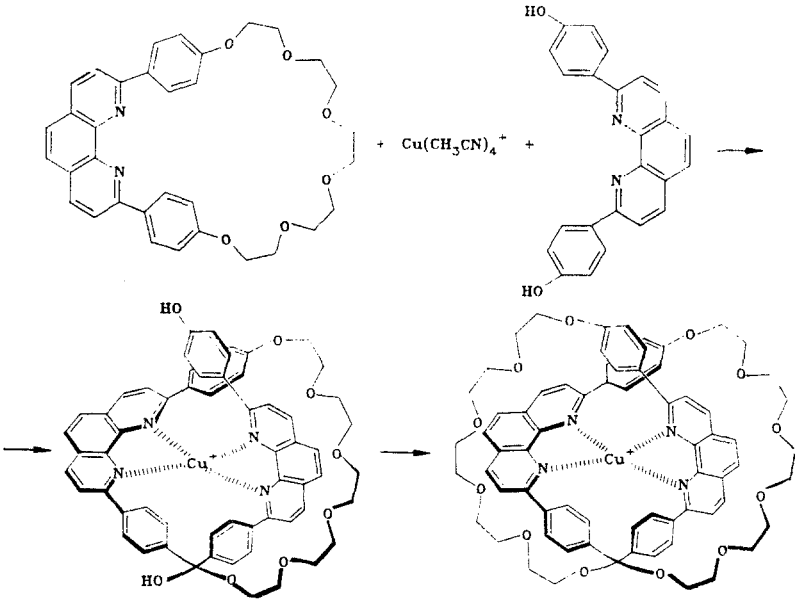
A recent marked trend is interest in the synthesis of macrocycles tending to selective complexation with organic molecules. This is required for the development of a new generation of drugs and models of enzymes and for other biological and chemical studies. Such compounds are suitable for binding nitromethane molecules (XXIII) [34], guanidinium ions (XXIV) [35], and amino acid, peptide, and dopamine betaines (XXV) [36].

Intensive work is under way on the synthesis of a ligand for the efficient complexation of urea, which may find use, in particular, in blood dialysis [35].

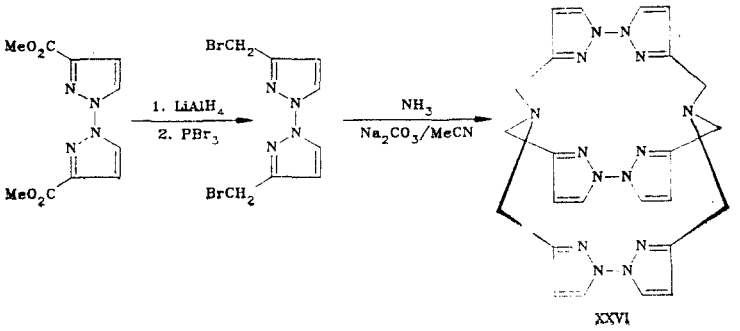


XXIII XXIV XXV

One of the outstanding events in organic chemistry was the synthesis of catenands, which are heteroanalogs of catenanes, by Sauvage and coworkers [37-39]. There was an almost complete standstill in this area after the preparation of the first catenanes at the beginning of the 1960s [40]. The preparation of these compounds was very laborious and no practical significance was seen. Cleverly using the known properties of phenanthroline as a good ligand for various metal ions, Sauvage and Weiss [38] employed a template synthesis to close not only two but even three rings. This work is now being extensively elaborated. A notion of the strategy for the synthesis of catenands (complexes of catenands with metal ions are termed catenates) is given by the following scheme:



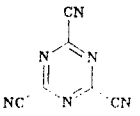
Work is also under way on the design of macrocyclic heterosystems consisting of azoles. Thus, pyrazole cryptand XXVI was synthesized from 3,3'-di(methoxycarbonyl)-1,1'-dipyrazole [41]:



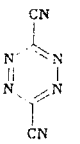
XXVI

A second direction in research in heterocyclic chemistry holding practical significance is related to the preparation of various conducting materials, including "organic metals." While the search for electron donors for the preparation of conducting radical-ion salts is centered on tetrathiofulvalene and its π-excess analogs, containing sulfur, selenium, and tellurium, π-deficient azaheterocycles, containing strong electron-withdrawing groups, are

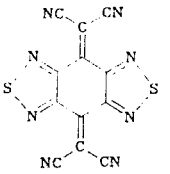
often selected as electron acceptors. An example of such acceptors may be found in 1,3,5-tricyanotriazine (XXVII), 3,6-dicyanotetrazine (XXVIII) [42], or quinone XXIX [43]. All these compounds form highly conducting radical-ion salts with tetrathiofulvalene.



XXVII

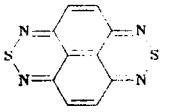


XXVIII

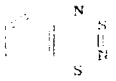


XXIX

Considerable attention is being given to heterocyclic systems, containing nitrogen–sulfur bonds, found in a conjugation chain. This has led to the discovery of high conductivity for the polymer $(SN)_x$. Heterocycles XXX-XXXII [44-46] and many similar compounds have been synthesized for such research.



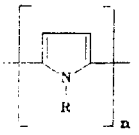
XXX



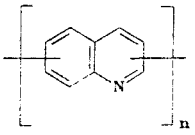
XXXI

XXXII

A great number of studies have been devoted to the preparation of conducting polymer films, which are used, in particular, for electrode coatings, especially films derived from polypyrrole (XXXIII) [47] and polyquinoline (XXXIV) [48]. These products are obtained by the electrochemical oxidation of the corresponding heterocycles or their derivatives but a convenient chemical oxidation method has also been proposed [47].



