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Advances in the Chemistry of Azaindoles

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The results of research into the chemistry of azaindoles during the last ten years are examined and the advances in the development of new methods for the synthesis and the study of the chemical and physicochemical characteristics of the behaviour of azaindole systems containing condensed rings with an excess and a deficiency of π-electrons are discussed. The studies on the nature of the biological activity of various derivatives of isomeric azaindoles are summarised.
The bibliography includes 267 references.

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I. INTRODUCTION

As a result of vigorous research by Soviet and foreign investigators, new significant results have been obtained in the chemistry of azaindoles during the ten years which have elapsed since the publication of two previous reviews on this field[1,2]. The methodological possibilities of the synthesis of azaindole structure have greatly expanded and the study of the characteristics of the structure of azaindoles compared with indoles revealed new chemical transformations (the cleavage of the N-N bond in hydrazones with simultaneous alkylation of the nitrogen atom[3-5], etc), which are outside the framework of the problem under consideration.

Azaindoles proved to be convenient models for the study of the mutual influence in condensed systems of *N*-heteroaromatic rings with opposite shifts of the π-electron density within each ring—a problem which is of general interest for the chemistry of heterocyclic compounds and theoretical organic chemistry.

Studies on the tautomerism of hydroxy-, amino-, and acylamino-azaindoles[6] served as the starting point of the investigation of a number of general problems of tautomeric equilibria involving *N*-heteroaromatic compounds[7-10], while consideration of the protonation of azaindoles showed that these compounds are effective models for a more detailed study of the mechanisms of protolytic equilibria[11-13].

Studies on the interrelations between tryptophan, heteroauxin, and other biologically important indole compounds, on the one hand, and their 7-aza-analogues on the other, in biochemical processes have been greatly expanded and carried out in greater depth. The observation of a high activity of new antibiotics—tubercidin, toyocamycin, and sangivamycin—which are *N*-glycosylated derivatives of diazaindoles[14], stimulated research into the synthesis and activities of *N*-glycosylated indoles as the antimetabolites in the metabolism of nucleic acids[15,16].

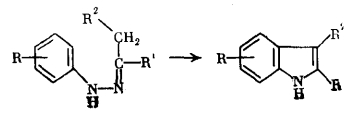
The above factors as well as the psychotropic and cardiovascular activities of a wide variety of synthetic azaindole derivatives, discovered in recent years, led to an extensive development of synthetic research into this series of compounds. Chemical and biochemical investigations in the field of porphobilinogens—derivatives of azaindoles linked to porphyrins, protoporphyrins, and their analogues, have been prosecuted vigorously[17-19].

Within the framework of a single review, it is difficult to cover the entire wide range of problems associated with azaindoles and we therefore decided to disregard in the present review studies on condensed azaindole systems (a small section dealing with the formation of new condensed heterocyclic systems based on 7-azaindole derivatives is an exception) as well as studies on fully or partly hydrogenated azaindoles (with the exception of azaindolines and systems in which aromaticity breaks down as a result of tautomerism). The studies on the chemistry and biology of azaindoles published up to 1967 and discussed in earlier reviews[1,2] are quoted in exceptional instances where it is necessary to describe the general characteristics of the state of the problem.

II. METHODS OF SYNTHESIS OF AZAINDOLE STRUCTURES

1. Syntheses Based on Pyridylhydrazines

The attempts to apply to the series of azoindoles the Fischer reaction, on which one of the main methods for the synthesis of indole derivatives is based[20], yielded few positive results under the usual conditions of acid catalysis:

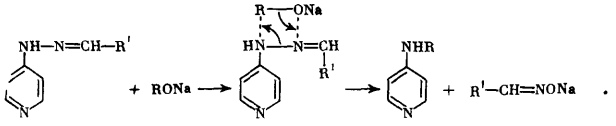


azaindole derivatives were isolated in low yields or were not obtained at all, owing to the relative inertness of the pyridine ring with respect to electrophilic attack on the carbon atoms and the ease of such attack on the pyridine nitrogen atom[21]. Modification of the reaction conditions, involving a transition to "non-catalytic" thermal cyclisation, extended somewhat the possibilities of the method[22]. Thus the 4-pyridylhydrazones of isobutyraldehyde and ethyl methyl ketone were converted into 2,3-dimethyl-5-azaindole on being refluxed in diethylene glycol, while the 4-pyridylhydrazones of propionaldehyde and 2-methylbutyraldehyde were converted into 3-methyl- and 2-ethyl-3-methyl-5-azaindoles[23-25].

1,2-Dialkyl (or-diaryl)-4-methyl-7-azaindoles have been obtained from 4-methyl-2-pyridylhydrazones of propionaldehyde, phenylacetaldehyde, acetophenone, and deoxybenzoin[26], while the analogous 4-azaindole derivatives have been synthesised from 3-pyridylhydrazones of propionaldehyde, ethyl methyl ketone, acetophenone, and certain others[25]. 4-Substituted 5-azaindoles have been synthesised on the basis of 2-hydroxy-6-methyl-4-pyridylhydrazine[27].

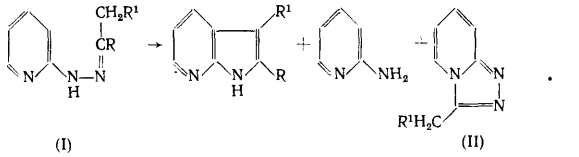
Studies designed to optimise the conditions of the "normal" Fischer reaction in the synthesis of azaindoles have not ceased either. It has been established[28-35] that the yields of the "normal" products of the conversion of 2- 4-pyridylhydrazines by the Fischer reaction vary within wide limits, depending on the nature of the initial hydrazine and that of the substituents in the hydrazine component, as well as the structure of the carbonyl component and the catalyst employed. The introduction of electron-donating substituents into the pyridine ring facilitates the "normal" Fischer cyclisation; on the other hand, electron-accepting groups hinder this process and promote an "anomalous" course of the reaction with formation of aminopyridines of products of cyclisation via the pyridine nitrogen atom.

It has been possible to carry out the Fischer reaction in the presence of not only acid but also alkaline catalysts[34,35]. In the course of this research a new type of cleavage of the N-N bond in isomeric 2-, 3-, and 4-pyridylhydrazones under the influence of alkali alkoxides was discovered; it results in the formation of monoalkylaminopyridines and *syn*-oximes of the carbonyl components of the hydrazones[4,35]:



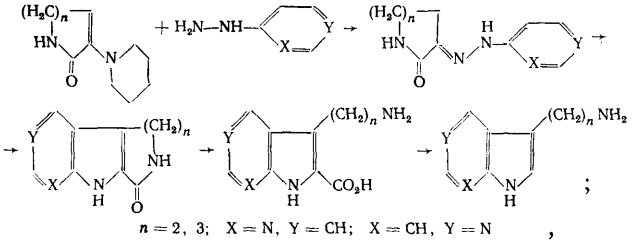
The use of aromatic aldehydes as the carbonyl component in those cases where the "normal" course of the Fischer reaction becomes impossible led to the development of a new preparative method of synthesis of *N*-monoalkylaminopyridines[4,36].

Azaindole structures are formed also in the Fischer cyclisation under the conditions of high-temperature heterogeneous catalysis[37,38]. 7-Azaindole and its 2-methyl- and 2,3-dimethyl-derivatives have been obtained from the 2-pyridylhydrazones of acetaldehyde, acetone, and ethyl methyl ketone (I) by the above method in the presence of alumina. The reaction was accompanied by the formation of 2-aminopyridine and the product of the cyclisation via the pyridine nitrogen—3-methyl-*s*-triazolo[4,3-*a*]pyridine (II).



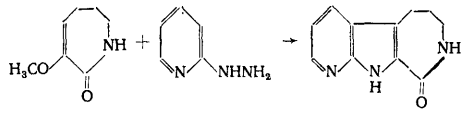
(I) (II)

The synthesis of 5- and 7-azatryptamines and 5- and 7-azahomotryptamines from α- or γ-pyridylhydrazines and lactam α-enamines[39] via the mechanism



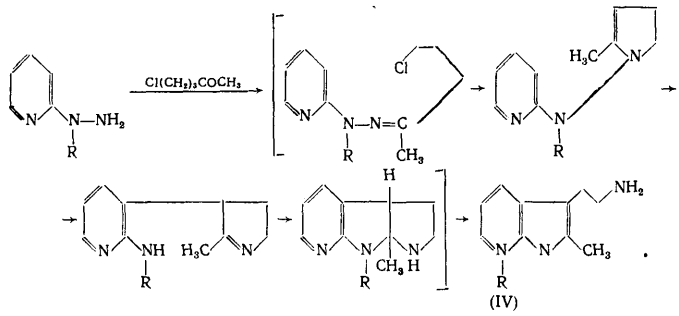
$n = 2, 3$; X = N, Y = CH; X = CH, Y = N

has been described. The use of pyridylhydrazine and 3-methoxy-2-oxo-2*H*,1,5,6,7-tetrahydroazepine (III) in the Fischer reaction yielded the new system of 1-oxo-9-aza-1*H*,2,3,4,5-tetrahydrazepine[3,4,-*b*]indole[40]:



(III)

The synthesis of 2-methyl-7-azatryptamine (IV, R = H) and 1,2-dimethyl-7-azatryptamine (IV, R = CH_3) has been achieved[41,42] by the reaction of 2-pyridylhydrazine with γ-chloropropyl methyl kentone:

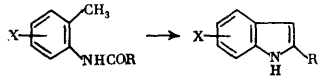


(IV)

2. Syntheses Based on *o*-Nitro- or *o*-Acylamino-picolines and Their Derivatives

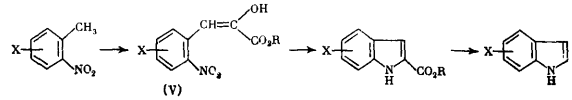
This group of methods includes primarily the Madelung and Reissert reactions which are widely used in the chemistry of indoles.

