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# The Chemistry of Azaindoles [Pyrrolo[2,3]pyridines†]

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The review discusses the chemical properties and the biological activity of aza-analogues of indole compounds, i.e. substances containing fused pyridine and pyrrole systems.
The interest taken in azaindole derivatives is due on the one hand to the ever broadening application during recent years of the principle of building up aza-analogues of biologically active substances (purines, pyrimidines, steroids, etc.) as bases in the search for new medicinal preparations, and on the other hand to the appearance in such systems of characteristic chemical properties, indicating a redistribution of electron density caused by the interaction of the "π-electron-deficient" and "π-electron-excessive" rings involved in the fusion.
The above problems are fully reflected in the review. Considerable attention is paid to discussing the chemical peculiarities of azaindoles associated with the presence in the fused systems of rings which have directly opposite displacements of π-electrons relative to carbon atoms, describing the features of lactam-lactim and amino-imino tautomerism in azaindole and azaindoline systems, and also examining routes and methods for introducing substituents both into the pyridine and into the pyrrole parts of the molecule. Exhaustive consideration is given to data on the biological activity of azaindoles. A special section is concerned with the choice of methods for building up azaindole systems and the characteristics of ring-closure in azaindoles compared with indoles.
The review covers all information available in the world's literature on the chemistry and the biological activity of azaindoles. The list of references comprises 159 items.

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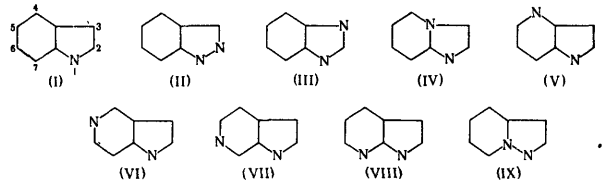
## I. INTRODUCTION

In recent years the search for new medicinal preparations has been based with increasing frequency on the possible similarity or antagonism of the pharmacological action of biologically important compounds and their aza-analogues, substances in which one or more carbon atoms have been replaced by nitrogen.

Investigation of aza-analogues of pyrimidine and purine bases has enabled substances exhibiting considerable tumorstatic activity[6,7] to be obtained in the series of azaguanines[1], azauracils[2,3], azacytosines[4], and azathymines[5]. It has been established that aza-analogues of purine and pyrimidine bases, subjected in the organism to the processes of ribosidation and phosphorylation, become powerful inhibitors of several successive steps in the biosynthesis of pyrimidine nucleotides. Thus 6-azacytosine is converted in the tumour cells of Ehrlich's ascitic cancer into 6-azacytidine 5'-phosphate, which is an orotidylic acid decarboxylase inhibitor[4]. An analogous enzymic conversion product of 6-azauracil—6-azauridine monophosphate—blocks orotic acid decarboxylase, and interferes with the synthesis of uridylic acid[8,9].

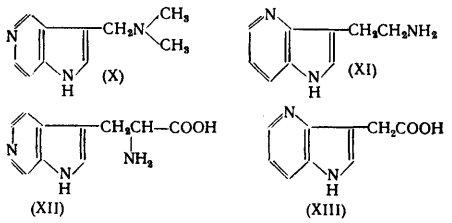
Study of the aza-analogues of steroid hormones[10-16] has brought to light compounds of interest not only from the point of view of their hormonal activity. This makes understandable the interest shown by chemists and biologists in the investigation of azaindoles, the simplest aza-analogues of the physiologically important indole compounds.

All products in which one of the carbon atoms of the indole ring (I) has been replaced by nitrogen are formally azaindoles. However, such a broad interpretation, adopted by several authors[17], includes in this class substances which are extremely diverse in chemical properties—pyrrolopyridines (V)–(VIII), benzimidazoles (III), indazoles (II), pyrimidazoles (IV), and pyrazolopyrimidines (IX):

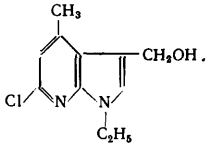



It appears advisable to restrict the concept of "azaindoles" by retaining this name only for products in which one of the atoms not common to the two rings in the indole molecule has been replaced by nitrogen (V)–(VIII), without, in contrast to Adler and Albert[18-20], regarding benzimidazole (III) and indazole (II) as azaindoles.

The nomenclature of the azaindoles is based on the principles used in constructing the names of indole compounds. The most widely used is addition of the position of the aza-substituent to the name of the corresponding indole derivative—4-azaindole (V), 5-azaindole (VI), 6-azaindole (VII), 7-azaindole (VIII), 5-azagramine (X), 4-azatryptamine (XI), 6-azatryptophan (XII), 4-azaindol-3-ylacetic acid (XIII), 6-chloro-1-ethyl-4-methyl-7-azaindol-3-ylmethanol (XIV), etc.:




† Although the "aza" system of nomenclature should strictly be based on the corresponding homocyclic compounds, the Reviewer's nomenclature has been followed in the Translation, especially as he discusses his choice of nomenclature in the Introduction (Ed. of Translation).

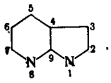


(XIV)

This most widely used principle of nomenclature is adopted in the present review.

It should be noted, however, that other terms of azaindole compounds are met in the literature. Azaindoles are most often named as diaza-analogues of indane[21-23], e.g. 1,4-diazaindane (V), 1,6-diazaindane (VII), etc. In American journals azaindoles are not infrequently considered to be derivatives of pyrrolopyridines[24-27], e.g. 1*H*-pyrrolo[2,3-*b*]pyridine (VIII), 1*H*-pyrrolo[3,2-*c*]pyridine (VI), etc.‡. An analogous nomenclature is found also in German papers[28], e.g. pyrrolo(2,3 : 2'3')pyridine (VIII).

In earlier papers azaindoles were termed pyrindoles[29,30]. Besides the above numbering of the rings, e.g. 7-pyrindole (VIII)[29], another system was also used, according to which the compound (VIII) was termed 8-pyrindole[31]:



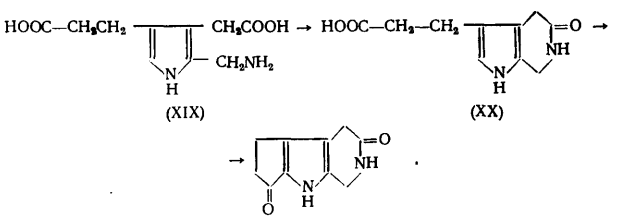
Quite often trivial names are used—harmyrine for 6-azaindole, and apoharmine for its 7-methyl derivative—reflecting the historical relation between 6-azaindoles and the harmine group of alkaloids.

## II. METHODS OF PREPARING AZAINDOLES

### 1. Naturally Occurring Azaindoles

Most azaindole derivatives are synthetic products. The only naturally occurring unsubstituted azaindole which has yet been found is 7-azaindole, discovered in 1943 by Kruber[28] in the lepidine fraction of coal-tar. Nevertheless, the bicyclic 6-azaindole system is widely distributed as part of the fused polycyclic structures of various groups of alkaloids—yohimbine, canthine, harmine, corynanthine—alstonine, sarpagine–ajmaline, etc. Since such fused systems are not discussed in the present paper, we merely mention them, referring readers who are interested to specialised reviews on the chemistry of the alkaloids[32-35].

Derivatives of 6-azaindole are of definite value also in the chemistry of porphobilinogen (XIX), an intermediate in the biosynthesis of porphyrins[36]. A key compound in the study of the structure of porphobilinogen[37-39] was its lactam (XX)[40], a derivative of tetrahydro-oxo-6-azaindole. Conversion of porphobilinogen (XIX) into the lactam (XX) followed by closure of the five-membered ketone ring enabled the position and the nature of the side-chains in (XIX) to be determined[40]:



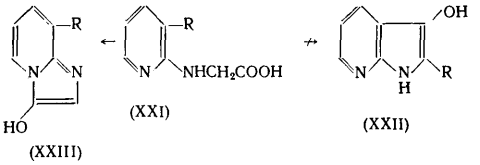
(XIX) (XX)

‡ The preceding examples in this paragraph are consistent with the recommendations of the International Union of Pure and Applied Chemistry (Ed. of Translation).

### 2. Features of the Synthesis of Azaindole Systems

Synthetic investigations in the azaindole series began in connection with the modification of indigoid dyes, when the idea arose of synthesising pyridine analogues of indigo, and publications appeared on a "new class of indigoid dyes", which were "pyrindole" derivatives. The key reaction in these syntheses was the cyclisation of substituted pyrid-2-ylaminoacetic acids (XXI) into the corresponding 7-azaindoxyls[41,42].

However, further research showed[43-45] that the course of this reaction in the pyridine series was different from that found in benzene derivatives. Ideas on the structure of the bicyclic pyridine product, based solely on analogies with indole derivatives, proved to be erroneous. Actually, cyclisation of the substituted pyrid-2-ylaminoacetic acids (XXI) led to the formation not of 7-azaindoxyls (XXII) but of compounds of the pyrimidazole series (XXIII):

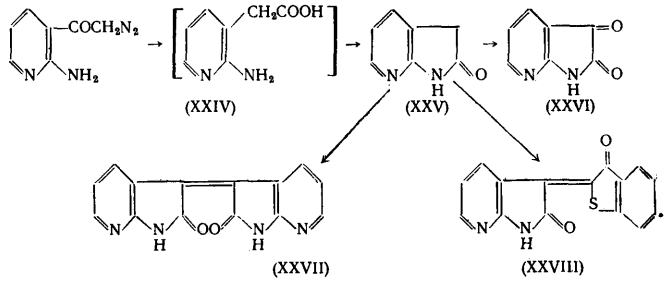


(XXIII) (XXI) (XXII)

where R = H, COOH.