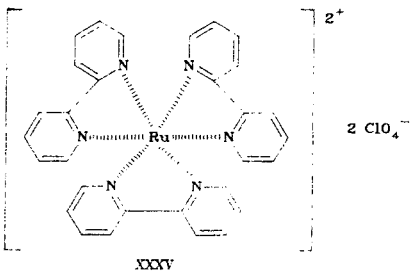
XXXIII



XXXIV

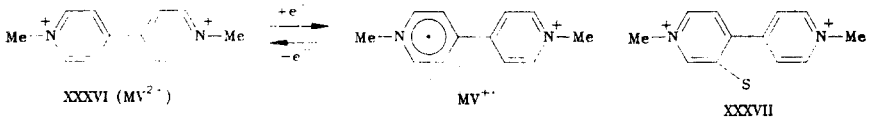
The third area of applied research on heterocycles has centered on the preparation of molecular systems for the photodecomposition of water by the action of sunlight in order to obtain hydrogen as a cheap fuel [49]. One of the central compounds here is the tris-bipyridyl complex of ruthenium(II), $[Ru(bpy)_3^{2+}]$ (XXXV), which acts as a photocatalyst. In this regard, considerable attention is now being given to a study of diazines and their complexes. The complex of the Ru^{2+} ion with 2,2'-bipyrazine has been shown to have the best photocatalytic and electrophysical properties [50].

In addition to a photocatalyst, the preparation of hydrogen from water also requires two dark reaction catalysts. One of these catalysts is an electron transfer agent, while the other is a reduction catalyst as well as an electron donor, whose role consists in the conversion of the oxidized photocatalyst to the starting state.



XXXV

Methylviologen (MV^{2+}) (XXXVI) has found common use as an electron transfer agent. Colloidal platinum is used as the reduction catalyst, while triethanolamine or ethylenediaminetetraacetic acid usually serves as the electron donor. An operational scheme for such molecular photosystems was given by Prasad and Hoffman [51].



XXXVI (MV^{2+}) $MV^{+\cdot}$ XXXVII

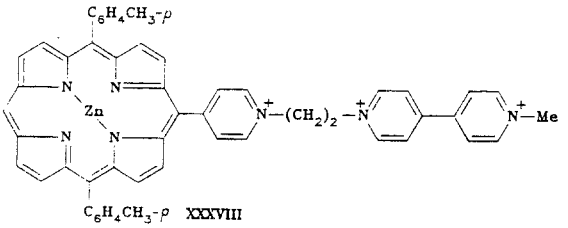
1) $Ru(bpy)_3^{2+} \xrightarrow{h\nu} {}^*Ru(bpy)_3^{2+}$;

2) ${}^*Ru(bpy)_3^{2+} + MV^{2+} \rightarrow Ru(bpy)_3^{3+} + MV^{+\cdot}$;

3) $MV^{+\cdot} + H_2O \xrightarrow{\text{coll. Pt}} MV^{2+} + {}^1/_2H_2 + OH^-$;

4) $Ru(bpy)_3^{3+} + EDTA \rightarrow Ru(bpy)_3^{2+} + EDTA^{+\cdot}$ → decomposition products

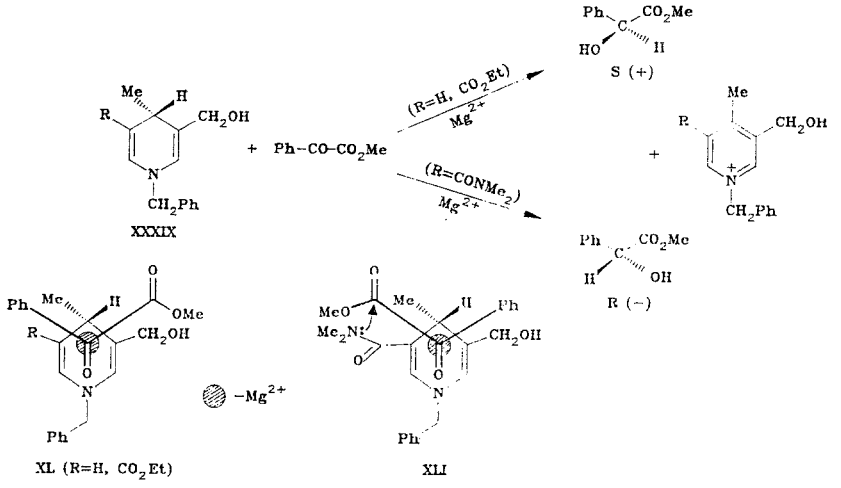
A broad field of activity in this area, in particular, is related to the modification of the catalyst structures and the construction of complex molecules capable of several catalytic functions. Thus, a recently synthesized analog of viologen with a condensed thiophene ring XXXVII proved to be a much more efficient electron transfer agent in the photodecomposition of water than viologen itself [52]. Zinc complex XXXVIII is a compound with electron transfer and photocatalyst sites [53]. The role of the photocatalyst in this case is played by the porphyrin fragment instead of tris-bipyridylruthenium. This fragment more closely corresponds to natural systems. The photodecomposition of water by the action of XXXVIII proceeds in the presence of colloidal platinum and 1,4-dihydronicotinamide, which is an electron donor.



$C_6H_4CH_3$-p XXXVIII

Many enzymes are derivatives of nitrogen heterocycles. Thus, research is being conducted on creating simple, but rather efficient enzyme models. A characteristic feature of the action of coenzyme NADH consists in the circumstance that substrates are reduced by this coenzyme with high steric specificity and recognize inequivalent sides of the ring, arbitrarily termed A and B [54]. Most of the substrates are reduced from side A, which is located within a boat conformation, but some substrates react only on the opposite side. The reason for this effect lies in nonbonding interactions, which stabilize one of the two transition complexes.