The Madelung synthesis, which consists in the cyclisation of *o*-acylaminomethyl derivatives of aromatic compounds, was of the greatest importance in the synthesis of azaindole compounds until the last decade:



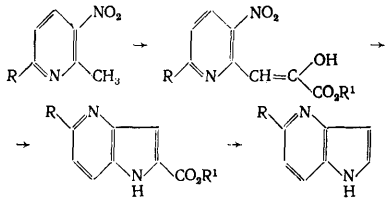
Unsubstituted 4-, 5-, and 7-azaindoles and some of their alkyl derivatives have been synthesised with the aid of this reaction[1]. However, during the last 10 years the Madelung method has not been specially developed for the synthesis of azaindoles owing to inadequate yields and the limited range of substituents which can be introduced into the azaindole system. Among the studies carried out in this field mention should be made of the confirmation[26] of the superiority of sodium *N*-methylanilide over sodium ethoxide as the catalyst in the synthesis of 2-methyl, 2-phenyl-, and 2-pyridyl-7-azaindoles, which agrees well with the hypothesis[43] concerning the roles of amidines as intermediates in the Madelung reaction. The 2-phenyl derivatives of 4-, 5-, 6-, and 7-azaindoles have been synthesised in low yields by the cyclisation of *o*-benzamidopicolines under the conditions of alkaline catalysis[44].

The Reissert method, which consists in the condensation of *o*-nitromethyl derivatives of aromatic compounds with diethyl oxalate, further reductive cyclisation of the intermediates (V) followed by the hydrolysis of indole-2-carboxylic acid esters, and decarboxylation has found extremely limited applications in the series of azaindoles[2]:



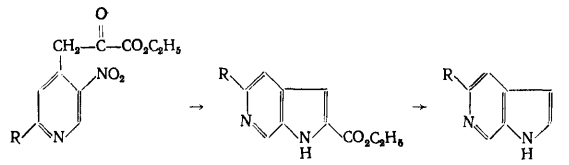
(V)

It was not until 1968 that the Reissert method began to be used successfully[45-48] in preparative synthesis of 4-azaindole and 5-alkoxy-derivatives:

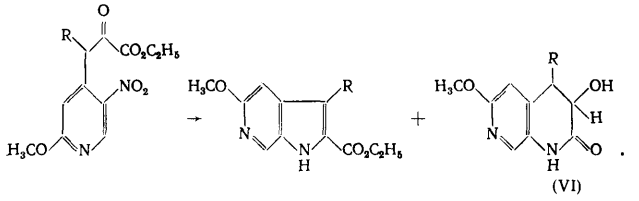


The greatest difficulty in this synthesis was the decarboxylation of 4-azaindole-2-carboxylic acids, for which satisfactory conditions could not be found initially[46]. Later a convenient method was developed[45,47,48] for the direct elimination of the carboxy-group by refluxing the acids in biphenyl in the presence of copper bronze.

The Reissert method has been used widely also in the synthesis of 6-azaindole derivatives[17,18,46,49,50]:

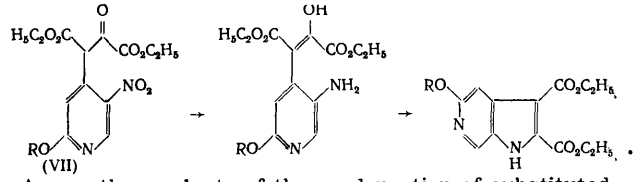


The presence of substituents in the α-methylene group of the side chain complicates the process: together with 6-azaindole derivatives, partly hydrogenated 1,7-naphthyridines (VI) are produced[51]:



(VI)

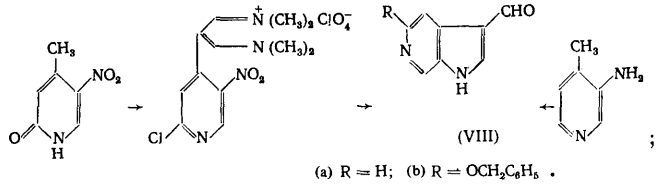
The reduction of the diethyl esters (VII) leads to the preferential formation of 3-aminopyridine derivatives, which are converted into 2,3-diethoxycarbonyl-6-azaindoles in the presence of phosphoryl chloride[51]:



(VII)

Among the products of the condensation of substituted 2-chloro-3-nitropyridine with malonic[52] or cyanoacetic[53,54] esters, 4-azaoxindole and its derivatives were synthesised.

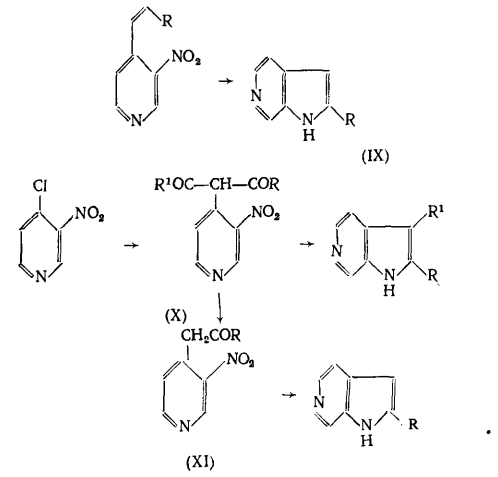
The synthesis of 3-formyl-6-azaindole (VIIIa) [55] and its 5-benzyloxy-derivative (VIIIb) [9] has been achieved in low yields under the conditions of the Wilsmeyer reaction:



(VIII)

(a) R = H; (b) R = $OCH_2C_6H_5$.

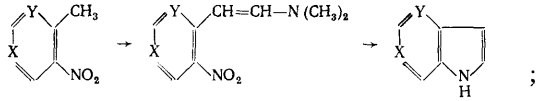
2-Substituted 6-azaindoles (IX), R = alkyl or heteroaryl, have been synthesised in yields of 12–22% by the reductive cyclisation of 3-nitro-4-vinylpyridines with triethyl phosphite[44]:



(IX) (X) (XI)

Various 2-substituted and 2,3-disubstituted 6-azaindoles have been synthesised by the reaction of 4-chloro-3-nitropyridine with β-dicarbonyl compounds (malonic, acetoacetic, and benzoylacetic ester, etc) or with cyanoacetic ester followed by reductive cyclisation of compounds (X) obtained or their reaction products (XI).[52,56-58]

The use of condensation of *o*-nitropicolines (XII) with the dimethylformamide (DMF) acetal followed by the reductive cyclisation of nitroenamines (XIII) proved to be fruitful in the synthesis of isomeric 4- and 6-azaindoles[59,60]. The yields of the azaindoles (XIV) (with respect to the readily available *o*-nitropicolines) are nearly quantitative when this method is used:



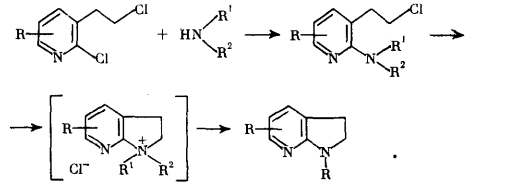
(XII) (XIII) (XIV)

X = CH, Y = N; X = N, Y = CH .

The employment of 3-bromo-5-nitro-γ-picoline as the starting compound yielded 4-bromo-6-azaindole[61], while the introduction of (3-nitro-4-pyridyl)acetone or ethyl (3-nitro-4-pyridyl)acetate instead of *o*-nitropicolines led to 3-substituted 6-azaindoles[62].

3. Syntheses from Halogeno-Derivatives of 3-(β-Chloroethyl)Pyridines via the Corresponding Azaindolines

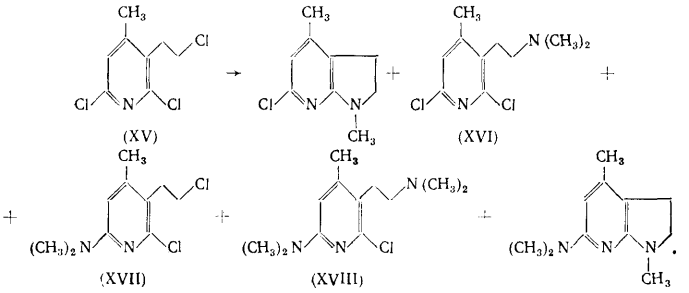
A general method of synthesis of a wide variety of derivatives of 5- and 7-azaindoles had been developed previously[1] on the basis of the reaction of 3-(β-chloroethyl)pyridines, containing halogen atoms in the 2- or 4-positions, with ammonia and primary or secondary amines:



During the last ten years, the study of this method was continued in relation to the reaction of 2,6-dichloro-3-(β-chloroethyl)-4-methylpyridine (trichlorocollidine) (XV) with

asymmetric secondary amines[63]. It was established that the ease of elimination of the substituent at the pyrroline nitrogen atom in the intermediate quaternary azaindoline salt increases in the sequence aryl < alkyl < benzyl, while for alkyl substituents the sequence is hexyl < ethyl < methyl[64].