Nor did subsequent work on the cyclisation of 4-carboxymethylamino-2,6-dimethylpyridine-3-carboxylic acid lead to azaindigoid dyes[46].

It was only in 1941 that Kägi[29] was able to obtain 7-azaoxindole (XXV) by the cyclisation of 2-aminopyrid-3-ylacetic acid (XXIV) and accomplish the conversion of (XXV) into 7-azaisatin (XXVI) and 7-azaindigoid vat dyes (XXVII) and (XXVIII). These researches have been further developed by the synthesis of 4-, 5-, and 6-azaindigos[47]:



(XXIV) (XXV) (XXVI) (XXVII) (XXVIII)

The initial failures to synthesise azaindigoid dyes were not fortuitous, and are of considerable interest for the chemistry of the azaindoles. In contrast to compounds of the benzene series, in which electrophilic substitutions occur comparatively readily, analogous reactions are accomplished with great difficulty in the pyridine ring, where the electron-acceptor properties of the cyclic nitrogen atom diminish the electron density on the carbon atoms. Furthermore, pyridine derivatives contain a ring nitrogen enriched with electrons, which easily acts as a nucleophilic centre in an addition reaction, and in the case of 2-aminopyridine derivatives also in nucleophilic substitution (with migration of the reaction centre).

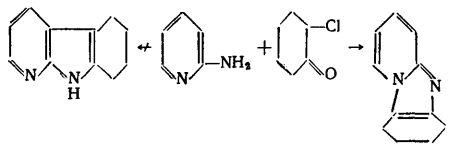
The peculiarities in the closing of azaindole compared with indole rings are due to these two factors—the lower electron density on the ring carbon atoms and the presence of a heteroatom having increased electron density.

The above method for obtaining indoxyls, and also the numerous reactions (Fischer, Harley-Mason, Reissert, Bischler–Napieralski, Pictet, Pomeranz–Fritsch reactions, etc.), which are widely used for synthesising various

heterocyclic systems from benzene derivatives, necessarily pass through a stage of electrophilic substitution in the benzene ring.

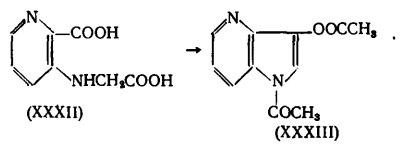
An analogous electrophilic substitution at a carbon atom is always more difficult and requires severe conditions on passing to the corresponding pyridine derivatives[48]. Furthermore, the competing process at the pyridine nitrogen becomes in several cases the main reaction, and prevents the use for preparing azaindoles of synthetic methods which have been widely and successfully employed in the chemistry of indole compounds.

Disregard of the peculiarities of the pyridine molecule in comparison with the benzene molecule led to errors not only in studying the cyclisation of pyrid-2-ylaminoacetic acid but also in several other cases. For example, a patent was applied for[49] in 1930 claiming the preparation of 9,10,11,12-tetrahydro-$\alpha$-carboline (XXIX) by the reaction of 2-aminopyridine (XXX) with 2-chlorocyclohexanone. Later workers have shown[50] that the product of this reaction is not (XXIX) but 6,7,8,9-tetrahydropyrido[1,2-$a$]-benzimidazole (XXXI):



(XXIX) (XXX) (XXXI)

Thus in this case the reaction follows the general path of interaction between $\alpha$-halogeno-carbonyl compounds and 2-aminopyridine discovered by Chichibabin[51]. A pyrimidazole derivative was probably formed also in the cyclisation of 2-carboxymethylaminopyridine-3-carboxylic acid described by Willette[52]. The analogous process of cyclisation of 2-carboxypyrid-3-ylaminoacetic acid (XXXII) yielded 1-acetyl-4-azaindol-3-yl acetate (XXXIII)[52]:



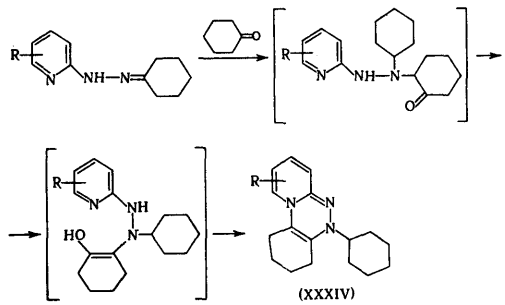
(XXXII) (XXXIII)

3. Application of the Fischer Reaction

The peculiar features of the chemical behaviour of pyridine compounds noted above have been responsible for the restricted application in the azaindole series of one of the most general methods for synthesising various indole compounds, the Fischer reaction. While going easily and smoothly with various arylhydrazones[53-55], this reaction does not usually give positive results with pyridyl- and quinolyl-hydrazones[21,22,56-60]. Successful synthesis of azaindoles by the Fischer method could be accomplished only from the pyridylhydrazones of a few ketones—cyclohexanone[58-60], 3-methylbutan-2-one[21,22], desoxybenzoin[60,61], cyclopentanone[62], indan-1-one[62], and $\alpha$-tetralone[62].

A study of condensing agents has shown that in all cases considerably more severe conditions are required for the cyclisation of pyrid-2-ylhydrazones than for that of the corresponding arylhydrazones[63]. For example, catalytic quantities of zinc chloride or copper(I) chloride, which with cyclohexanone phenylhydrazone ensure that the Fischer reaction shall occur normally from 180°C,[64,65] enable only the original compound to be isolated in the case of the pyrid-2-ylhydrazone even at 240°C.[66] The Fischer cyclisation of pyrid-2-ylhydrazones is difficult even when boron trifluoride is used as catalyst. Only the application of strong mineral and arenesulphonic acids has made it possible to accomplish the conversion of cyclohexanone pyrid-2-ylhydrazones into 5,6,7,8-tetrahydro-$\alpha$-carbolines in yields up to 98%.[67] Electron-donor substituents in the 5- and 6-positions of the pyridine ring, by increasing the electron density on the third carbon atom, facilitate the reaction, whereas electron-acceptor substituents hinder the process[66].

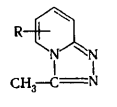
Nevertheless, it has been shown[63] that the cyclisation of cyclohexanone pyrid-2-ylhydrazones in the presence of hydrochloric acid, and also with an acetic-acid solution of the boron trifluoride–ether complex, involves "anomalous" reactions caused by the nucleophilic character of the nitrogen of the pyridine ring. The "anomalous" products of cyclisation in hydrochloric acid which have been isolated[63] are 9-cyclohexyl-5,6,7,8,9,12-hexahydro-9,10,12-triazaphenanthrene derivatives (XXXIV), the mechanism of whose formation can be written



(XXXIV)

In strongly acid medium the initial hydrazone is partly hydrolysed with the formation of cyclohexanone, which, by means of the reactive methylene group, adds at the C=N bond of the hydrazone. Subsequent enolisation of the ketone and elimination of water are facilitated by formation of the energetically favourable dihydro-1,2,10-triazanaphthalene system. Such a mechanism for the process is supported by the fact that the yield of (XXXIV) is more than trebled by the addition of an equimolecular quantity of cyclohexanone to the reaction mixture.

The "anomalous" course of the Fischer reaction in an acetic-acid solution of the boron trifluoride–ether complex is also due to acid hydrolysis. The pyrid-2-ylhydrazines which are thus obtained are acylated by the acetic acid, with further cyclisation of the acetyl derivatives into 3-methyl-1,2,9-triazaindenes (XXXV)[66]:

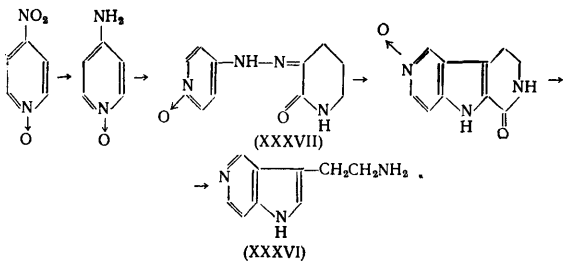


(XXXV)

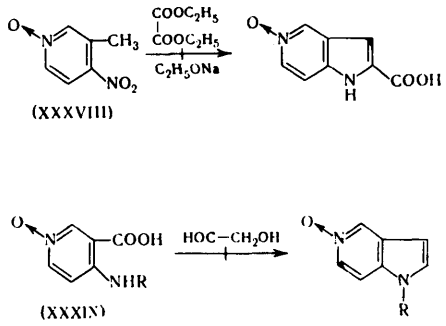
The above "anomalous" reactions are general in character, and are repeated with various substituted pyrid-2-ylhydrazones of cyclohexanone (R = H, 5-$CH_3$, 6-$CH_3$, 5-Cl, 5-Br, etc.)[66,67].