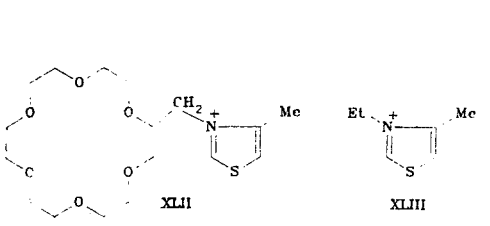
It has recently been possible to prepare at least three NADH models, which have a high degree of steric specificity in reduction [55-57]. One such model is 1,4-dihydropyridines XXXIX with a hydromethyl group at C-3 and methyl group at C-4. The stereochemistry of the reduction of the methyl ester of benzoylformic acid and a series of other substrates by XXXIX is largely determined by the nature of the substituent at C-5. When R = H and $CO_2C_2H_5$, the reduction proceeds to give the (+)-enantiomer of the methyl ester of mandelic acid, while the (−)-enantiomer is formed when R = $CON(CH_3)_2$. The optical purity of the reduction prod-



XXXIX S (+) R (−) XL (R=H, CO_2Et) XLI

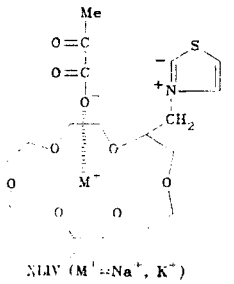
ucts reaches 97%. The nonbonding interaction between the 3-hydromethyl group of the dihydropyridine and the methoxycarbonyl group of substrate XL likely predominates in the enzyme–substrate complex in the reduction to give the (+)-enantiomer. On the other hand, the electrostatic interaction between the dimethylamino group and methoxycarbonyl group of the substrate may play an important role in the reduction to give the (−)-enantiomer as shown in structure XLI. The reduction using XXXIX, as in the case of NADH itself, is catalyzed by magnesium ions, which participate in the formation of ternary complex XL or XLI.

Thirty years have now passed since Breslow [58] discovered the mechanism of the action of thiamine, which carries out the decarboxylation of pyruvic acid in living organisms. This process occurs by an ylide mechanism (the ylide is formed due to ionization of the $C_{(2)}$–H bond of the thiazolium ring) and is catalyzed by alkali metal ions. An original model has recently been obtained for thiamine, namely 4-methylthiazolium cation XLII, which bears an 18-crown-6 residue as the N-substituent [59]. In the presence of potassium or sodium ions (but not lithium ions), this salt accelerates the decarboxylation of pyruvic acid by an order of magnitude in comparison with 3-ethyl-4-methylthiazolium (XLIII). The mechanism of the action of this catalyst is logically represented by structure XLIV.



XLII

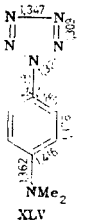
XLIII



XLIV (M^+ = Na^+, K^+)

In analyzing inherent fundamental problems in heterocyclic chemistry, we should initially note the high level of development of the structural theory and physical chemistry for these compounds. The major π-electron and geometric characteristics and donor–acceptance and acid–base properties are generally clear and are largely predictable. Indeed, for at least the past 5 years, i.e., since fundamental information appeared on the behavior of heterocycles in the gas phase, there have been no major breakthroughs in this area. Information is gradually accumulating on the σ-constants and electronic transmission of hetaryl groups, the oxidation–reduction potentials of heterocycles, and their acid–base properties in the gas phase. Future developments in this area will apparently depend on the introduction of new physicochemical methods and access to information on the properties of new types of heterosystems.

The problem of heteroaromaticity is now in a relatively stable phase [10, 15]. The Hückel rule continues to work well and the prediction of aromatic or antiaromatic properties of new heterocycles virtually always proves correct. The most significant advance in this area in the past 3-4 years may be considered the development of a structural aromaticity index, which reflects the levelling of the bond orders in heterocycles calculated using x-ray diffraction structural data [10, 15, 60]. For example, x-ray diffraction structural data for 1-(p-dimethylaminophenyl)pentazole (XLV) [61] indicate a high extent of equalization of the π-electron cloud in the pentazole ring, whose aromaticity according to this parameter is 82% of benzene aromaticity. Hence, the instability of pentazole and, especially, of the hexazine rings (XLVI) [62] is a consequence mainly of the high stability of nitrogen molecules, which are formed upon their decomposition.

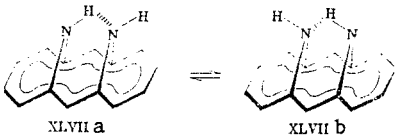


XLV

XLVI

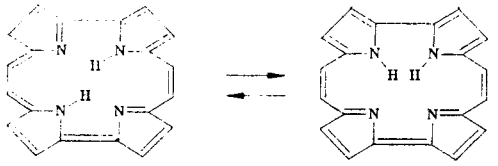
The most interesting direction in research on heteroaromaticity probably lies in the design and synthesis of new types of heterocycles. The attention on researchers has been

mainly centered on macrocyclic systems, often with an unusual or original structure. A typical example is found in syn-1,6:8,13-diimino[14]annulene. A special feature of this molecule is the low barrier to configurational inversion of the two nitrogen atoms and the existence of an equilibrium between invertomers XLVIIa and XLVIIb [63].



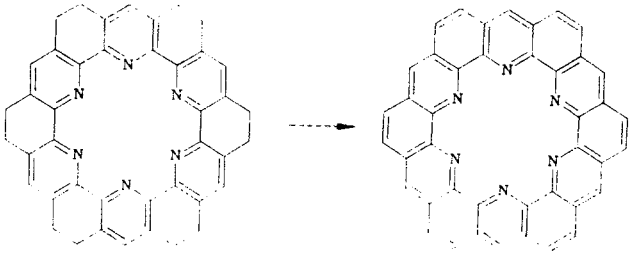
XLVII a XLVII b

Vogel and coworkers have recently synthesized porphicene, which is a new aromatic isomer of porphyrin [64]. A rapid nondegenerate tautomeric interconversion between structures XLVIIIa and XLVIIIb is characteristic for this compound, which gives blue solutions in organic solvents with a beautiful red-violet luminescence.



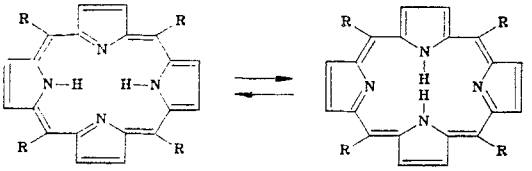
XLVIII a XLVIII b

Work is being completed on the synthesis of hexaazakekkulene (L). This macrocycle has been a tempting target for many chemists. German [65] and American chemists [66] have been approaching hexaazakekkulene and have synthesized its partially hydrogenated derivative XLIX.