Detailed study of the side reactions occurring when compound (XV) interacts with dimethylamine[65] established the possibility of controlling the process by altering the reactant ratio, temperature, the reaction time, the polarity of the medium, and the catalytic effect of metal salts. It was shown that side processes leading to the monocyclic products (XVI)–(XVIII) can be suppressed by increasing the polarity of the medium:



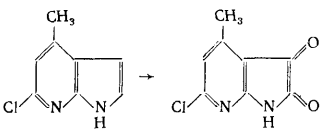
(XV) (XVI) (XVII) (XVIII)

Trichlorocollidine (XV) reacts with sterically hindered primary amines of the type of β-phenylisopropylamine as well as *N*-substituted anilines to form 6-chloro-7-azaindolines and not the 6-amino-derivatives[66]. On passing to t-butylamine, the nucleophilic attack on the α,α′ positions in the pyridine ring becomes sterically impossible and the main reaction pathway becomes the dehydrohalogenation of compound (XV) to 2,6-dichloro-4-methyl-3-vinylpyridine.

5-Azaindolines have been obtained in analogous processes from 4,6-dichloro-3-(β-chloroethyl)pyridine[47,67], while 4-chloro-(5-chloroethyl)pyrimidines gave rise to derivatives of 5,7-diazaindoles[68].

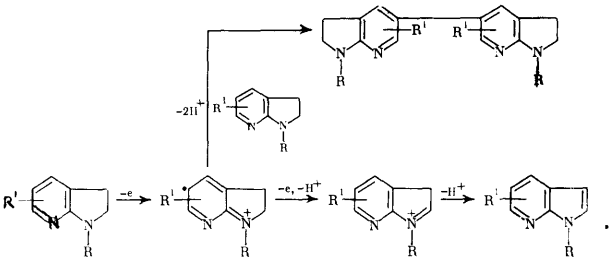
The hydrogenation of azaindolines, i.e. conversion into aromatic azaindole systems, has been achieved successfully by reaction with chloranil and dichlorodicyanoquinone and catalytically in the presence of palladium[47,63,66,69–71]. The dehydrogenation reaction involves *N*-debenzylation[63] and even *C*-dealkoxylation[69].

Studies on the polarographic dehydrogenation of azaindolines and the mechanism of this process have been published[72–77]. It has been shown that azaindolines with an oxidation potential $E_{1/2}$ < 1.1 V are capable of being dehydrogenated by chloranil, those with $E_{1/2}$ up to 1.2 V can be dehydrogenated by dichlorodicyanoquinone, and those with a potential up to 1.4 V can be dehydrogenated by activated manganese dioxide[78]. Azaindoles are oxidised by chromium trioxide to azaisatins[79]:



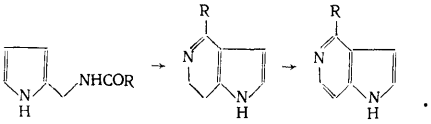
The conversion of 7-azaindolines into indolines without electron-accepting pyridine nitrogen is facilitated by dehydrogenation[72–74], while the conversion to 5-azaindolines and 5,7-diazaindolines gives rise to a successively enhanced hindrance to this process[75].

A mechanism has been proposed for the polarographic oxidation of 7-azaindolines via the formation of intermediate radicals of the semiquinonoid type with further aromatisation to give7-azaindoles or dimerisation to give the corresponding 5,5-bis-7-azaindolines, which have been isolated on a preparative scale[76]:

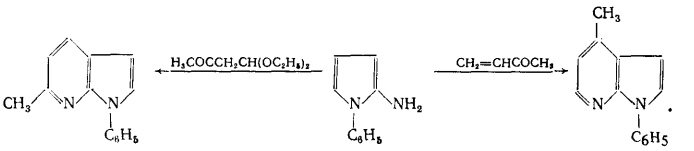


4. Syntheses Based on Pyrrole Derivatives

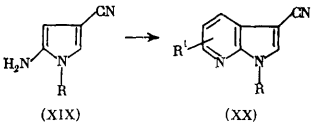
Up to 1968 there were only isolated publications concerning the syntheses azaindole systems based on pyrrole derivatives which dealt[1] with the preparation of 5-azaindoles from acylated 1-(β-aminoethyl)pyrroles by the Bischler–Napieralski reaction:



The synthesis (with a yield of 18–23%) of 4-methyl- and 6-methyl-1-phenyl-7-azaindoles by the reaction of 2-amino-1-phenylpyrrole with methyl vinyl ketone and the acetal of acetoacetaldehyde in the presence of zinc and iron chlorides was reported in 1973 [80]:



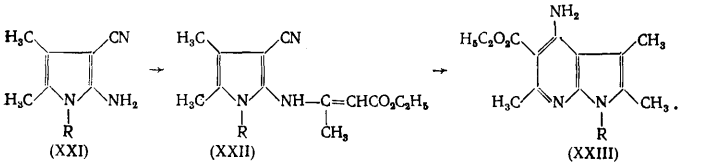
The use of cyanaminopyrroles as the starting materials for the extension of the range of dicarbonyl compounds employed led to the synthesis of a wide variety of 7-azaindole derivatives[81,82]. Thus 1-alkyl(or aryl)-2-amino-4-cyanopyrroles (XIX) undergo cyclocondensation with 1,3-dicarbonyl compounds and their acetals to form unsubstituted 1-alkyl(or aryl)-3-cyano-7-azaindoles (XX) or derivatives substituted in the pyridine ring[81]:



(XIX) (XX)

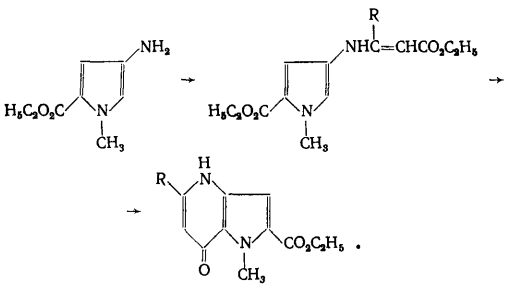
R′ = H or alkyl.

When 1,4,5-trisubstituted 2-amino-3-cyanopyrroles (XXI, R = aryl or cyclohexyl) were allowed to react with acetoacetic ester, the products were propenylaminopyrroles (XXII), which were converted by reductive cyclisation into bifunctional polysubstituted 7-azaindoles (XXIII) [82]:

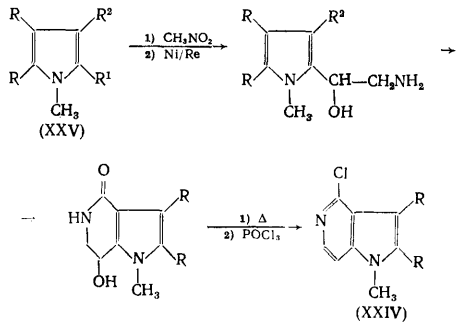


(XXI) (XXII) (XXIII)

The successful use of the 2-ethoxycarbonyl derivative of the isomeric 4-amino-pyrrole in syntheses of substituted 4-azaindoles has been reported[83]. The reaction with β-dicarbonyl compounds proceeds in this case also via propenylaminopyrroles, whose cyclisation can yield 2-ethoxycarbonyl-1-methyl-4-azaindoles with substituents in the pyrridine ring:



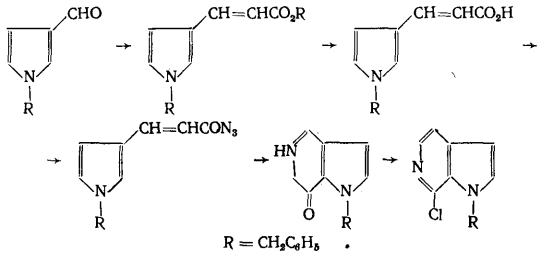
The method of synthesis of 4-chloro-1-methyl(or benzyl)-5-azaindole (XXIV, R = H) and its 2,3-dichloro-derivative (XXI, R = Cl) from 3-ethoxycarbonyl-2-formyl-*N*-methyl(or benzyl)pyrrole and its 4,5-dichloro-derivative (XXV, R = Cl, R^1 = CHO, $R^2 = CO_2C_2H_5$) [84,85] via the mechanism



is of interest.

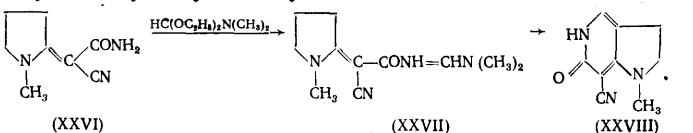
Compound (XXIV, R = H) has also been obtained[86,87] by the reaction of 2-formyl-*N*-methylpyrrole (XXV, $R = R^2 = H$, R^1 = CHO) with malonic acid and by the cyclisation of the azide of the resulting substituted acrylic acid derivative (XXV, $R = R^2 = H$, $R^1 = CHCHCO_2H$) followed by treatment with phosphoryl chloride[88].