Since it has been established that the cyclisation of pyrid-2-ylhydrazones can be influenced by introducing substituents into the pyridine ring[66], it is worth looking into the Fischer synthesis of azaindoles from 6-chloropyrid-3-ylhydrazones of acetone and propionaldehyde[68], and also the successful application of the scheme of Abramovich and Shapiro for preparing 5-azatryptamine (XXXVI) from

the $N_{(1')}$-oxide of 2,3-dioxopiperidine 3-pyrid-4'-yl-hydrazone (XXXVII)[69]:



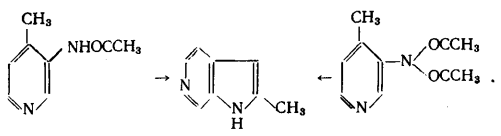
These results are especially interesting because attempts to synthesise 5-azaindole derivatives from the *N*-oxide of 3-methyl-4-nitropyridine (XXXVIII) by the Reissert reaction and from the $N_{(1')}$-oxide of 4-methyl(or phenyl)aminonicotinic acid (XXXIX) by the Harley-Mason reaction were unsuccessful[70]:



where R = $CH_3$, $C_6H_5$.

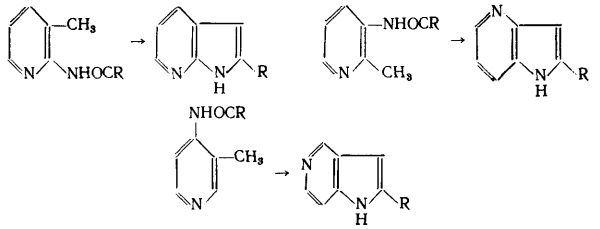
## 4. Application of the Madelung Reaction

Among methods which are widely used in the chemistry of indole, the Madelung synthesis[71] has found the widest application for the preparation of azaindole compounds. In 1927 Koenigs and Fulde[30] used this reaction to prepare the first synthetic azaindole derivative, 2-methyl-6-azaindole, a yield of 23% being obtained by the cyclisation of 3-acetamido-4-methylpyridine in the presence of sodium ethoxide. Somewhat better yields (up to 40%) were achieved from the corresponding 3-diacetylamino-4-picoline[25]:



It has proved impossible to convert the corresponding 3-formamido-derivative into unsubstituted 6-azaindole[30]. In all other cases formamidopyridines are poorer starting materials for azaindoles than are aminopyridines acylated by other acids.

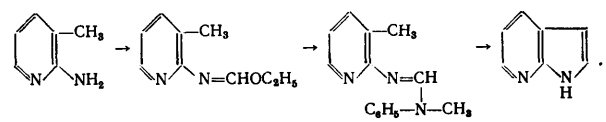
The Madelung method was later used for the synthesis of 4-, 5-, and 7-azaindole derivatives[72,73]:



The best results (yield 20%) were obtained in the case of 4-azaindole, while the yield of 7-azaindole was 3%, and unsubstituted 5-azaindole could not be synthesised by this method. The cyclisation of 4-acetamido-3-picoline to 2-methyl-5-azaindole took place with a yield of only ~ 1%. The same method enabled 5-methyl-4-azaindole (yield 12%) to be synthesised from 3-acetamido-2,6-lutidines, as well as the corresponding 2-methyl and 2-phenyl derivatives (yields 55% and 67% respectively)[23,74], while from 3-acylamino-4-picolines 12–24% yields were obtained of 2-phenyl-, 2-pyrid-2'-yl-, and 2-pyrid-4'-yl-6-azaindoles[75].

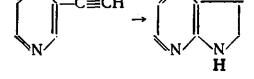
Further improvement of the Madelung reaction involved the use of sodium anilide and potassium formate as condensing agents[76], which enabled the yield of 7-azaindole at the cyclisation stage to be increased to 51%.[77] Rather lower yields (13–38%) are obtained for 4-, 5-, and 6-methyl-7-azaindoles[78]. Unfortunately, this modification of the Madelung reaction did not give favourable results for the 5- and 6-azaindoles. Conversion of 4-formamido-3-picoline in the presence of sodium anilide into a 21% yield of 5-azaindole[79] could not subsequently be repeated[24,25]. Published data[20,25] on the possibility of obtaining 4-azaindole by this method are also contradictory.

An interesting modification of the Madelung method was described in 1965 by a group of American workers[80], who showed that the best results are obtained by cyclising not formamidopicolines but the corresponding formamidine derivatives:



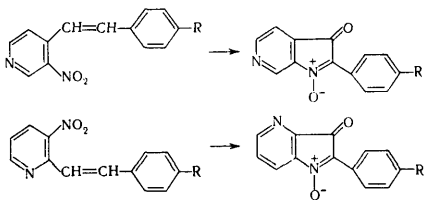
This procedure gives yields, based on the initial aminopicolines, of 70%, 37%, and 6% respectively of 7-, 5-, and 4-azaindoles.

It is worth noting the synthesis, recently published by Reisch[81,82], of unsubstituted 7-azaindole from 3-ethynylpyridine and sodamide, the yield being 54%:



The 2-amino-3-ethynylpyridine formed by the Chichibabin reaction in the course of the synthesis is immediately cyclised to 7-azaindole. A fundamental defect of this method is the relative inaccessibility of the initial 3-ethynylpyridines[83–85]. As Kost et al.[85] have shown, the preparation of 3-ethylnylpyridines from 3-vinylpyridines via the dihalogeno-derivatives is usually accompanied by the formation of 3-1'-alkoxyvinylpyridines as a side-reaction. In some cases the production of acetylenic derivatives of the pyridine series is so unsatisfactory that the method of synthesis via 3-ethynylpyridines loses its practical value.

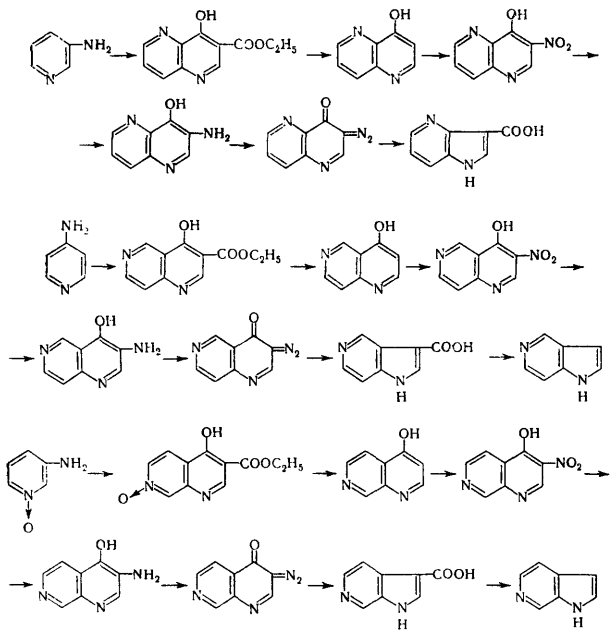
For example, Hooper et al.[75] intended to synthesise 1-hydroxy-3-oxo-4(and 6)-azaindolines from 3-nitro-2-(and 4)-styrylpyridines via the corresponding phenylethynyl derivatives. However, failures in obtaining the initial ethynyl compounds forced them to reject this scheme. The use of Splitter and Calvin's method[86] in this case enabled 2-aryl-1-hydroxy-3-oxo-4(and 6)-azaindolines to be obtained by the ultraviolet irradiation of substituted 3-nitro-2(and 4)-styrylpyridines[75]:

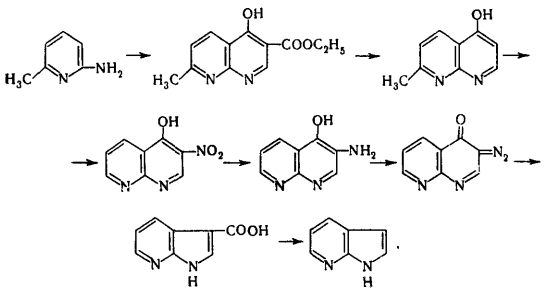


where R = $N(CH_3)_2$, OH.

5. Synthesis of Azaindoles by Süs and Möller's Method

An original photochemical method for preparing azaindoles from 3-diazo-3,4-dihydro-4-oxonaphthyridine isomers was described by Süs and Möller[87-89]. The starting materials used for the preparation of 4- and 5-azaindoles were respectively 3- and 4-aminopyridines, which were converted into 4-hydroxynaphthyridine-3-carboxylic esters by condensation with ethoxymethylenemalonic ester[90]. Subsequent stages consisted in saponification of the ester, decarboxylation, nitration, reduction of the nitro-group, and diazotisation of the 3-amino-4-hydroxynaphthyridines[87-89]. In the case of 6-azaindoles[88] the starting material for the preparation of 1,7-naphthyridine derivatives had to be 3-aminopyridine *N*-oxide, since unoxidised 3-aminopyridine could be converted only into substituted 1,5-naphthyridine[91]. In the preparation of 7-azaindole[89] 2-amino-6-methylpyridine was treated with ethoxymethylenemalonic ester; 2-aminopyridine which is not substituted in the 6-position forms in this case a pyrido[1,2-*a*]pyrimidine derivative, owing to cyclisation of the pyridine ring at the nitrogen atom[91]:



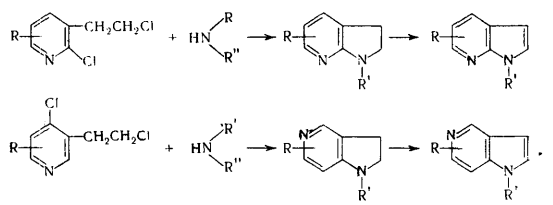


Photochemical ring contraction in the 3-diazo-3,4-dihydro-4-oxo-derivatives of the isomeric 1,5-, 1,6-, 1,7-, and 1,8-naphthyridines yields respectively the 4-, 5-, 6-, and 7-azaindole-3-carboxylic acids. With the exception of 4-azaindole-3-carboxylic acid, these are readily decarboxylated to isomeric azaindoles[87-89].