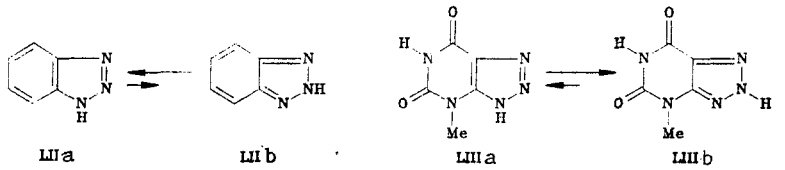
XLIX L

In the study of tautomerism, fundamentally new information has been related predominantly with tautometry in solid samples. Thus, the use of NMR spectroscopy has indicated that rapid proton migration between nitrogen atoms occurs even in crystalline porphyrins and phthalocyanines [67]. These molecules exist, as in solution, in an equilibrium mixture of degenerate forms LIa and LIb. Of course, such tautomerism is favored by an entropy factor, i.e., the fixed position of the heteroatoms within the ring. The importance of this factor is indicated by the lack of tautomerism for crystalline samples of imidazole and pyrazole, in which intermolecular hydrogen bonding is highly pronounced [68].



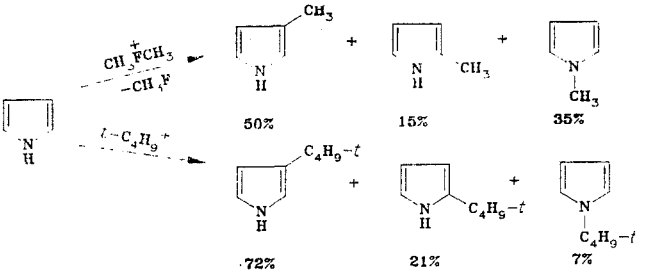
LI a $R=C_6H_4CH_3$-p LI b

Fortunately, findings, which would have been difficult to predict beforehand, are made occasionally in the study of tautomerism, as in the study of other properties of heterocyclic compounds. This again confirms the leading role of experimental research. In this regard, let us elucidate why the benzotriazole molecule in all states is found completely in the benzoid 1H form LIIa, while the quinoid 8H form LIIIb predominates in 8-azaxanthine [69]:



LIIIa LIIIb LIIIa LIIIb

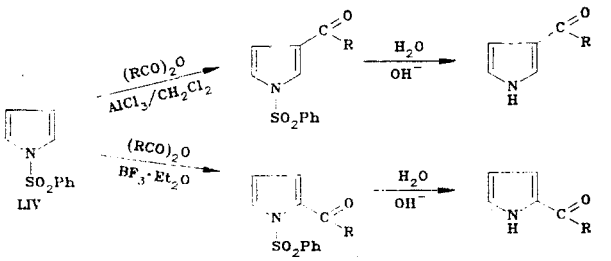
Significantly more unresolved problems and gaps in our knowledge remain in the theory of heterocyclic reactivity. Let us first examine the electrophilic substitution reaction, in which the major problem lies in the factors determining the positional and substrate selectivity and the methods of introducing electrophiles into nonstandard positions, such as the β-position in pyrrole [70, 71]. The most important advance in this area in the past 4-5 years is clearly the gas-phase electrophilic substitution in pyrrole and other five-membered heterocycles with one heteroatom [72, 73]. The results of the reaction of pyrrole with the dimethylfluoronium ion and the tert-butyl cation are given below. The dimethylfluoronium ion is considered hard, while the tert-butyl cation is considered relatively soft:



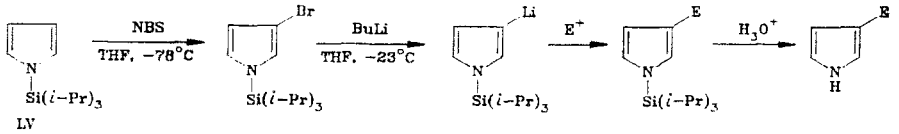
The major result of these experiments is the strong predominance of the β-substitution product over the α-substitution product in the case of pyrrole. It is now known that the π-charge in the pyrrole β-positions is greater than in the α-positions. Thus, the course of the reaction in the gas phase is controlled by charge. The formation of the α-substitution product as the major product in solution is due to solvation. The solvated σ-complex corresponding to α-substitution is more stable than the complex corresponding to β-substitution. Electrophilic substitution in pyrrole is also sometimes observed to proceed at C-3 in solution. Thus, Whipple et al. [74] noted in 1963 that pyrrole is protonated by sulfuric acid initially at a β-site but the adduct formed very rapidly rearranged to the more stable α–σ-complex.

The second important result of the gas-phase experiments is the demonstration of the possibility of the direct attack of the pyrrole nitrogen atom by the electrophile. Such an effect has been observed in solution only very rarely, such as in the protonation of carbazole [75]. Of course, broader generalizations on the direction of gas-phase electrophilic substitution may be made after azoles will be subjected to an analogous research.

The development of heterocyclic chemistry in solution is now progressing such that it is often possible to direct the entering substituent to a site usually uncharacteristic for a given type of compound by the proper selection of reaction conditions, substituents, and reagents. For example, Kakushima et al. [76] have shown that 1-benzenesulfonylpyrrole (LIV) undergoes Friedel—Crafts acylation exclusively at C-3. Elimination of the benzenesulfonyl group may give 3-substituted pyrroles, which were previously difficult to prepare, in high yield. It is interesting that replacing $AlCl_3$ in this reaction by boron trifluoride etherate leads to α-acylation. In one case, specifically in the formylation of LIV by dichlorodimethyl ether, the reaction proceeds at the α-position also in the presence of aluminum chloride. We may only presently conjecture concerning the reasons for this orientation.