1-Benzyl-7-chloro-6-azaindole has been synthesised using an analogous scheme[87] from 1-benzylpyrrole-3-aldehyde via 1-benzyl-3-pyrrolylacrylic acid:



The synthesis of 4,6-dihydroxy-5-azaindole (3,7-didesazaxanthine) has been achieved recently by the alkaline cyclisation of 3-ethoxycarbonyl-2-pyrrolylacetamide[89].

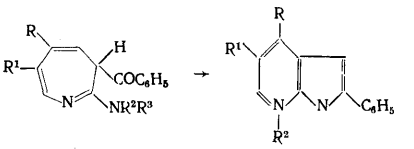
In the reaction of 2-(2-cyano-2-carbamoylmethylene)-1-methylpyrrolidinone (XXVI) with the DMF acetal the condensation involves the amide NH_2 group and the resulting substituted acylformamidine (XXVII) readily cyclises to the 7-cyano-6-hydroxy-1-methyl-5-azaindoline (XXVIII) [90,91]:



An analogous synthesis based on the *N*-benzyl derivative of pyrrolidinone makes it possible to obtain 1-benzyl-7-cyano-6-hydroxy-5-azaindoline, which splits off the cyano- and benzyl groups simultaneously on being refluxed with hydrobromic acid and gives rise to a high yield of 6-hydroxy-5-azaindoline[92].

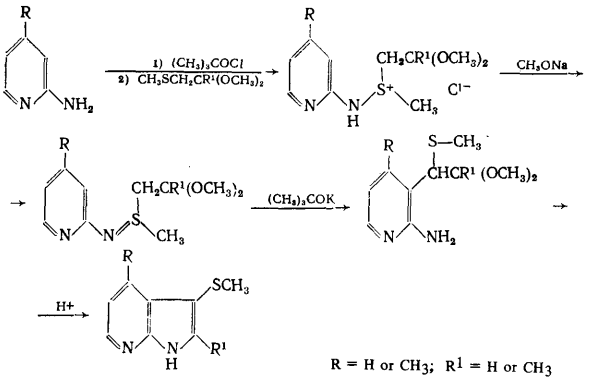
5. Other Syntheses

Certain syntheses of azaindolines by specific methods have been described in the literature. An example is provided by the thermal rearrangement of 3-acyl-2-amino-3*H*-azepines (XXIX) to 7-azaindoles (XXX) [93]:



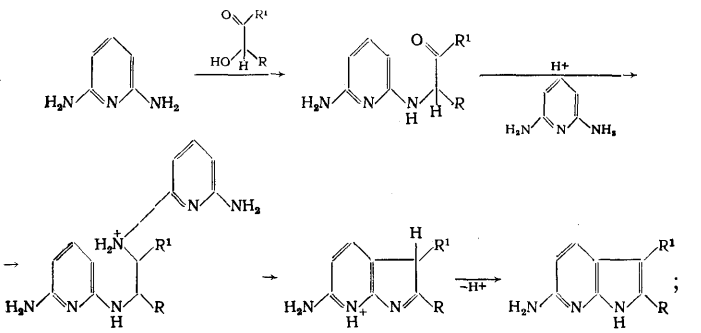
R, R^1 = H, Cl; R^2 = H, C_6H_5, or n-C4H9.

The synthesis of 3-methylthio-7-azaindoles from 2-aminopyridines via the mechanism

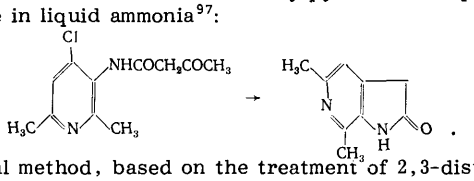


has been reported.

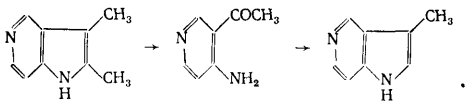
The use of the Bischler reaction, which involves the interaction of α-hydroxy-ketones with 2,6-diaminopyridine, for the synthesis of 7-azaindoles has also proved to be successful[96]:



5,7-Dimethyl-6-azaoxindole has been obtained by cyclising 3-acetoacetamido-4-chloro-2,6-dimethylpyridine with potassium amide in liquid ammonia[97]:

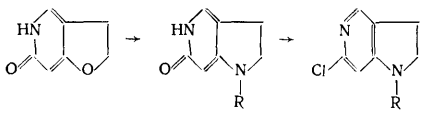


An unusual method, based on the treatment of 2,3-disubstituted 5-azaindoles or 6,7,8,9-tetrahydro-γ-carbolines with hydrogen peroxide in acetic acid, has been proposed[98] for the synthesis of 3-substituted 5-azaindoles. The process takes place with the opening of the pyrrole ring and further cyclisation of the resulting *o*-aminopyridyl ketones or *o*-aminopyridinecarboxylic acids with dimethylsulphonium methyid:



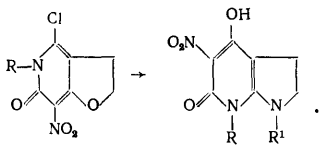
An analogous closure of the pyrrole ring is believed[98] to be possible also for 7-azaindoles. However, the yields in both stages of the process are low so that the method is of no practical value.

Satisfactory results have been obtained in the synthesis of 1-phenyl and 1-benzyl-5-azaindolines[47,70,99,100] by the reaction of 6-oxo-2,3-dihydro-5-azabenzofuran (XXXI) with primary amines:



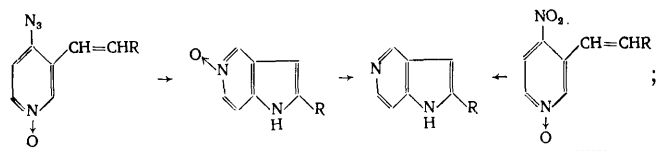
(XXXI)

The interaction of 4-chloro-7-nitro-6-oxo-2,3-dihydro-5-azabenzofurans (XXII) with primary and secondary amines involves the substitution of the chlorine atoms by amine residues and recyclisation of the compounds to 7-azaindoline derivatives[101]:



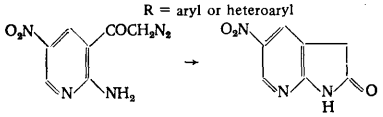
(XXXII)

The synthesis of azaindoles by the thermal cleavage of 4-azido-3-styrylpyridine 1-oxide (XXXIII) with subsequent *N*-deoxidation of the resulting 2-phenyl-5-azaindole 5-oxide[44] as well as the synthesis of 5-nitro-7-azaoxindole by the thermal decomposition of 2-amino-3-diazoacetyl-5-nitropyridine[102] have been described:



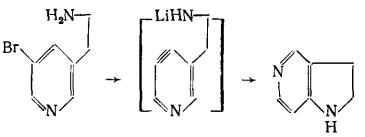
(XXXIII) (XXXIV)

R = aryl or heteroaryl



2,3-substituted 5-azaindoles have been obtained[44] by the reduction of the *N*-oxides of 4-nitro-3-styrylpyridines (XXXIV).

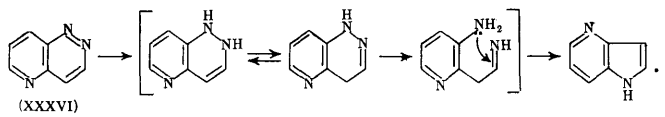
The reaction of 3-(2-aminoethyl)5-bromopyridines with lithium diethylamide proceeds via the hetaryne (XXXV) and gives rise to 5-azaindoline[103] in 56% yield:



(XXXV)

We may note that the above reaction is the first example of the intramolecular addition of a base in the series of hetarynes.

A novel synthesis of unsubstituted 4-azaindoles has been achieved by the reduction of 5-azacinnoline (XXXVI) [104] via the mechanism



(XXXVI)

III. PHYSICOCHEMICAL STUDIES ON AZAINDOLES

1. Ionisation Constants and Electronic Structures of Azaindoles and Their Protonated Forms. The Study of Azaindole Bases and Their Cations by Spectroscopic Methods

As mentioned previously[1,2], the properties of azaindoles are determined by the involvement in their condensed bicyclic system of two *N*-heteraromatic rings with opposite shifts of π-electron density within each ring: pyridine with a deficiency of π-electrons and pyrrole with an excess of π-electrons. During the last decade a number of theoretical and experimental studies have been carried out on the interaction of π-electron systems of this kind. The study of the ionisation constants of a large group of derivatives of 4- and 5-azaindoles using correlation methods made it possible to generalise the relations governing the transmission of the influence of such substituents and to calculate the transmission factors for isomeric 4-, 5-, 7-azaindoles and 5- and 7-azaindolines[105].

In order to estimate the ability of isomeric azaindoles to undergo electrophilic substitution reactions, a study was made of the kinetics of deuterium exchange involving 4-, 5-, and 7-azaindoles[106]. The penetration integrals have been determined[107] for isomeric azaindoles and indole by the Pariser–Parr method, the calculated $\pi-\pi^*$ transition energies agreeing satisfactorily with experimental data.