In spite of the multistage character of the process, it has proved valuable in the preparation of unsubstituted azaindoles. However, the comparatively severe reaction conditions restrict its use for obtaining azaindoles containing functional substituents.

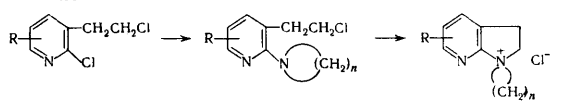
6. Syntheses of Azaindolines from 2(and 4)-Chloro-3-2'-chloroethylpyridines

A general method for synthesising various derivatives of 5- and 7-azaindoles[66,92-101] is to treat 3-2'-chloroethylpyridines containing halogen in position 2 or 4 with ammonia or a primary or secondary amine. The resulting azaindolines lose two hydrogen atoms on dehydrogenation, and are converted into the substituted azaindoles:



The reaction between 2(or 4)-chloro-3-2'-chloroethylpyridine and a secondary amine involves a novel type of pyrroline ring-closure accompanied by *N*-dealkylation. The reaction begins with replacement of the 2(or 4)-chlorine atom by the radical of the secondary amine, which is followed by cyclisation with formation of a quaternary azaindolinium salt, and this splits off alkyl halide, being thereby converted into a 1-alkyl(or aryl)-7-azaindoline.

The use of cyclic secondary amines (piperidine and pyrrolidine), by breaking up the process, permitted observation of the two successive stages—replacement of chlorine in the 2-position of the pyridine ring by the residue of the secondary amine, and subsequent cyclisation with the formation of spiro-7-azaindolinium compounds[102]—the reactions terminating at the latter stage, since in this case the quaternary 7-azaindolinium salt is unable to split off alkyl halide:



where $n$ = 4, 5.

Study of the factors governing the ease of formation of 7-azaindoline derivatives by the above procedure indicates that the first stage of the reaction—replacement of the chlorine atom in the pyridine ring by the residue of the

secondary amine—is fundamentally influenced by the reactivity of the attacking nucleophilic agent, the lability of the halogen under attack, and also the competition of side-reactions. A decisive factor in the concluding stage of the synthesis is the ease of rupture of the carbon–nitrogen bonds in the quaternary azaindolinium derivative.

If steric factors are disregarded, increasing the basic strength of the secondary amine facilitates reaction with 2-chloro-3-2′-chloroethylpyridines and the formation of 7-azaindoline derivatives; secondary processes are facilitated at the same time. Thus, for example, *N*-substituted anilines ($pK_a < 6$) react with 2,6-dichloro-3-2′-chloroethyl-4-methylpyridine (trichlorocollidine) only at 190°C,[92,94] whereas aliphatic secondary amines ($pK_a > 9$) react similarly at only 80–140°C.[92] Nevertheless, 1-arylazaindolines are obtained from reactions with *N*-substituted anilines invariably in high yields, sometimes close to theoretical. The presence of electron-acceptor substituents in the *para*-position of *N*-alkylanilines hinders the reaction, whereas electron-donor groups facilitate the process[97].

When aliphatic secondary amines are used, formation of azaindolines is accompanied by that of secondary products[92,103], primarily derivatives of 2-chloro-3-vinylpyridine. Raising the temperature accelerates both processes—replacement of the 2-chlorine by the radical of the amine, which increases the yield of azaindoline derivative, and elimination of hydrogen chloride from the side-chain, which shifts the reaction towards the 2-chloro-3-vinylpyridine—the rate of the second process increasing more rapidly than that of the first with rise in temperature.

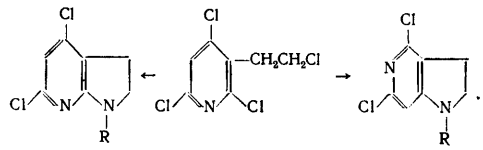
In the case of diphenylamine interaction with trichlorocollidine begins only at 300°C, the product being not an azaindoline derivative but 2-chloro-6-diphenylamino-4-methyl-3-vinylpyridine[92]. This course of the reaction is due not only to the low basic strength of the aromatic secondary amine ($pK_a$ 0.9) but also to steric hindrance. The influence of steric factors appears also in other cases of reaction between 2-chloro-3-2′-chloroethylpyridines and secondary amines. For example, the ease of formation of azaindolines varies inversely with the length of the alkyl chain in the secondary amine[92]. Reactions with homologous dialkylamines or *N*-alkylanilines at the same temperatures reveal an increase in the yield of azaindoline derivatives as the alkyl chain becomes shorter[92,94].

The question of the relative reactivity of different electrophilic centres in substituted 2-chloro-3-2′-chloroethylpyridines towards amines has been examined most generally in the case of 2,6-dichloro-3-2′-chloroethyl-4-methylpyridine (trichlorocollidine), study of whose reactions with various nucleophilic agents has shown[104] that the chlorine in the side-chain of this compound is easily eliminated as hydrogen chloride and is very resistant to nucleophilic substitution.

Of the two ring chlorine atoms, that in position 2 is the more mobile, while nucleophilic attack at position 6 plays no important part, except where reaction at position 2 is sterically hindered[103]. As a consequence, only 1-substituted 6-chloro-7-azaindolines are formed at temperatures up to 270°C with various secondary aliphatic and aliphatic–aromatic amines, as also with *N*-alkyl(and aralkyl)anilines. The chlorine atom in position 6 is retained even in the presence of large excesses of secondary amines.

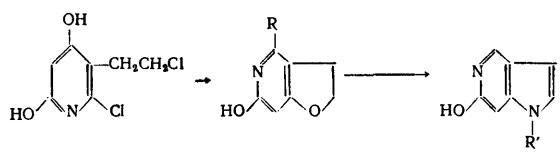
Further rise in temperature levels off the difference in reactivity between the halogen atoms in positions 1 and 6. At 300°C, for example, trichlorocollidine and *N*-methylaniline form no longer 6-chloro-4-methyl-1-phenyl-7-azaindoline but 4-methyl-1-phenyl-6-phenylamino-7-azaindoline[94]. It is interesting that in this case the *N*-dealkylation involved in closure of the pyrroline ring is accompanied by *N*-dealkylation of the 6-substituent. Since the product of the reaction of 6-chloro-4-methyl-1-phenyl-7-azaindoline with *N*-methylaniline, also occurring at 300°C, is 4-methyl-6-*N*-methyl-*N*-phenylamino-1-phenyl-7-azaindoline, not the corresponding *N*-desmethyl derivative, it can be assumed that replacement of the 6-chlorine by the amine residue in the high-temperature reaction of trichlorocollidine with *N*-methylaniline takes place either before or during, but not after, closure of the pyrroline ring[94].

The synthesis of azaindolines is considerably influenced by substituents in the initial 2-chloro-3-2′-chloroethylpyridines, which produce definite quantitative and in several cases even qualitative differences in the course of the reaction[66,92,93,97,98]. 2,4,6-Trichloro-3-2′-chloroethylpyridine undergoes two competing reactions with amines, with the formation of 5- and 7-azaindolines[96]:



The use of 2,4-dichloro-5-2′-chloroethylpyridine opened up the possibility of the directed synthesis of 5-azaindoline derivatives[66].

Dehydrohalogenation with closure of a dihydrofuran ring takes place extraordinarily easily in the case of 2-chloro-3-2′-chloroethyl-4,6-dihydroxypyridine, which opens new routes to the preparation of the hitherto difficultly accessible bicyclic 1-oxa-5-azaindane system[66]. Derivatives of this system on treatment with amines are readily converted into the corresponding 5-azaindoles[66]:



where R = Cl, H.

Further study of ways of synthesising azaindoline derivatives showed that not only 2-chloro-3-2′-chloroethylpyridines but also the corresponding 2-chloro-3-2′-hydroxyethyl and 2-chloro-3-2′-methoxyethyl-pyridines could react with secondary amines[105]. In this case, however, azaindoline derivatives could be synthesised only at higher temperatures (300–350°C). The mechanism of the formation of azaindolines from these 3-2′-hydroxy- and 3-2′-methoxy-ethylpyridines is probably analogous to that obtaining in the case of the 2-chloro-3-2′-chloroethylpyridines. The differences in reaction conditions are probably connected with the influence of the substituents in the side-chain (methoxy, hydroxy, chloro) on the lability of the 2-halogen atom. Transmission of the inductive effect of substituents through a chain of two carbon atoms and a pyridine ring can be observed also in other cases[105].