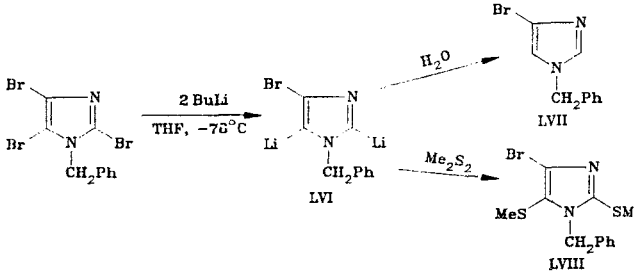


Another such example is the bromination of 1-(triisopropylsilyl)pyrrole (LV) by N-bromosuccinimide at C-3, which is apparently facilitated by the large bulk of the N-substituent [77]. After the replacement of bromine with lithium and the subsequent action of various electrophiles on the 3-lithium derivative, this reaction opens a pathway to other 3-substituted pyrroles.

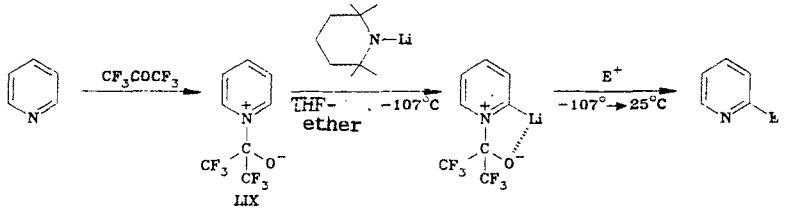


$E^+ = D_2O$, AlkX, PhSSPh, PhCOCl, PhCHO, $HCONMe_2$

The extent of the use of organometallic compounds in heterocyclic chemistry has greatly expanded in recent years. Both the direct metallation of C–H bonds and metal–halogen exchange are used to prepare such compounds. The introduction of two or even three metal atoms has often been proved synthetically. For example, the action of two equivalents of butyllithium on readily available 1-benzyl-2,4,5-tribromoimidazole gives only 2,5-dilithium derivative LVI, which may yield, for example, less available 1-benzyl-4-bromoimidazole LVII or LVIII [78].



However, the greatest progress has been achieved in the developments for the metallation of azines, in particular, of pyridine. Organometallic azine compounds were previously obtained almost exclusively using metal-halogen exchange since the addition of the nucleophile positions 1,2 or 1,4 is usually observed upon the action of metallating agents on azines. By varying the reaction conditions and selecting various activating groups and metallating agents, it has recently become possible to effect the metallation of C–H bonds in this series. Thus, pyridine in the presence of hexafluoroacetone gives adduct LIX, which is selectively metallated at low temperature by lithium tetramethylpiperidide at C-2. The action of electrophiles on the 2-lithium derivative may yield various 2-substituted pyridines [79]:



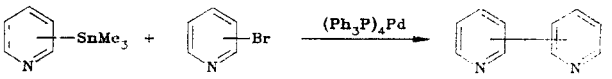
$E^+ = CH_3OD$, I_2, PhCHO, etc.

2-Pivaloylaminopyridine is metallated by n-butyllithium at C-3 [80], while 3-pivaloylaminopyridine is metallated by this reagent at C-4 [81]:

$E^+ = D_2O$, Me_3SiCl, $HCONMe_2$, etc.

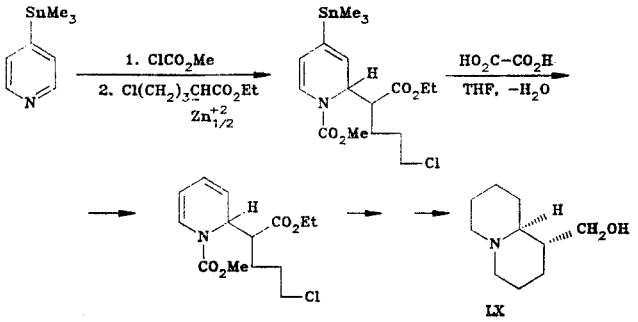
The metallation of pyridine at low temperature may be carried out using the n-butyllithium–potassium tert-butylate system [82]. In this case, the reaction may be directed, depending on the conditions, toward the predominant formation of either 2- or 4-lithopyridine (3-lithiopyridine is also always formed in small amounts).

Ever-increasing interest is being found in heterocyclic organotin compounds. For example, trimethylstannylazines in the presence of $(Ph_3P)_4Pd$ react with bromoazines to give diazines in good yield [83]:

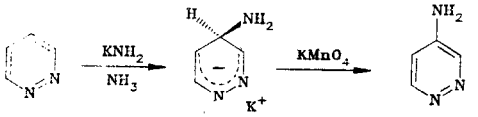


This method permits us to connect residues of identical or different azines.

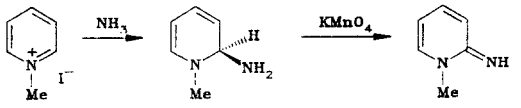
The use of the trimethylstannyl group as a blocker of one of a number of potentially active ring carbon atoms is an original approach. Thus, the addition of the ethyl ω-chlorovalerate residue to the γ-position of the pyridine ring must be avoided in the first step in the preparation of the alkaloid, lupinine LX. The use of 4-trimethylstannylpyridine as the starting compound permits us to achieve this goal [84]. After the addition of the enolate-anion of ethyl ω-chlorovalerate to the α-position of the 1-methoxycarbonyl-4-trimethylstannylpyridinium cation, the trimethylstannyl group is removed by means of oxalic acid:



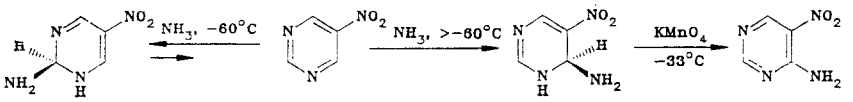
In the past, major attention in the study of nucleophilic substitution was directed toward the nucleophilic exchange of some groups by others, which has now become a routine synthetic instrument, and the detailed study of such reactions has largely been accomplished. Perhaps one of the few exceptions may be found in the studies of van der Plas on the Chichibabin reaction in liquid ammonia, in which the major problem of this reaction, namely the elimination of the hydride ion from the σ-complex, which usually proceeds in liquid ammonia only with great difficulty, was resolved. Potassium permanganate proved to be a convenient oxidizing agent for the elimination of the hydride ion. The use of this reagent permits the amination of a large number of heterocycles, which are poorly aminated under the standard Chichibabin reaction conditions involving an aprotic solvent and high temperature. For example, the amination of pyridazine in liquid ammonia gives its 4-amino derivative in 91% yield [85]:



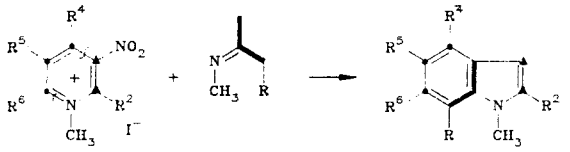
The imination of quaternary salts was achieved similarly, with the difference that the use of liquid ammonia by itself as the nucleophile is sufficient [86]:



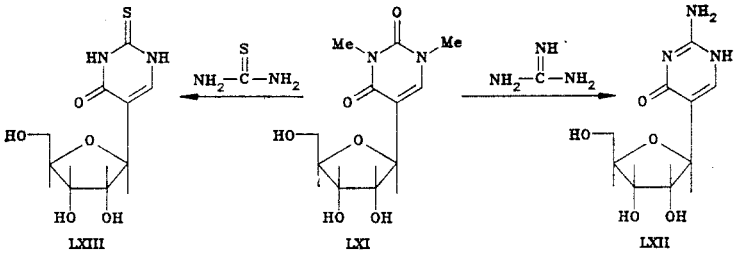
We should incidentally note that such imination was first achieved in work by the present author, in which 10-methyl-9-acridonimine was obtained from N-methylacridinium iodide in liquid ammonia in the presence of ferric nitrate as the oxidizing agent [87]. The use of liquid ammonia and potassium permanganate permits the amination of nitroazines, in particular 4-amino-5-nitropyrimidine may be obtained under thermodynamic control conditions from 5-nitropyrimidine [88]:



A major direction in the study of the reaction of heterocycles with nucleophiles is presently the combined transformation of heterocycles: recyclization, the replacement of certain ring fragments by others, and the removal of whole parts of rings. A typical example of such transformations may be found by the reaction of nitropyridinium salts with aliphatic N-alkylketimines (or mixtures of ketones with amines) leading to the formation of polyalkylindoles, which was discovered a few years ago by Yurovskaya et al. [89] at Moscow State University:



This transformation does not find analogy in the literature and entails the insertion of a ketimine fragment between pyridinium salt fragments. The promising nature of the use of 3-nitropyridinium salts as now synthones has been shown to lie in their capacity to decompose during a reaction not only as in the scheme for indole formation but, depending on the structure of the starting compounds, at all the other bonds (with the exception of the $C_{(5)}$—$C_{(6)}$ bond) and form new carbo- and heterocycles from these fragments with the participation of one or several ketone fragments. Thus, the capacity of 3-nitropyridinium salts to undergo transformation to o-dialkylaminobenzyl ketones, p-nitroanilines, 2,2-dialkyl-4-nitromethylene-1,2,3,4-tetrahydropyridines, 6-nitro-1,2-dihydroquinolines, and 6-nitro-1,2,3,4-tetrahydroquinolines was discovered for the first time.

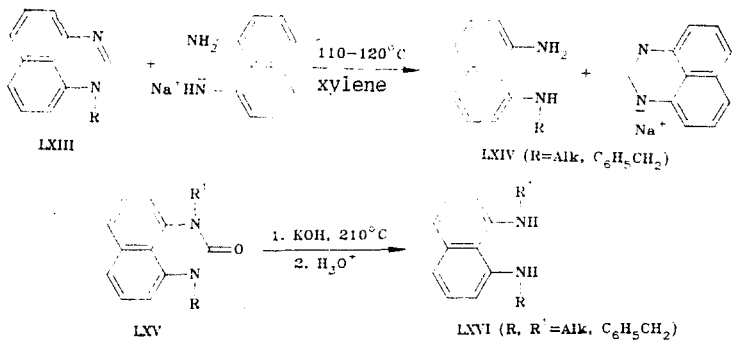


LXIII LXI LXII

Complex transformations of heterocycles has now becomes as standard a synthetic method as the simple replacement of functional groups [90, 91]. Thus, Watanabe et al. [90] synthesized the antileukemia drug ψ-isocytidine (LXII) in good yield by the action of guanidine on the C-nucleoside of uracil LXI. This transformation proceeds by an ANRORC mechanism. Alkylguanidines or thiourea may be used analogously. Thiouracil derivative LXIII is formed when thiourea is used.

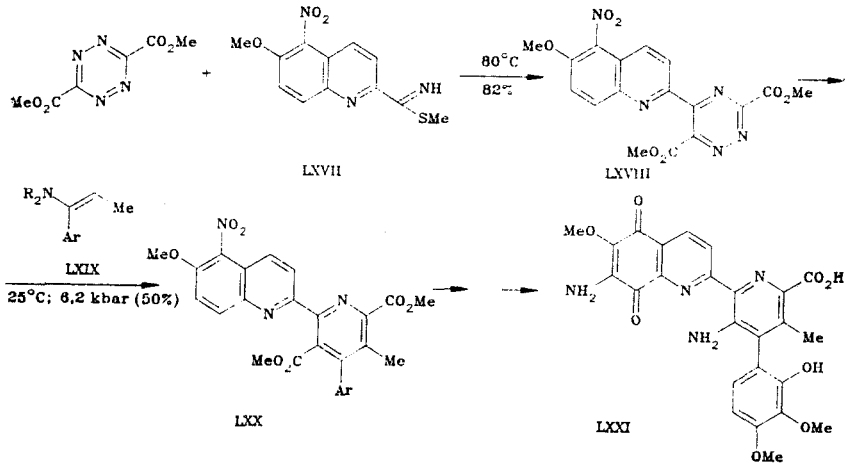
Great importance is found for the elimination of individual heterocycle fragments in order to obtain acyclic compounds, which are difficult to prepare by other methods. For example, 1-substituted perimidines LXIII by the action of a strong nucleophile as the anion of 1,8-diaminonaphthalene transfers its μ-carbon atom to the anion, leading to the formation of mono-N-substituted 1,8-diaminonaphthalene LXIV in good yield; the nucleophile is thereby converted to perimidine [92]. Molten KOH powder removed the C=O group from 1,3-dialkylperimidone LXV, leading to N,N'-dialkylnaphthalenediamines LXVI, which are difficult to obtain by other methods [93]. Both reactions also proceed in the benzimidazole series and have preparative value (see scheme at top of following page).