Calculations have been made for the molecules of isomeric azaindole and indole by the Hückel and Pariser–Parr–Pople methods, the nature of the mutual influence of the five- and six-membered rings has been examined within the framework for the π-electron approximation, and the energies of the lowest excited states have been calculated by the method of limited interaction of the configurations[108,109]. The results indicate a relatively large π-electron charge on $C_{(3)}$ in all azaindoles and indole. The distribution of π-electron density in the $C_{(1)}-C_{(2)}-C_{(3)}$ atomic group changes little from molecule to molecule, i.e. the rotation of the pyridine ring has little effect on the electronic structure of the five-membered ring. The π-electronic charges in the six-membered ring are as it were rotated when the position of the pyridine nitrogen atom is altered, without undergoing significant distortions in this process[109].

Calculations for the cations of isomeric azaindoles indicate a relatively high charge on the $C_{(3)}$ atom, which enables the protonated azaindoles to react via an electrophilic mechanism.

The shielding of the positive charge of the cation as a result of solvation enhances this possibility[110]. It has been found that the electron affinity increases in the sequence indole < 5- < 6- < 7- < 4-azaindoles. The ionisation potentials increase in the sequence indole < 5- < 7- < 6- < 4-azaindoles[109].

On the other hand, the experimental basicities of azaindoles are correlated neither with the charge on the nitrogen atom of the six-membered ring nor with the analogous value for the protonated molecules. The discrepancy between the experimental and theoretical data has been attributed[110] to the characteristic features of the structure of the σ-skeleton of azaindoles, as a result of which the basicity of azaindoles can be influenced by the relatively positively charged nitrogen atom of the pyrrole ring.

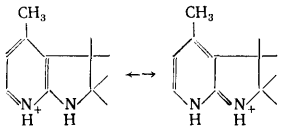
Attempts have been made[111,112] to estimate experimentally the electron distribution in the 7-azaindole system. This was done taking into account the measured chemical shifts (with a correction for the shielding influence of the ring), the magnetic anisotropy of the neighbouring atoms, and the electric field of the free electron pair of the heteroatom dipole. However, in this case too the agreement between the experimental and calculated data was not very satisfactory. In particular the positive charge on the carbon atoms of the rings proved to be greater than the calculated value, experiment revealing an excess negative charge on the heteroatoms and on the bridging carbon atoms. The authors[111,112] do not rule out the possibility that the contradictory data are due to insufficient allowance for the mutual influence on the five-and six-membered rings in the condensed azaindole systems.

^{1}H NMR has been used to investigate the protonation of 5-azaindoles and 5-azaindolines in media with different dielectric constants[11-13]. It has been shown that the structures of the monocations of 5-azaindole, 5-azaindoline, and their 1-substituted derivatives indicate an appreciable contribution of quinonoid structures with transfer of the positive charge to the nitrogen atom of the pyrrole or pyrroline fragment.

The dependence of the chemical shifts of the proton signals of 1-substituted 5-azaindoles or 5-azaindolines on the concentration of trifluoroacetic acid in methylene chloride, acetonitrile, and deuteroacetone led[11,12] to a protonation mechanism in which the proton transfer from the donor to the acceptor in media of low polarity takes place via the formation of a hydrogen-bonded molecular complex of the base and the acid, which is followed by conversion into an ion pair and dissociated ions.

The relative equilibrium position in reactions involving proton transfer via a hydrogen bond and dissociation of hydrogen-bonded complexes with formation of solvated ions has been determined as a function of the concentration of acids on the basis of a model of the amine—acid system in which the amine component is 4-methyl-7-azaindoline[113]. Near the equimolar reactant ratio in the amine—trifluoroacetic acid system, the protolytic equilibrium is fully displaced towards hydrogen-bonded complexes of the ion pair type. The interaction with acetic acid under the same conditions involves a molecular complex ⇌ ion pair equilibrium. The enthalpy and entropy of the proton transfer reaction have been determined.

In a neutral molecule the greatest sensitivity to the effects of the medium and to the formation of hydrogen bonds is shown by the proton in the α-position with respect to the nitrogen atom of the pyridine ring ($H_{(6)}$). On passing from the neutral molecule to the cation, the changes in the ^{1}H NMR spectrum, particularly the upfield shift of the $H_{(6)}$ signal, correspond to the addition of a proton to the pyridine nitrogen with formation of a conjugated ion of the amidinium type (XXXVII)[113]:

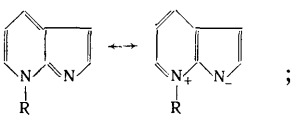


(XXXVII)

A detailed study[114] of the ^{1}H NMR spectra of 5-azaindole and its 1- and 3-methyl derivatives showed that the protons in the 3- and 7-positions interact, while the $H_{(1)}$—$H_{(3)}$—$H_{(2)}$—$H_{(6)}$ and $H_{(4)}$—$H_{(6)}$ interactions were not observed in any one spectrum.

Mass-spectrometric studies on 7-azaindole and a large number of its derivatives established[115] that, on fragmentation on electron impact, the common intermediates for many compounds are naphthyridines and pyrido[2,3d]pyrimidines.

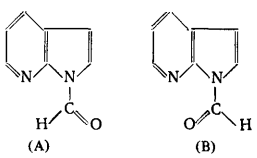
The structure of anhydro-salts of the (XXXVIII) series was determined with the aid of absorption spectroscopy[116] and the contribution of each resonance structure, which varies as a function of the type of solvent, was estimated:



(XXXVIII)

R = alkyl or aryl.

The rotation of the acyl groups about the N—C bond has been studied by ^{1}H NMR for a set of *N*-acylindoles[117] and it has been shown that, in contrast to other *N*-acyl derivatives, 1-formyl-7-azaindole exists predominantly in form A:

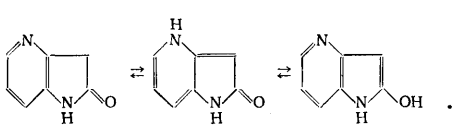


(A) (B)

The chromatographic mobilities of azaindole derivatives have been investigated[118] by thin-layer chromatography.

2. Problems of the Tautomerism of Azaindole Systems

Studies in recent years on tautomeric transformations of isomeric azaindoles have dealt mainly with problems of the lactam—lactim tautomerism of hydroxy-derivatives. It has been established[52,54] that 4-azaoxindole exists in the lactam form (a) in the crystalline state; in protic solvents it has been possible to detect by ultraviolet spectroscopy all three tautomeric forms (a, b, and c) [54]:

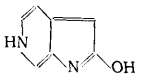


a b c

A change of solvent or the introduction of substituents into the molecule influences significantly the position of the tautomeric equilibrium.

6-Azaoxindole exists as a mixture of comparable amounts of the tautomeric lactam and lactim forms in solution in dimethyl sulphoxide and in the crystalline state[52,56,119], although the possibility of the presence of form (XXXIX) as

well is not ruled out:



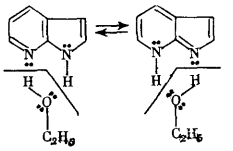
(XXXIX)

In the crystalline state 3-ethoxycarbonyl-6-azaoxindole exists as a mixture of two tautomeric forms, the equilibrium being strongly displaced towards the lactam, in contrast to 3-ethoxycarbonyl-4-azaoxindole, which exists in the lactim form in the crystalline state[52,56].

The lactam—lactim tautomerism of 7-azaindole and 7-azaindoline systems containing the oxo-group in the α-position with respect to the pyridine hydrogen atom had been studied fairly completely previously[1]. It was noted that, in contrast to other analogous *N*-heteroaromatic systems, a complete shift of equilibrium towards lactams is not observed in 6-hydroxy-7-azaindolines and 6-hydroxy-7-azaindoles. This is due to the inductive effect of the nitrogen atom of the pyrrole ring on the α-hydroxy-*N*-heteroaromatic system which exhibits a tendency towards tautomerism. On passing from 7-aza-compounds to the analogous 5-aza-derivatives, the inductive effect on the nitrogen atom of the five-membered ring is greatly weakened, which is responsible, in particular, for the shift of the lactam—lactim tautomeric equilibrium involving 6-hydroxy-5-azaindolines[120] and 4-hydroxy-5-azaindoles[84] almost completely towards the lactam forms. The tautomeric lactam form predominates also in derivatives of 2-ethoxycarbonyl-7-hydroxy-1-methyl-4-azaindole containing a methyl or phenyl group in the 5-position[83].

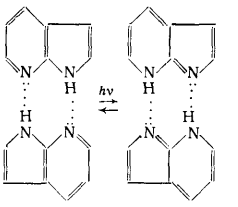
A study of the temperature dependence and the thermodynamic characteristics of the lactam—lactim tautomeric equilibrium of 1-substituted 6-hydroxy-4-methyl-7-azaindoles established[121] that the conversion of the lactim into the lactam is an exothermic process in most of the forms investigated. On passing to less polar solvents, the process becomes less exothermic and in dioxan, where the lactim form predominates to a large extent, the process becomes endothermic. An increase of temperature in more polar solvents promotes a decrease of the content of the lactam forms; the opposite behaviour is observed in less polar solvents.