The final stage in the formation of 1-substituted 7-azaindolines from 2-chloro-3-2′-chloroethylpyridines and secondary amines is dealkylation of the quaternary azaindoline derivative. In the case of symmetrical secondary amines *N*-dealkylation is practically unambiguous: detachment of the alkyl (aralkyl) group is energetically more favourable than cleavage of the pyrroline ring. With unsymmetrical secondary amines which carbon–nitrogen bond undergoes cleavage in the quaternary azaindolinium

derivative is determined by the relative strengths of the bonds linking the substituents to the nitrogen atom: benzyl groups are more readily detached than are alkyl groups, and the latter considerably more easily than aryl groups[66].

The alkyl (or aralkyl) chloride which is eliminated in the process of dealkylation reacts under the given conditions with excess of the secondary amine, converting it into a tertiary amine. The corresponding tertiary amines have been detected and determined quantitatively by gas–liquid chromatography, after which samples were isolated[66].

## 7. Dehydrogenation of Azaindolines

Various methods of dehydrogenation have been used to convert azaindolines into the corresponding azaindoles. In the case of 1-alkyl(aryl)-7-azaindolines the most general method proved to be boiling with chloranil in xylene[93-97]. In most cases the reactions go smoothly with yields of 45–91%.

Dehydrogenation is facilitated by the presence of a 6-methoxy-group in the azaindoline molecule. With 4,6-dichloro- and 1-aryl-6-chloro-7-azaindolines, on the other hand, the oxidising potential of chloranil is inadequate, and a stronger oxidant, 2,3-dichloro-5,6-dicyanobenzoquinone, is required to convert such compounds into the azaindoles[96].

The process of dehydrogenation is considerably affected by the nature of the substituent attached to the pyrroline nitrogen. The introduction of an electron-acceptor substituent into position 1 of the azaindoline molecule hinders dehydrogenation, while the process is facilitated by an electron-donor substituent[66]. In the case of such strong electron-acceptor residues as acyl groups, dehydrogenation takes place neither on boiling with chloranil in xylene nor on heating with sulphur or with selenium to 240–300°C.[95]

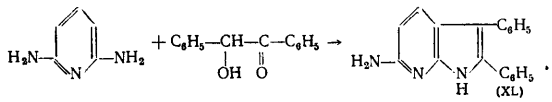
On passing from indolines and azaindolines to their *N*-sodio-derivatives (more accurately anions), when the electron density on the pyrroline nitrogen is greatly increased, the reduction potentials of the compounds rise markedly, and even air is a sufficiently strong oxidant to convert these substances into the corresponding indoles and azaindoles[106]. The dehydrogenation of indolines and azaindolines is accomplished in this case by treating their solutions in liquid ammonia with sodium in the presence of air. Separate experiments have shown that dehydrogenation does not take place in the absence of atmospheric oxygen[107].

Other strong bases—sodium hydride, sodamide, caustic soda—can be used instead of sodium. The yield of dehydrogenation products then varies directly with the strength of the base: with sodium hydride the extent of the process is about 80–85%, roughly the same as with metallic sodium, with sodamide 50–55%, with caustic soda 30–35%, and with sodium carbonate only traces of dehydrogenation products are formed[107]. Liquid ammonia is a convenient solvent for this reaction, and although the process goes also when indolines and azaindolines are treated with sodium in boiling toluene, formation of the corresponding anions is difficult under the conditions of a heterogeneous reaction, and the yields of dehydrogenation products are diminished.

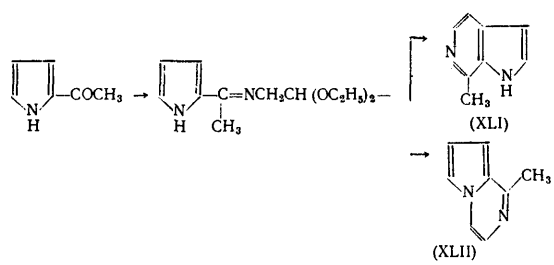
The possibility of combining into one stage, by the method which has been developed, the dehydrogenation of azaindoline derivatives with dehalogenation, and also the elimination of *N*-acyl and *N*-benzyl protective groups, is of considerable preparative interest[106].

## 8. Other Methods of Synthesising Azaindoles

Apart from the more or less general methods for obtaining azaindoles described above, syntheses have been published which are applicable only to individual compounds of this type. For example, formation of 6-amino-2,3-diphenyl-7-azaindole (XL) in 89% yield was observed on the reaction of 2,6-diaminopyridine and its hydrochloride with benzoin[26]. Unfortunately, this example proved to be unique, and in no case could azaindole compounds be isolated by the reaction of 2,6-diaminopyridine with other hydroxy-ketones:



Apoharmine (XLI) was synthesised[108,109] from 2-acetylpyrrole by the Pomeranz–Fritsch reaction:

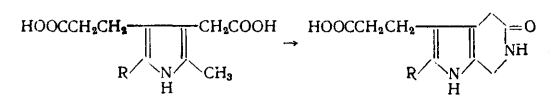


However, cyclisation of the 2-*N*-(2,2-diethoxyethyl)acetimidoylpyrrole went unexpectedly: together with (XLI), the stable yield of which did not exceed 5%, the formation was observed of a substituted 5,8-diazaindene (XLII). In the analogous synthesis from the corresponding 2-formidoyl derivative, the pyrrolopyrazine derivative was practically the only product of the reaction.

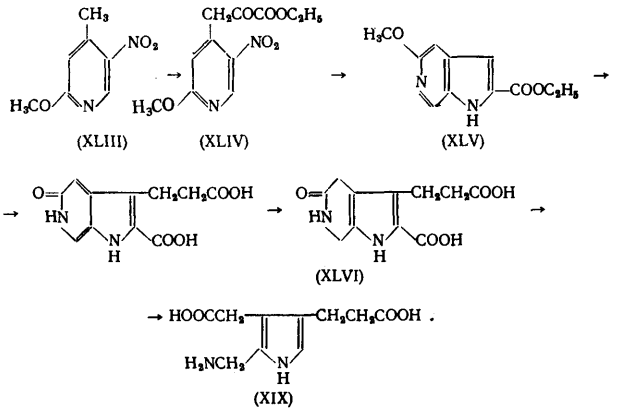
Low yields (1–7%) of 7-azaindole derivatives were obtained, accompanied by other compounds, by Johnson and his coworkers by treating diethyl 4-cyano-4,5-dihydro-2,7-dimethylazepine-3,6-dicarboxylate with silver nitrate[110] and by the reaction of potassium cyanide with dimethyl 4-chloromethyl-1,4-dihydro-1,2,6-trimethylpyridine-3,5-dicarboxylate[111].

The cyclisation of amino-carboxylic acids of the pyridine or pyrrole series to the corresponding lactams has occupied a definite place in the synthesis of azaindoles. As noted above, 7-azaoxindole was prepared from 2-aminopyrid-3-ylacetic acid by this method[29]. However, the poor accessibility of other aminopyridylacetic acids has not permitted the isomeric 4-, 5-, and 6-azaoxindoles to be synthesised[24,60].

3-Carboxyethyl-4-carboxymethyl-5-methylpyrroles, both substituted and unsubstituted in position 2, were used as starting materials in the synthesis of lactams of porphobilinogen and its analogues[112-115]. The 5-methyl group in these compounds was converted into aminomethyl either via the aldehyde, oxime, and nitrile[113,114] or via bromomethyl. Cyclisation of the substituted 5-aminomethyl-4-carboxymethylpyrroles was brought about by heating in acetic anhydride. The products of the synthesis were various 2-substituted 4,5,6,7-tetrahydro-5-oxo-6-azaindol-3-ylpropionic acids:

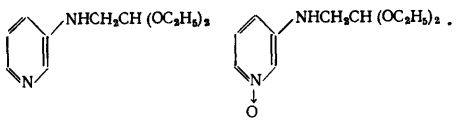


An interesting synthesis of porphobilinogen from 2-methoxy-5-nitro-4-methylpyridine (XLIII), proposed in 1965,[116] is based on Claisen condensation of the latter with oxalic ester followed by reductive cyclisation of the product (XLIV). Saponification of the methoxy-group in the resulting ethyl 5-methoxy-6-azaindole-2-carboxylate (XLV), introduction of a carboxyethyl group in position 3, and reduction of the pyridine ring with palladium gave the lactam of porphobilinogen-2-carboxylic acid (XLVI). Saponification of the lactam and decarboxylation enabled porphobilinogen (XIX) to be synthesised in an overall yield throughout the synthesis of 19%:



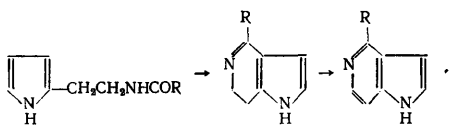
Methods of synthesising (XIX) suggested previously[112-115] gave yields not exceeding 2%.