Special attention has been given recently to reverse Diels—Alder reactions featuring π-deficient azines such as tetrazines, triazines, and pyridazines, while electron-rich ethylenes, acetylenes, or their heteroanalogs are used as the dienophile [94, 59]. The importance of these reactions lies in the possibility of resolving synthetic problems related to complex transformations of one type of heterocycle to another. Thus, two key steps in the multistep synthesis of the alkaloid, streptonigrin LXXI, are based on reverse Diels—Alder reactions. Initially, 3,6-di(methoxycarbonyl)tetrazine is subjected to cycloaddition with the



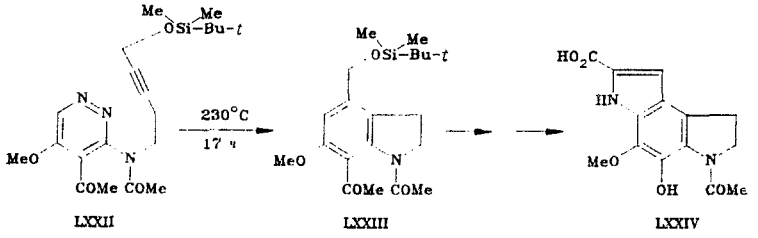
LXIII LXIV (R=Alk, $C_6H_5CH_2$) LXV LXVI (R, R′=Alk, $C_6H_5CH_2$)

exocyclic C=NH bond of quinoline derivative LXVII to give triazine LXVIII, which is subjected to cycloaddition with enamine LXIX to give the pyridine ring in LXX containing the required substituents. In both cases, the reaction is accompanied by the elimination of a nitrogen molecule, initially from a tetrazine and then from a triazine.



LXVII LXVIII LXX LXXI

Intramolecular cycloaddition has found common use. For example, aminopyridazine LXXII containing an acetylenic bond in the side chain is converted to indoline LXXIII, from which the important phosphodiesterase inhibitor LXXIV is then synthesized [95].



LXXII LXXIII LXXIV

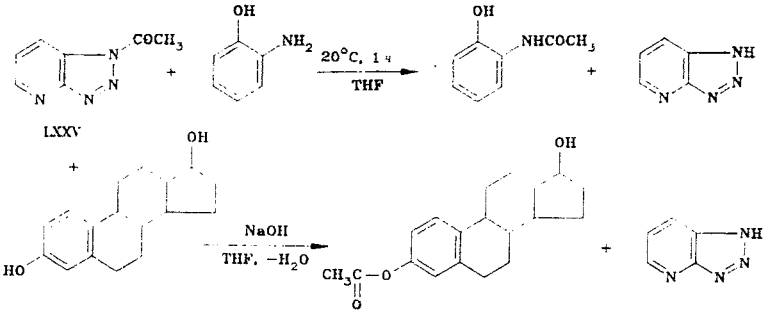
Let us now briefly examine problems related to the reactivity of heteroatoms. One of the outstanding theoretical problems is the question of the stereochemistry of the pyrrole nitrogen atom. In the classical viewpoint, this nitrogen atom should be planar since such a configuration provides for maximal overlap of the π-electron clouds participating in the aromatic system. However, Dewar [96] has shown that the conjugation of the nitrogen unshared electron pair with the other ring π-electrons is even greater in the case of a pyramidal nitrogen atom. Hence, this author proposed that rapid degenerate inversion between two forms with a pyramidal nitrogen atom is possible. The available x-ray diffraction structural data on a series of such compounds alternately support both viewpoints. Thus, the nitrogen atoms in 10π-electron aromatic 1,4-dihydrodiazocine have planar configuration [97]. On the other hand, the nitrogen atom in N-substituted carbazoles and in carbazole itself is largely pyramidalized [98]. Further studies on the stereochemistry of nitrogen in compounds such as pyrrole, indole, and azoles are clearly required.

Another problem is related to the oxidation of azoles to N-oxides. The oxidation of azines by hydrogen peroxide or peracids is the common method for their conversion to N-oxides. On the other hand, in the case of azoles, despite their rather high basicity, this reaction

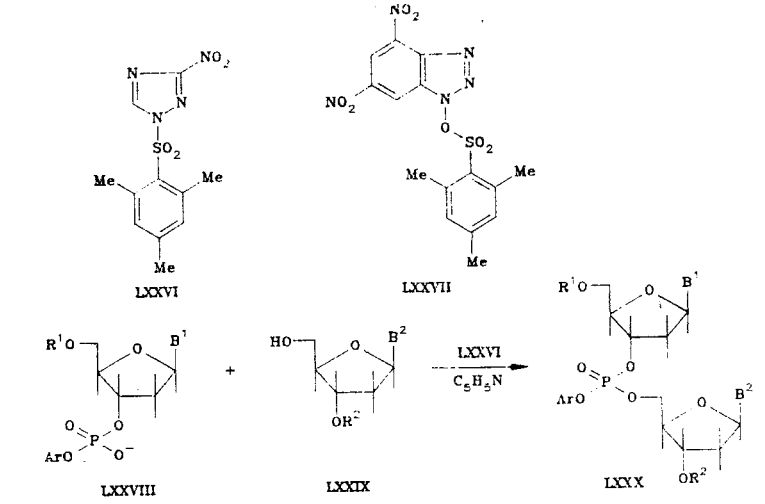
either proceeds with very low yield or, more frequently, leads to decomposition [15]. This behavior is probably a consequence of the circumstance that the HOMO of the azoles is usually of the π-type rather than the n-type, as in the case of most azines. Hence, the oxidizing agent initially removes an electron from the π-orbital of azoles, converting them to radical-cations, which rapidly undergo extensive transformations. New ideas are required to solve this synthetic problem. Prior blocking of the π-orbitals of azoles by means of complexation with transition metal ions or special oxidation agents may be helpful in this case.