Examination of the optical, absorption, and luminescence spectra of 7-azaindole in ethanol revealed a two-proton phototautomerism[122]. The influence of the tunnel effect and of the migration of the excited proton cannot explain the changes in the luminescence but does show that the excited state of the molecule is the cause of the ready two-sided migration of the two combined protons:



The spectra of solutions of 7-azaindole in aprotic solvents have two fluorescence maxima, the relative intensities of which depend on the concentration of the solution, temperature, pH, wavelength, and irradiation intensity. The second maximum is apparently caused by the tautomeric form produced as a result of the rapid intramolecular migration of the proton doublet in the excited state, and constitutes a doubly hydrogen-bonded dimer[122-128].

A study of the cleavage of the 7-azaindole dimer in 3-ethylpentane by investigating its fluorescence at 77 and 4.2 K led to the determination[127] of the potential energy barrier to the double prototropic intermolecular reaction. The rate of deuterium exchange involving the excited 7-azaindole molecule and the rate of migration of the proton in the excited non-deuterated 7-azaindole molecule have been determined[127]:



IV. SYNTHETIC STUDIES BASED ON AZAINDOLES

The characteristic features of the chemical behaviour of condensed pyrrolopyridines (azaindoles), associated with the nature of the electron density distribution in their molecules, have been examined in fair detail in earlier reviews[1,2]. Further studies did not alter the fundamental ideas concerning the chemical properties of compounds of this class but greatly extended the synthetic possibilities in the series of azaindole derivatives and led to the discovery of new ways of constructing condensed heterocyclic systems on the basis of 7-azaindole derivatives.

1. Reactions of Azaindoles Involving Nitrogen Atoms

One of the commonest reactions of isomeric azaindoles is alkylation at the pyrrole nitrogen atom[24,114,129-131]. This process takes place fairly readily in the presence of strong bases (sodium amide, sodium hydride, etc.) which convert azaindole compounds into the corresponding anions[1]. In the absence of strong bases the reaction usually takes place via several pathways and leads to a mixture of products of alkylation at the pyrrole and pyridine nitrogen atoms[132-135]. In some instances the alkylation of 7-azaindole derivatives in the presence of alkali involves the expansion of the pyrrole ring with formation of 1,8-naphthyridine derivatives[26].

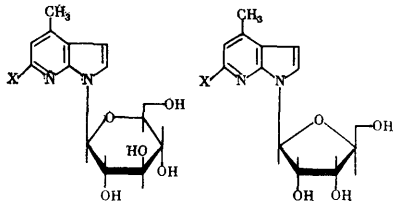
7-Azaindole reacts with ethylmagnesium iodide to form a Grignard compound, which is converted into the 1-acetyl and 1-ethoxycarbonyl derivatives on treatment with acetyl chloride and ethyl chloroformate respectively[26].

Oxidation of 5- and 7-azaindoles with *m*-chloroperbenzoic acid converts them into the *N*-oxides[52,136], which like the *N*-oxides of other six-membered *N*-heteroaromatic compounds, are capable of rearrangement under the influence of acetic anhydride, phosphoryl chloride, and other analogous reagents.

Certain mercury derivatives of 7-azaindole substituted at the pyrrole nitrogen atom[137] as well as cobalt[138] and copper[139] complexes of 7-azaindole, which exhibit antiferromagnetic properties of practical interest, have been synthesised.

The synthesis of *N*-glycosylated azaindoles by fusing 7-azaindole with 1,2,3,5-tetra-*O*-acetyl-β-*D*-ribofuranose did not give positive results[140]. The use of the indoline—indole method[15,16], which consists in the glycosylation of 7-azaindoline derivatives by *D*-glucose or 5-*O*-trityl-*D*-ribofuranose residues with subsequent dehydrogenation to 1-β-*D*-glucopyranosyl-7-azaindole (XL) and 1-β-*D*-ribofuranosyl-7-

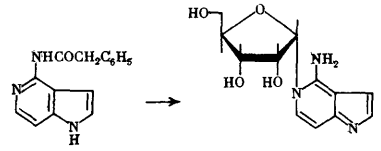
azaindole (XLI), was more successful:



(XL) X = H or Cl. (XLI)

1-Glycosyl derivatives of 5-azaindole have been obtained by the glycosylation of the chloromercury salt of 5-azaindole by acetylated bromosugars[141].

Direct glycosylation of 4-benzamido-5-azaindole (XLII) by 2,3,3-tri-*O*-benzoyl-*D*-ribofuranosyl bromide takes place at the nitrogen atom of the pyridine ring, subsequent debenzoylation yielding 4-amino-5-β-*D*-ribofuranosyl-5-azaindole (XLIII) [87,142]:



(XLII) (XLIII)

2. Electrophilic Substitution Reactions in the Series of Isomeric Azaindoles and Azaindolines

The influence of the π-electron-deficient pyridine ring is responsible for certain characteristic features in the behaviour of azaindole molecules under the conditions of the electrophilic substitution reaction in relation to indoles[1,2]. The earlier investigations of the Mannich, Vilsmeier, cyanomethylation, halogenation, and nitration reactions of 7-azaindoles have been extended during the last decade to 4-, 5-, and 6-azaindoles[26,62,71,133,134,143-148], which exhibited the same features as 7-azaindoles. It is of interest to note that 7-azagramine has been used as a model of a polymer oxidation inhibitor[149]. New literature data[145] disproved earlier conclusions[1,2,150] that 5-azaindole is incapable of undergoing electrophilic substitution reactions.

A quantitative study of the comparative reactivities in the electrophilic substitution reactions of isomeric azaindoles has been carried out in relation to the acid-catalysed deuterium exchange involving the 3-position[106].

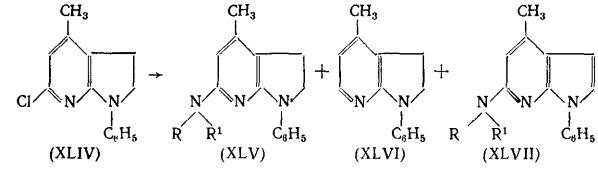
Electrophilic substitution reactions of azaindolines have been studied in relation to 6-chloro-7-azaindolines[151,152], which, in contrast to 7-azaindolines, lacking a halogen atom in the α-position with respect to the pyridine nitrogen, are readily brominated, chlorinated, and nitrated with formation of 5-substituted 6-chloro-7-azaindolines. In the absence of an *N*-acyl protecting group, nitration yields the 1-nitro-isomer in addition to the 5-nitro-isomer.

3. Nucleophilic Substitution Reactions in the Series of Isomeric Azaindoles and Azaindolines

Nucleophilic substitution reactions of azaindole and azaindoline compounds are difficult[1,2]. Thus 4-methyl-7-azaindoline and its 1-phenyl derivative are not aminated under the conditions of the Chichibabin reaction[153]. The pyrrole ring in 1-phenyl-5-azaindole is opened under the influence of sodium amide and 4-phenylamino-3-vinylpyridine is formed. Nor was it possible to achieve the Chichibabin amination of 4-azaindole[153]. These results can be accounted for by the enhanced electron density, compared with pyridine, in the pyridine ring of azaindoles.

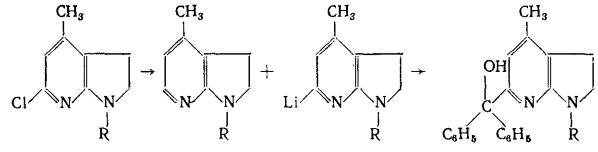
Substitution of the chlorine atom in the 6-position by hydrogen in derivatives of 7-azaindoline[63,66,71] and 5-azaindoline[67,70] as well as the chlorine atom in the 4-position in 5-azaindole[87] proceeds smoothly in the presence of a palladium catalyst. Nucleophilic substitution of chlorine by alkoxy-groups[67] by reaction with alkali metal alkoxides requires severe conditions. Even more severe conditions are necessary for the substitution of chlorine atoms in the pyridine component of the molecules of 5- and 7-azaindoles by nucleophiles such as primary or secondary amines[84,85,87,154-158]. A kinetic study of the nucleophilic substitution of chlorine in 4-chloro-1-methyl-5-azaindole by the piperidine residue revealed an autocatalytic effect[156].

In the reactions of primary and secondary amines with 6-chloro-4-methyl-1-phenyl-7-azaindolines (XLIV), which take place under severe conditions, the normal nucleophilic substitution process is accompanied by the reduction of the hitherto unreacted compound (XLIV) by the *N*-substituted 6-amino-4-methyl-1-phenyl-7-azaindole (XLV) formed to 4-methyl-1-phenyl-7-azaindoline (XLVI) with simultaneous oxidation of compound (XLV) to *N*-substituted 6-amino-4-methyl-1-phenyl-7-azaindole (XLVII) [154,155]:



(XLIV) (XLV) (XLVI) (XLVII)

The interaction of 6-chloro-7-azaindolines with lithionaphthalene at temperatures between -35° and -40 °C in tetrahydrofuran followed by treatment with benzophenone yielded substituted 7-azaindoline-6-yldiphenylmethanols together with 6-unsubstituted 7-azaindolines[159]:

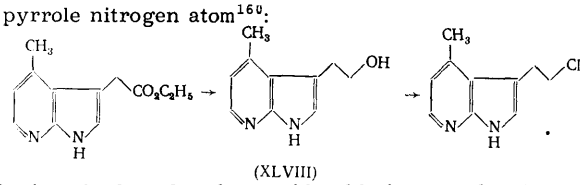


4. Transformations of Azaindole Compounds Associated with Reactions Involving the Carbon Side Chain

The characteristics of the distribution of electron density in azaindole systems do not interfere with a number of classical reactions involving their side chains. Thus 3-formyl-1-phenyl-7-azaindole has been reduced to the alcohol, the hydroxy-group of which is readily acetylated and substituted by chlorine; the latter can in its turn be substituted by various acyloxy-groups[146].