Experiments on the cyclisation with polyphosphoric acid of 3-*N'*-diethoxyethylaminopyridines and their *N*-oxides, made by analogy with the synthesis of benzothiophens from aryl 2,2-dimethoxyethyl sulphides[117,118], did not give positive results in the case of azaindoles[25]:



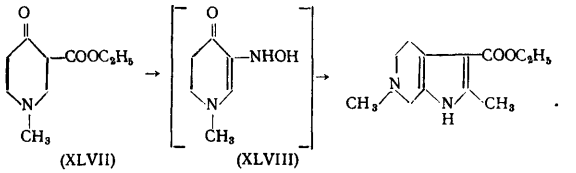
Attempts to cyclise 4-acetamido-3-bromopyridine to the corresponding 5-azaindole derivative[79] by the method of Hrutford and Bunnett[119] were also unsuccessful.

More interesting results have been obtained by synthesising 5-azaindole derivatives from acylated 2-2'-aminoethylpyrroles[120] by the Bischler–Napieralski reaction:

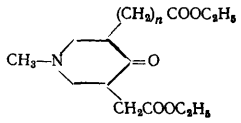


The acetyl and benzoyl derivatives were cyclised to the 4-methyl- and 4-phenyl-6,7-dihydro-5-azaindoles in yields of 18% and 24% respectively[27]. 2-*N'*-Formamido- and 2-*N'*-(3,4-dimethoxyphenylacetamido)-ethylpyrroles could not be converted into 5-azaindole derivatives[27].

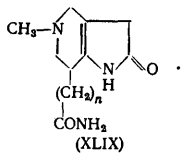
The synthesis of certain partly hydrogenated 6-azaindoles was accomplished by means of the reaction of ethyl 1-methyl-4-oxopiperidine-3-carboxylate (XLVII) with sodium nitrite, followed by reductive cyclisation of the 3-hydroxyimino-1-methyl-4-oxopiperidine (XLVIII) with acetoacetic ester[121]:



The cyclisation of other 1-methyl-4-oxopiperidines of general formula



by the action of ammonia has enabled several new 7-substituted 4,5,6,7-tetrahydro-5-methyl-5-azaoxindoles (XLIX) to be obtained, these existing in the oxo-form[122]:



## III. CHEMICAL PROPERTIES OF AZAINDOLES

### 1. Chemical Peculiarities of Azaindoles due to Fusion of π-Electron-deficient and π-Electron-excessive Heterocycles in a Bicyclic System

A characteristic feature of azaindoles is that their fused bicyclic system is formed by two nitrogenous heteroaromatic rings with directly opposite displacement of the π-electrons inside each ring—the "π-electron-deficient" (in Albert's terminology[123]) pyridine ring and the "π-electron-excessive" pyrrole ring—and it is therefore interesting to examine the interaction of π-electron systems of this type and compare the chemical properties of azaindoles with those of the corresponding derivatives of pyridine, pyrrole, and indole.

Papers on the chemistry of the azaindoles have repeatedly noted their differences from indole compounds. In comparison with the latter, azaindoles have higher melting points[20], better aqueous solubility[20], and stability in acid and alkaline media[28,124], they do not give with a pine splint the colour reaction characteristic of indoles[30,73], and they exhibit more intense fluorescence[19].

Study of the basic strengths of unsaturated azaindoles revealed that three of them (4-, 5-, and 6-azaindoles) are stronger bases than is quinoline ($pK_a$ 4.94), while 7-azaindole has a considerably smaller ionisation constant[20] (see Table 1).

The peculiarities of the 7-azaindole molecule in this case are due to the inductive effect on the 7-nitrogen atom of the closely placed 1-nitrogen[20]. An analogous effect is observed in benzimidazole ($pK_a$ 5.53) and still more in indazole (1.22). Furthermore, the resonance contribution of *o*-quinonoid forms in 4- and 7-azaindoles is smaller than is that of *p*-quinonoid forms in 5- and 6-azaindoles, as a consequence of which the two former azaindoles have a lower $pK_a$ value than have the latter isomers[20]. A

theoretical examination of the factors influencing the $pK_a$ has enabled steric hindrance to be rejected in the case of 7-azaindole, since such hindrance would not be greater than in quinoline.

The ionisation constants of methylated 7-azaindoles[78], as was to be expected, are larger than that of unsubstituted 7-azaindole, diminishing in the sequence 4-, 6-, and 5-methyl-7-azaindoles ($pK_a$ 5.23, 5.18, and 4.91 respectively).

Table 1.

| Compound | M.p., °C | $pK_a$ | $\lambda_{max}$, nm (lgε), in water |
|---|---|---|---|
| Indole | 52 | <1 | 273—278, 288(3.79+3.78; 3.69) |
| 4-Azaindole | 127 | 6.94 | 292 (3.92) |
| 5-Azaindole | 112 | 8.26 | 265.273 (3.59; 3.50) |
| 6-Azaindole | 135 | 7.95 | 260.291 (3.59; 3.68) |
| 7-Azaindole | 105 | 4.59 | 290 (3.91) |

Examination of a large amount of information on the transmission of the effect of 1- and 6-substituents on the ability of 7-azaindoles and 7-azaindolines to undergo protonation at the nitrogen atom has shown[66,125] that a single aromatic system is present in 7-azaindoles, whereas in 7-azaindolines the effect of a substituent in the 1-position correlates well with the Taft induction constant for non-aromatic compounds. The application of correlation methods has enabled cross correlation equations to be obtained: for 1- and 6-substituted 7-azaindolines $-pK_a = -5.43 + 1.29\sigma^* + 8.0\sigma_i$, where $\sigma^*$ and $\sigma_i$ are the constants of substituents present in positions 1 and 6 respectively; and for 1- and 6-substituted 7-azaindoles $-pK_a = -3.80 + 8.57\sigma_{i\Sigma}$, where $\sigma_{i\Sigma}$ is the total constant of the substituents in positions 1 and 6.[66,125]

Table 2.

| Compound | $\tau_1$ | $\tau_2$ | $\tau_3$ | $\tau_4$ | $\tau_5$ | $\tau_6$ | $\tau_7$ | $J_{1.2}$ | $J_{1.3}$ |
|---|---|---|---|---|---|---|---|---|---|
| Indole | —0.12 | 2.73 | 3.55 | 2.45 | 3.00 | 2.92 | 2.60 | 2.5 | 2. |
| 7-Azaindole | — | 2.53 | 3.52 | 2.04 | 2.95 | 1.73 | — | — | — |
| | $J_{1.4}$ | $J_{2.3}$ | $J_{3.7}$ | $J_{4.5}$ | $J_{4.6}$ | $J_{4.7}$ | $J_{5.6}$ | $J_{5.7}$ | $J_{6.7}$ |
| Indole | 0.8 | 3.1 | 0.7 | 7.8 | 1.2 | 0.9 | 7.0 | 1.2 | 8.0 |
| 7-Azaindole | — | 3.4 | — | 7.7 | 1.5 | — | 4.7 | — | — |

The good agreement between $pK_a$-values calculated by means of the correlation equations and those found experimentally shows that, in the case of 1- and 6-substituted 7-azaindoles and 7-azaindolines, the ionisation constants are influenced mainly by the induction effect of the substituents. A considerably smaller part is played by direct conjugation (except in 4-methyl-1-*p*-nitrophenyl-7-azaindole) and also by steric factors in these cases[66].

A special investigation[126] has been made of the nuclear magnetic resonance spectra of several heteroaromatic systems, including indole and 7-azaindole. However, this was confined to measurement of the proton chemical shifts and the spin–spin interaction constants, no attempt being made to characterise the distribution of electron density in azaindole systems (Table 2).

In order to examine theoretically the mutual influence of conjugated π-electron-deficient and π-electron-excessive rings in a fused system, the 7-azaindole[127] and indole[127,128] molecules have been calculated to the Hückel π-electron approximation. The results are presented in the form of tables (Table 3) and molecular diagrams (that of pyridine[129] is given for comparison):

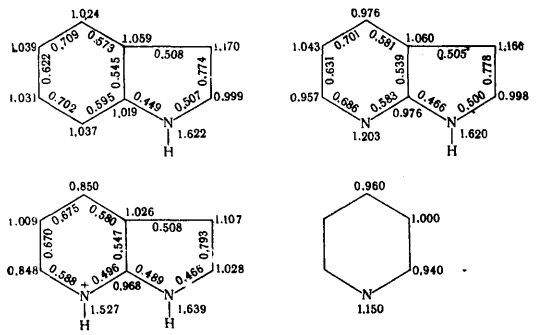


Table 3.

| Compound | Vacant levels | | Occupied levels | | Total energy of π-electrons | Delocalisation energy | Resonance energy |
|---|---|---|---|---|---|---|---|
| Indole | —2.158<br>—1.500 | —1.179<br>—0.853 | 0.534<br>0.796 | 1.280<br>1.669<br>2.420 | 13.399 | 11.399 | 3.399 |
| 7-Azaindole | —2.120<br>—1.460 | —1.174<br>—0.770 | 0.571<br>0.829 | 1.366<br>1.702<br>2.455 | 13.847 | 11.447 | 3.408 |
| 7-Azaindolinium cation | —2.012<br>—1.336 | —1.044<br>—0.481 | 0.742<br>1.022 | 1.603<br>2.174<br>2.932 | 16.944 | 11.844 | — |

From the distribution of effective charges it has been shown[127] that in the carbon portion of the 7-azaindole electrophilic substitutions should occur most readily at position 3, and nucleophilic substitutions at positions 4 and 6.