The search for new protecting groups for the pyrrole nitrogen atom remains an important problem. Various types of protective groups are required, including acid-stable, base-stable, heat-resistant groups, and groups capable of blocking adjacent carbon sites or, on the other hand, activating rings. Typical examples of such protective groups have been noted above, such as LIV and LV.

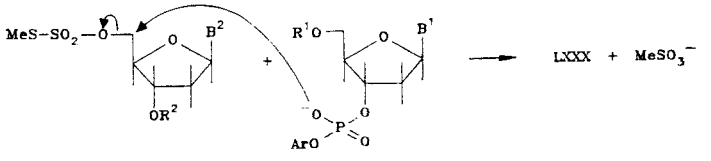
Another long-standing area of research is related to the preparation of new reagents using N-substituted azoles or azinium salts. The action of these reagents is most often based on the capacity of the N-hetaryl residues to be good leaving groups. Well-known examples of such reagents are N,N'-carbonyldiimidazole, which is a reagent for the synthesis of peptides and other carbonyl compounds, N-nitropyridinium salts, which are selective nitrating agents, and N-chlorobenzotriazole, which is a mild chlorinating agent. The improvement of such reagents relative to their selectivity is constantly progressing. In this regard, triazole and tetrazole derivatives have the highest promise. Thus, 1-acetyl-v-triazolo[4,5-b]pyridine (LXXV) is a mild acylating agent, which may be used for the selective acetylation of the amino group in aminophenols in neutral media or of the phenolic hydroxyl group in the presence of an alcoholic hydroxyl group under alkaline conditions [99]. This reaction may be used effectively in steroid synthesis:



Mesitylsulfonyltriazoles such as LXXVI or LXXVII are used in the synthesis of oligonucleotides as condensing agents [100]. The key step in this synthesis is linkage of the 3'-phos-



Linking mechanism:



phodiester component LXVIII with the 5'-hydroxy group of nucleoside LXXIX. The condensing agent initially transfers the mesitylsulfonyl group to the alcoholic 5'-hydroxyl group of the nucleoside (the reaction requires the presence of pyridine). This activates the corresponding carbon atom to its subsequent nucleophilic attack by a phosphodiester group oxygen. The mesitylsulfonic acid residue serves as a leaving group (see scheme above).

Recent advances in heterocyclization reactions have virtually not been discussed in this review. Such reactions are specific for each type of heterosystem and are not readily generalized. However, this area in heterocyclic chemistry undoubtedly remains one of the most important.

In evaluating the state of affairs in heterocyclic chemistry today, we should first note the high level of development of the theory and physical chemistry of heterocycles, in which developed concepts and well-established patterns have not been greatly altered. It is not surprising that there have been no significant qualitative advances in this area in the past 4-5 years. Under these conditions, special interest is found in inexplicable and unexpected experimental findings, which are fortunately not rare in heterocyclic chemistry.

Second, we should acknowledge the increase in the complexity of synthetic problems. The design of new heteroaromatic structures, macrocycles, and models of a variety of enzymes has become a refined art and a well-developed area in chemistry. Hence, the major advances in heterocyclic chemistry in the next few years should come in the synthesis of complex natural products and biological catalyst models and the design of new types of heterocyclic systems, primarily of macrocyclic and, probably, framework systems.

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SYNTHESIS OF BENZO[c]-2-FURANONE DERIVATIVES FROM FUNCTIONALLY-SUBSTITUTED 2-BUTEN-2-OLIDES

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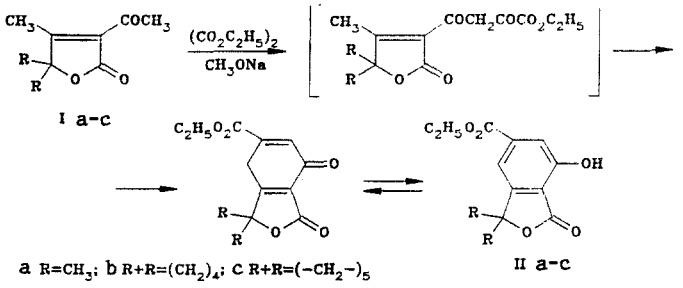
UDC 547.724.2'728.2.07

The reaction of substituted 2-acetyl-2-buten-4-olides with diethyl oxalate gives 3-hydroxy-5-ethoxycarbonyl-7,7-dialkylbenzo[c]-2-furanones. These products were also converted to their 5-carboxy derivatives and some salts.

In previous work [1], we showed that the condensation of 2-acetyl-2-buten-4-olides Ia-Ic with diethyl oxalate leads to the corresponding 2-(1-ethoxycarbonyl-1,3-diketopropyl)-3,4,4-trialkyl-2-buten-4-olides.

We have found that carrying out this condensation at 90-95°C in the presence of dry sodium methylate leads to a new heteroaromatic system, namely, 3-hydroxy-5-ethoxycarbonyl-7,7-dialkylbenzo[c]-2-furanones IIa-IIc, probably through the following transformations.



Erevan State University, Erevan 375049. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 24-26, January, 1989. Original article submitted July 17, 1987.

 0009-3122/89/2501-0018$12.50