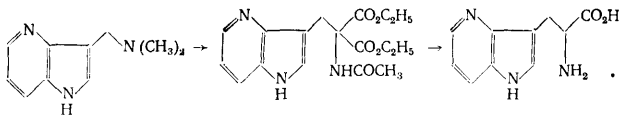
The reduction of the ethyl ester of 4-methyl-7-azaindole-3-acetic acid led to the synthesis of the alcohol (XLVIII), the hydroxy-group of which is also readily substituted by chlorine; the resulting compound is fairly readily acetylated at

the pyrrole nitrogen atom[160]:



(XLVIII)

During the last decade considerable interest has been shown in azaindoles containing nitrogen in the side chain[39,41,42,144,147]. 4-Azatryptamine has been obtained by the reduction of 4-azaindole-3-acetamide and 4-azatryptophan (XLIX) has been synthesised[161] by the reaction of 4-azagramine (L) with acetamidomalonic ester followed by hydrolysis or partial decarboxylation:

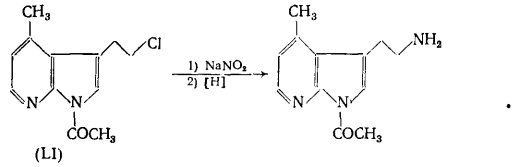


(L) (XLIX)

The method of synthesis of 3-aminoalkyl-7-azaindoles[1,2], consisting of the condensation of 3-formyl-7-azaindoles with nitroalkanes and subsequent reduction of the intermediates, has been developed further[71,143,147,162]. In particular, 7-azatryptamines, substituted at the pyrrole nitrogen atom by aliphatic or aliphatic-aromatic residues[71], have been synthesised by this procedure; 3-aminomethyl derivatives of 7-azaindole have been obtained by reducing the oximes of the corresponding 3-aldehydes[143,147].

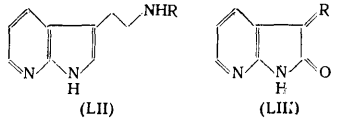
It has been shown that the oxime of 6-chloro-3-formyl-4-methyl-7-azaindole consists of *syn*- and *anti*-isomers in the crystalline state[163], while the crystalline oxime of 3-formylindole exists as the *anti*-isomer.

The synthesis of 1-acetyl-4-methyl-7-azatryptamine from 1-acetyl-3-(β-chloroethyl)-4-methyl-azaindole (LI), based on the substitution of a chlorine atom in the side chain by the nitro-group with subsequent reduction, has been investigated[160]. The interaction of compound (LI) with ammonia, potassium bis(dimethoxysilyl)amide, and potassium phthalimide (with subsequent removal of the phthalimide protecting group) involves the elimination of the *N*-acetyl group:



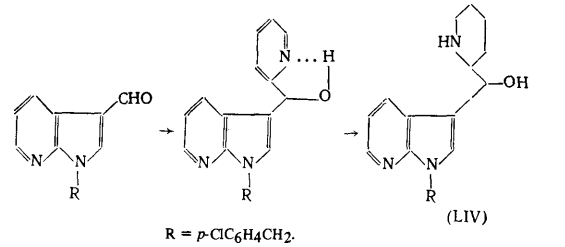
(LI)

Derivatives (LII) of 7-azatryptamine substituted in the amino-group have been synthesised from 7-azatryptamine itself[164]. The interaction of 7-azaoxindole with nitrosoketones yielded the oximes (LIII, R = CCH_3CH = NOH or CC_6. .H_5CH = NOH), which were then reduced to 2-(7-azaoxindol-3-yl)propylamines (LIII, R = $CCH_3CH_2NH_2$) [164]:



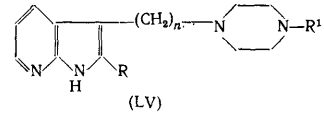
(LII) (LIII)

1-(*p*-Chlorobenzyl)-7-azaindol-3-yl-α-piperidinylmethanol (LIV) has been synthesised[133,134] by the interaction of 3-formyl-7-azaindole with 3-pyridyl-lithium and selective reduction of the product to a mixture of diastereoisomers:



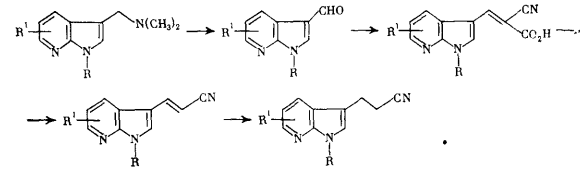
R = *p*-$ClC_6H_4CH_2$.

A large group of compounds of the type (LV, R = H or CH_3; $n = 1-3$; R^1 = alkyl, aryl, or heteroaryl) have been synthesised from 7-azaindole-3-ylalkanecarboxylic acids via the corresponding piperazides with reduction of the amide group by lithium tetrahydroaluminate[148,165]:



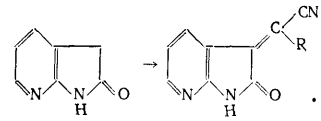
(LV)

3-Cyanoethyl derivatives of 7-azaindoles have been obtained from 7-azagramines, which were converted into 3-formyl-7-azaindoles under the conditions of the Duff reaction (with urotropine in aqueous acetic acid solutions) and were then condensed with cyanoacetic acid. The subsequent decarboxylation of the substance and catalytic reduction of the double bond leads to the required products[131]:



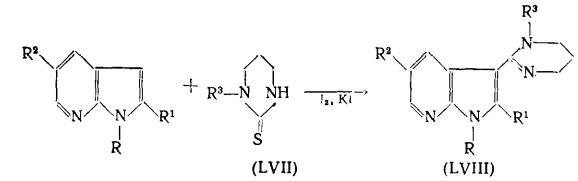
3-[β-(2-Imidazoline-2-yl)ethyl]-7-azaindoles have been synthesised from 3-cyanoethyl-7-azaindoles[131].

On reaction with compounds of the type RCOCN (R = CH_3, C_2H_5, or C_6H_5), 7-azaoxindole is converted into acetonitriles (LVI) [164]:



(LVI)

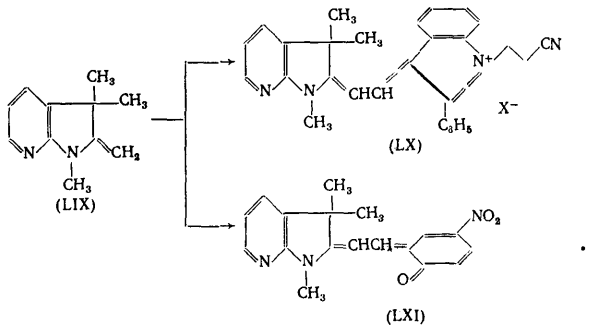
Compounds (LVIII), containing tetrahydropyrimidine residues in the 3-position in 7-azaindoles, have been obtained on condensing 7-azaindoles with tetrahydropyrimidinethione (LVII) in the presence of iodine[166,167]:



(LVII) (LVIII)

The interaction of 2,3-dihydro-1,3,3-trimethyl-2-methylene-7-azaindole (LIX) with 1-(2-cyanoethyl)-3-formyl-2-phenylindole leads to the cyanine (LX, X = *p*-$CH_3C_6H_4SO_3^-$ or

ClO_4^-) [168], while the reaction of compound (LIX) with nitrosalicylaldehyde makes it possible to obtain compound (LXI) [169]:

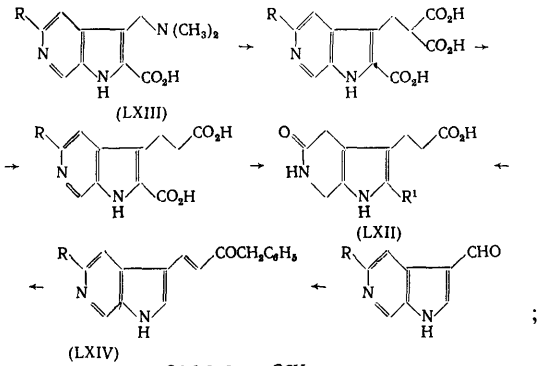


(LIX) (LX) (LXI)

Compounds of this type are of practical interest—as photosensitisers in colour photography[168-173].

A number of compounds have been synthesised from 3-formyl-6-azaindole[169], in particular its oxime, as well as 3-cyano-, 3-methyl-, 3-aminomethyl-, and 3-dimethylamino-6-azaindoles.

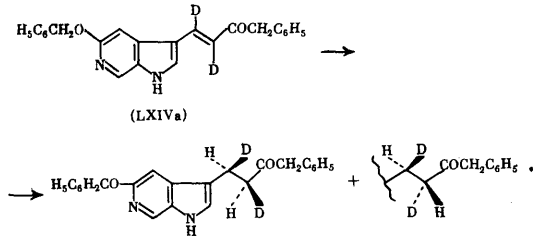
The lactams of porphobilinogen-2-carboxylic acids (LXII, R^1 = COOH) have been synthesised via the Mannich bases (LXIII) [17,18], introduced into the malonic ester synthesis and then subjected to familiar transformations in accordance with the scheme



(LXIII) (LXII) (LXIV)

R=$OCH_2C_6H_5$, or OCH_3 .