Comparison of the molecular diagrams of pyridine and 7-azaindole indicates[127] that, owing to the redistribution of charges in the 7-azaindole molecule, increased electron density is present at positions 4 and 6 compared with the corresponding positions 4 and 2 in the pyridine ring. This provides an explanation of the difficulty of nucleophilic substitutions in 7-azaindoles.

Chemical experiment has confirmed[66] that in 7-azaindole electrophilic substitution takes place most readily at position 3, while the sites of nucleophilic attack are the 4- and 6-carbon atoms. 7-Azaindole derivatives exhibit considerably less tendency to nucleophilic substitution in

comparison not only with pyridines but also with 7-azaindolines. For example[95], when 6-chloro-4-methyl-7-azaindole is treated with such a strong nucleophilic reagent as the methoxide ion, replacement of chlorine by methoxyl is only 39% complete even at 300°C. The analogous reaction with 6-chloro-4-methyl-7-azaindoline was more than 70% complete at 190°C, while the chlorine atom in 2-chloropyridine was replaced by the methoxy-group at only 70°C. 4-Methylpyridine reacts with *m*-nitrobenzaldehyde to give a 73% yield of *m*-nitrostilbazole, and the yield of styryl derivative when *m*-nitrobenzaldehyde is condensed under the same conditions with 1-butyl-4-methyl-7-azaindoline is 26%, while 1-butyl-4-methyl-7-azaindole does not react with aldehydes over a wide range of temperatures[93]. Nor have positive results been obtained from experiments[130] on the direct introduction of an amino-group into the 7-azaindole molecule in the presence of sodamide by the Chichibabin reaction, which is so characteristic of the pyridine series.

Electrophilic substitutions (the Mannich and Vilsmeier reactions, cyanomethylation, nitration, and bromination) are more difficult in position 3 of 7-azaindole derivatives than in the indole series. Groups present in positions 1 and 6 have a considerable effect here[66,131]. The ease of occurrence of these reactions increases, for example, on passing from 6-methoxy-7-azaindoles through the 6-unsubstituted compounds to 6-chloro-7-azaindoles[131], approaching in the last case analogous reactions in the indole series. The introduction of electron-acceptor groups into position 1 of the azaindole molecule hinders electrophilic substitutions in position 3, whereas electron-donor groups facilitate the process.

Substituents in positions 1 and 6 affect electrophilic substitution not only owing to change in the electron density at position 3 of the azaindole molecule but also because the ability of 7-azaindoles to be protonated at the pyridine nitrogen is changed[66,127]. The production, under the conditions of electrophilic substitutions, of forms in which the nitrogen atom is protonated leads to a general positive charge on the molecule and an associated redistribution of $\pi$-electron density, which, of course, hinders electrophilic attacks at position 3. This agrees well with calculation of the protonated form of 7-azaindole—the 7-azaindolinium cation[127].

## 2. Lactam–Lactim and Amino–Imino Tautomerism in 7-Azaindoles and 7-Azaindolines

Interesting results related to the interaction of the two nitrogen atoms in the 7-azaindole system have been obtained in a study of the lactam–lactim and amino–imino tautomerism of 6-hydroxy-7-azaindoles and also of 6-hydroxy-, 6-amino-, and 6-acylamino-7-azaindolines[66,132]. In contrast to other $\alpha$(or $\gamma$)-hydroxy-*N*-heteroaromatic compounds, no sufficiently complete displacement of the tautomeric equilibrium towards the lactam takes place in 6-hydroxy-7-azaindoles and 6-hydroxy-7-azaindolines. In solutions comparable quantities of the two tautomers are observed, and ultraviolet and infrared spectroscopy permit the influence of the polarity of the solvent, and also the nature of the substituents attached to nitrogen in the five-membered ring, on the position of the lactam–lactim tautomeric equilibrium to be clearly traced[66].

With 6-hydroxy-4-methyl-7-azaindoline in dioxan solution 88% of the lactim form is observed, dilution with alcohol diminishes the content of the lactim, and in absolute alcohol the compound is almost completely converted into the lactam form. In the case of 1-butyl-6-hydroxy-4-methyl-7-azaindoline such conversion is already achieved in the range dioxan : alcohol (9 : 1)–alcohol : water (3 : 1). 6-Hydroxy-4-methyl-1-phenyl-7-azaindoline contains 88% of the lactim form even in a 1 : 1 mixture of alcohol and dioxan, while sufficiently complete conversion to the lactam form is accomplished only in water containing 2% of alcohol.

The presence of the two tautomeric forms of 6-hydroxy-7-azaindolines together is confirmed by the infrared spectra in dilute carbon-tetrachloride solutions, where both the carbonyl bands of the lactam form at 1630–1645 $cm^{-1}$ and the absorption at 3580–3582 $cm^{-1}$ characteristic of hydroxy-stretching vibrations of the lactim form are clearly developed.

The decrease in electron density on the 7-nitrogen on passing from pyridines through 7-azaindolines to 7-azaindoles is made evident in a further shift in the lactam–lactim tautomeric equilibrium towards the lactim forms in 6-hydroxy-7-azaindoles compared with 6-hydroxy-7-azaindolines[133]. Ultraviolet spectroscopic data indicate that in 6-hydroxy-4-methyl-1-phenyl-7-azaindole, for example, the tautomeric equilibrium is shifted so far towards the lactim form that considerable quantities of the lactim remain even in strongly polar solutions (in water containing 2% of alcohol). In this case neither in the crystals nor in dioxan solution can lactam groups be detected by infrared spectroscopy, and only in carbon tetrachloride, where the dielectric constant is higher than in dioxan, is a weak band at 1642 $cm^{-1}$ due to the lactam carbonyl apparent together with the intense band at 3580 $cm^{-1}$ characteristic of the hydroxy-group of the lactim form[133].

6-Hydroxy-derivatives of 7-azaindole and 7-azaindoline are distinguished from other $\alpha$-hydroxy-*N*-heteroaromatic compounds not only in the position of the lactam–lactim tautomeric equilibrium but also in their chemical properties. For example, methylation with dimethyl sulphate in alkaline aqueous medium gives high yields not of *N*-methyl but only of *O*-methyl derivatives[66].

Investigation of the amino–imino tautomerism of 6-amino-4-methyl-1-phenyl-7-azaindoline and its $N_{(6)}$-acyl (acetyl, trichloroacetyl, and toluene-*p*-sulphonyl) derivatives by ultraviolet and infrared spectroscopy has shown that in this case the equilibrium is practically completely displaced towards the amino-forms, and even acylation with toluene-*p*-sulphonic acid does not lead to an appreciable shift in the tautomeric equilibrium towards the imino-form, in contrast to what happens with other *N*-heteroaromatic amines[66].

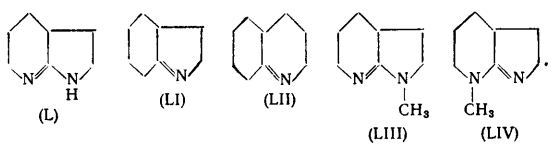
## 3. Substituted Azaindoles and Reduction of the Azaindole Ring

Synthetic investigations based on azaindole compounds developed by analogy with the chemistry of indole and pyridine. The various reactions were applied mainly to derivatives of 7-azaindole. Like the various pyridine bases, 7-azaindole forms salts (hydrochloride, picrate) and quaternary derivatives involving the nitrogen atom in the six-membered ring[28,124]; as in indole, the pyrrole nitrogen can be acylated and alkylated[95,124].

The hydrogenation of 7-azaindole by means of a nickel catalyst in decalin at 200°C and 118 atm yields 7-azaindoline[28]. 2-Amino-3-ethylpyridine was isolated as a side-product, and at higher temperatures became the chief product[134]. Analogous cleavage of the five-membered ring during hydrogenation at high temperatures is

observed also in the indole series[135]. 2-Alkyl-7-azaindoles are reduced under the same conditions with marked resinification, and satisfactory yields of 2-methyl- and 2-ethyl-7-azaindolines are obtained only with a copper–chromium catalyst[72]. Attempts to reduce ethyl 7-azaindole-1-carboxylate under mild conditions[134] did not yield positive results, unlike analogous experiments with other ethyl pyrrole-1-carboxylates[136].

The hydrogenation of 7-azaindole at room temperature and atmospheric pressure with a platinum catalyst yielded $\Delta^7$-hexahydro-7-azaindole (L), whose structure was established by a comparative analysis of the characteristic C=N stretching frequencies in the infrared spectra of (L) and a series of analogous compounds[134]. It was shown[137–139] that in $\Delta^{8(1)}$-hexahydroindole (LI) the C=N stretching vibrations have a frequency of 1647 $cm^{-1}$, while the analogous C=N bond in $\Delta^{9(1)}$-octahydroquinoline (LII) is characterised by a frequency of 1658 $cm^{-1}$. The hexahydro-derivative of 7-azaindole investigated had an absorption band at 1652 $cm^{-1}$, while the hexahydro-derivatives (LIII) and (LIV) obtained by the reduction of 1- and 7-methyl-7-azaindole absorbed at 1657 and 1615 $cm^{-1}$ respectively:




All these data indicate that, when 7-azaindole is hydrogenated in the presence of a platinum catalyst, the double bond in position 7(8) in the six-membered ring remains unreduced[134].