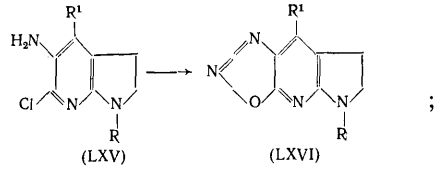
The reduction of the deuterated product (LXIVa) over a palladium catalyst gives rise to the racemate[19]. The separation of the optical isomers and their use in further synthesis yielded optically active lactams of porphobilinogens:



(LXIVa)

5. Synthesis of Condensed Heterocyclic Systems from 7-Azaindole Derivatives

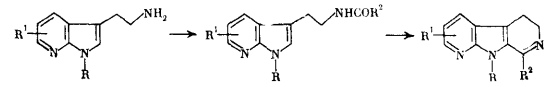
Derivatives of 7-azaindole have been used successfully in recent years to synthesise new more complex condensed systems. Thus the closure of the 1,2,3-oxadiazole ring has been achieved by the diazotisation of 5-amino-6-chloro-7-azaindoline (LXV) with formation of the 1,2,3-oxadiazolo[4,5-g]7-azaindoline system (LXVI) [151,174,175]:



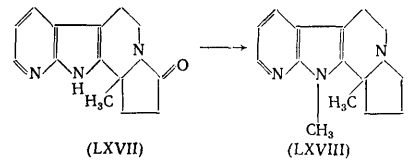
(LXV) (LXVI)

R and R^1 = H or alkyl.

The application of the Bischler–Napieralski and Pictet–Spengler reactions to 7-azatryptamines permitted the synthesis of derivatives of the new tricyclic system of 12-aza-β-carboline[176]:

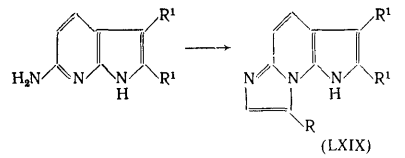


Cyclisation of 7-azatryptamine with laevulinic acid gave rise to the lactam (LXVII), which was converted into pyridopyrroloindolizine (LXVIII) by reduction and subsequent methylation[177,178]:



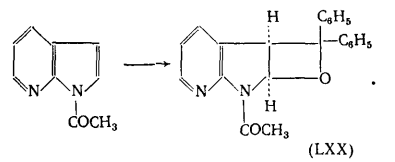
(LXVII) (LXVIII)

Derivatives of 1*H*-imidazo[1,2-*a*]pyrido[3,2-*e*]pyrrole (LXIX) have been obtained by condensing 6-amino-7-azaindoles with α-halogenocarbonyl compounds[179]:



(LXIX)

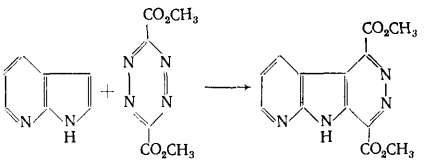
In contrast to furans and 2,3-dimethylthiophens, which interact with benzophenone under irradiation to form condensed oxetans, unsubstituted 7-azaindole, pyrrole, and imidazole do not react with benzophenone under these conditions[180]. This has been explained[180] by the quenching influence of the free electron pair of the pyrrole nitrogen atom on the excited ketone. Indeed, when a mixture of 1-acetyl-7-azaindole and benzophenone is irradiated, cycloaddition to the double bond of 7-azaindole and the formation of oxetano-7-azaindoline (LXX) in 4% yield are observed:



(LXX)

Condensed pyridazinoazaindoles (LXXI) have been obtained by the cycloaddition (of the type of the Diels–Alder reaction) of the tetrazine (LXXII) to the unsubstituted 7-azaindole, acting as the dienophile, with subsequent elimination of a

nitrogen molecule[181]:



(LXXII) (LXXI)

V. THE BIOLOGICAL PROPERTIES OF AZAINDOLE DERIVATIVES

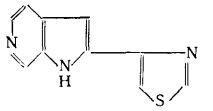
The range of studies of the biological activity of azaindole derivatives has significantly expanded in recent years, although the main information still concerns 7-azaindoles.

The high and varied biological activities of a wide variety of azaindole derivatives have been reported in the patent literature. It has been established[182] that 2,3-dimethyl-5-azaindole and its 1-glucopyranoside suppress the growth of the tumour cells of sarcoma-37 to the extent of 60–67% in experiments *in vivo* and at the same time exhibit a low toxicity. In experiments on sea urchins 4-methyl-1-phenyl-7-azatryptophan exhibited a cytotoxic activity[183].

(7-Azaindol-3-yl)alkylpiperazines showed a considerable psychotropic and cardiovascular effect[148,165]. Antidepressant properties have been found in a series of derivatives of azaindoles and their analogues[132,184,185]; 7-methyl-7-azaindole[132], which blocks certain effects of reserpine in experiments on mice, proved to be most active. Tryptamine-like properties have been found in 3-amino-methyl-4-methyl-1-phenyl-7-azaindole[147,186]; when 3-hydroxymethyl-4-methyl-1-phenyl-7-azaindole is administered to various animal species both internally and parenterally, it induces a state resembling narcosis[146].

A series of 7-azaindole derivatives, particularly 7-azaindole-3-acetoxime, exhibit a hypotensive activity[166,167,187,188]. There have also been reports of the vasoconstrictor activity of imidazolinylalkyl-7-azaindoles[131], the anti-inflammatory activity of 4-aminophenyl-5-azaindoles[86,157], the gonadotropic effect of 7-azatryptophan[189], the antiserotonine activity of 4-methyl-1-phenyl-7-azatryptamine[190,191], etc.

Chemotherapeutic research on laboratory animals revealed an activity of the 4-,5-,6, and 7-aza-analogous of thiabendazole, for example compound (LXXIII), as well as 2-phenyl-5-azaindole and 2-phenyl-6-azaindole against trichostrongylids[44]:



(LXXIII)

It has been shown that 7-azatryptophan does not exhibit a significant inhibiting activity on the development of *Heterodera trifolii*[192], while 7-azaindole to a large extent suppresses the formation of *Meloidogyne javanica* galls[193] and inhibits the stimulating effect of indole-2-carboxylic acid on the multiplication of *Aphelenchoides ritzema-bozi*[194].

One of the diastereoisomers of (1-*p*-chlorobenzyl-7-azaindol-3-yl)-2-piperidinylmethanol proved to be an effective antimalerial agent[133,134]. A study of the antifungal activity of coal tar led to the isolation of 2-isopropyl- and 2-isobutyl-7-azaindoles as active components[195]. 7-Azaindole and its condensed systems have been detected in tobacco smoke and tobacco[196]. The antimicrobial properties of 2-alkyl- and 2-alkenyl-7-azaindoles have been the cause of the incorporation of these compounds in the composition of cosmetics for the skin[197].

Numerous studies have been devoted to the involvement of 7-aza-analogues of tryptophan and its metabolites in biochemical processes in the cell[198–216]. The bacteriological synthesis[217–219] of *L*-7-azatryptophan by a whole series of bacterial and fungal strains from 7-azaindole has been reported. The similarity of the biological activities of 7-azaindole-3-acetic acid and indole-3-acetic acid (heteroauxin) has been confirmed[220]. A number of studies on the interrelations of 7-azatryptophan with plant objects have been carried out[221–225].

During the preparation of this review for the press, new data on the syntheses of isomeric azaindoles were published; substituted 4-azaindoles have been obtained from isoxazolylpyrrole[226] and enaminonitriles[227], derivatives of 5-azaindole (of the type of 3,7-dididesazaxanthine) have been obtained from pyrrole-2,3-dicarboxylic acid esters[228] and 2,3-disubstituted 6-azaindoles have been synthesised by the reduction of (3-nitro-4-pyridyl)dicarbonyl compounds[229]. A series of studies[230–236], which throw light on the "anomalous" course of the Fischer reaction, observed in the formation of azaindoles and associated with the homolytic dissociation of the N–N bond in hydrazones, have been carried out.

Physicochemical investigations of azaindoles dealt with the spectroscopic characteristics of substances of this class[237–239], the phototautomerism of 7-azaindole and its derivatives[240–242], the kinetics of deuterium exchange[243] and the nitration of isomeric azaindoles[244], etc[245]. The π- and σ-electron densities of the carbon atoms of isomeric azaindoles have been calculated, the results being used to estimate their capacities for electrophilic substitution reactions[246].

New data have been published on the behaviour of azaindoles under the conditions of electrophilic[247,248] and nucleophilic[249,250] attack. Studies have been continued on the synthesis of *N*-glycosylated azaindoles[251], and a cobalt complex of 7-azaindole has been obtained[252]; a series of compounds containing azaindole fragments proved to be of interest for photography[253–257].

The publication of studies on the biochemical and chemotherapeutic activities of azaindole derivatives has been continued[228,258–265]. Certain derivatives of 7-azaindoles exhibited an antiulcer activity[266] and inhibited the secretion of the gastric juice and the growth of malignant neoplasms[267].

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