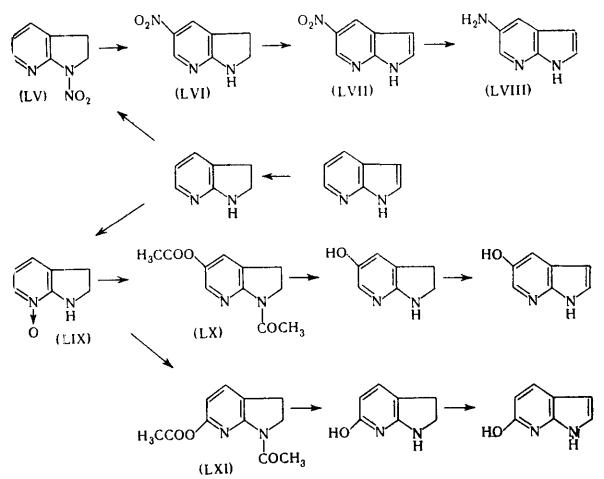
In contrast to 7-azaindole, the isomeric 5-azaindole could not be reduced in the presence of a platinum catalyst in acid medium[79].

When the 7-azaindole ring contains a 3-hydroxyimino-group, however, formation of 7-azaindoline derivatives is observed even in the presence of lithium tetrahydroaluminate[140].

## 4. Introduction of Substituents into the Pyridine Ring of Azaindoles

The conversion of 7-azaindoles into 7-azaindolines and the processes described above for dehydrogenating azaindoline derivatives have enabled a trial to be made in this series of compounds of an elegant method which has been widely used by Terent'ev, Preobrazhenskaya, and their coworkers in the chemistry of indole[141–144]. The method consists essentially in reducing indole or a derivative thereof to an indoline, which is an aromatic amine and hence capable of the usual reactions in the benzene ring. After the introduction of a substituent, the indoline is dehydrogenated, and the corresponding *Bz*-substituted indole is obtained.

This procedure has been used to introduce substituents at position 5 in 7-azaindole[130]. The 1-nitro-derivative (LV), obtained by nitrating 7-azaindoline, could be converted by thermal rearrangement into 5-nitro-7-azaindoline (LVI). The latter was dehydrogenated over palladium to 5-nitro-7-azaindole (LVII), from which 5-amino-7-azaindole (LVIII) was obtained by reduction. Another reaction used for the preparation of *Py*-substituted 7-azaindoles was rearrangement of the $N_{(7)}$-oxide of 7-azaindoline (LIX) in the presence of acetic anhydride. The rearrangement occurred unambiguously, and the corresponding 5- and 6-hydroxy-7-azaindolines were obtained as the *NO*-diacetyl derivatives (LX) and (LXI) in yields of 19% and 31%:[130]




In view of this, the directed synthesis of *Py*-substituted azaindoles[66] is more promising than the introduction of functional groups into unsubstituted azaindole structures.

## 5. Introduction of Substituents into the Pyrrole Ring of Azaindoles

Most work has been done on the preparation of 3-substituted 7-azaindoles. The 7-azaindoles are converted by the Mannich reaction into azagramines[66,77,131,145], the position of the 3-dimethylaminomethyl group in which has been confirmed by synthesis[77]. The nitration[66,77,131], bromination[66,131,146], and cyanomethylation[131] of 7-azaindoles have been described. The Vilsmeier reaction has proved a convenient general method for introducing a 3-formyl group into the 7-azaindole molecule[131,145,147]. The influence of the distribution of electron density and the nature of the substituents in 7-azaindoles on the above electrophilic substitution reactions has been considered above.

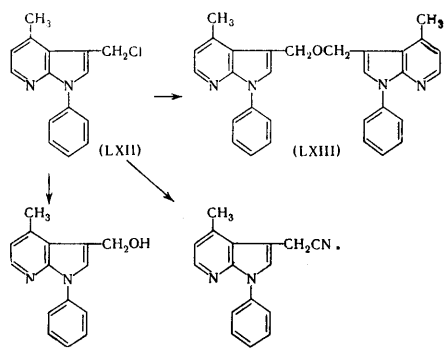
In the 5-azaindole series, in contrast to the 7-azaindoles, nitration, bromination, and other reactions did not give positive results. For example, various modifications of the Mannich reaction did not yield 5-azagramine[79]. Nor was it possible to synthesise[79] products of the reaction of 5-azaindole with piperidinomethylformamidomalonic ester by the method developed for the corresponding indole compounds[148]. Yet 2,5-dimethyl-4-azaindole undergoes electrophilic substitution at position 3 comparatively easily (even more readily than does 7-azaindole), which provided a method for preparing 2,5-dimethyl-4-azaindoles containing bromine, a nitro-group, formyl, and other substituents in position 3.[23] Information is lacking in the literature on the introduction of substituents into the ring of 6-azaindole.

The above peculiarities in the distribution of electron density in 7-azaindole govern not only the character of electrophilic substitution at position 3 but also the reactivity of substituents already present. For example, 3-bromo-7-azaindole, unlike analogous 3-bromoindoles, does not react with various nucleophilic reagents[146]. 7-Azagramine and its derivatives proved to be considerably weaker alkylating agents than the analogous gramines[145,146].

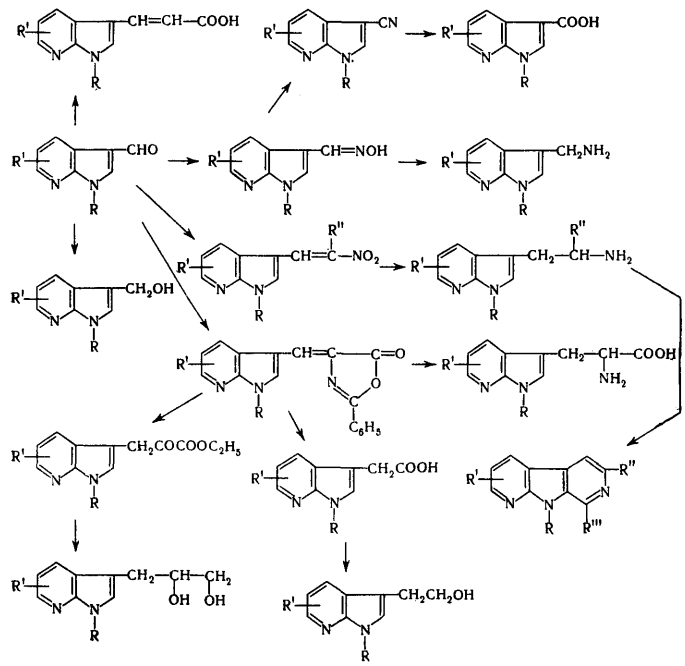
Although reaction of 7-azagramine with acetamidomalonic ester converts it into 7-azatryptophan[77], with malonic ester into 7-azaindol-3-ylpropionic acid[146], and with hydrocyanic acid into 7-azaindol-3-ylacetonitrile, syntheses based on 7-azagramines present certain difficulties. For example, even boiling unsubstituted 7-azagramine with hydrocyanic acid for many (64) hours does not raise the yield of 7-azaindol-3-ylacetonitrile above 49%.[146] Still lower yields were obtained in the analogous reaction with nitromalonic ester[146], and also in the reaction of substituted 7-azagramines with hydrocyanic acid[145].

In this connection considerable preparative interest attaches to 3-formyl-7-azaindoles[145,147] and the 3-chloromethyl-7-azaindoles which can be readily obtained from the former via the 3-hydroxymethyl derivatives[145]. The chlorine atom in the second series of compounds is allylic in character and is extremely labile. For example, it is replaced by hydroxyl even when the compound is dissolved in water, and can be titrated alkalimetrically[145].

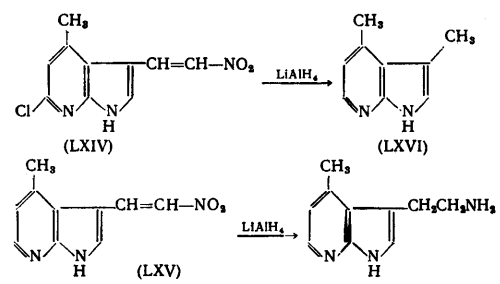
It is interesting that when, for example, 3-chloromethyl-4-methyl-1-phenyl-7-azaindole (LXII) is treated with potassium cyanide in 80% aqueous alcohol, bis-4-methyl-1-phenyl-7-azaindol-3-ylmethyl ether (LXIII) is formed in theoretical yield[145]. The cyano-group can be introduced only by the use of acetone cyanohydrin under anhydrous conditions[140]:



Comparison of various synthetic methods shows that the best results in the preparation of 3-aminomethyl derivatives are obtained by reducing the oximes of the corresponding 3-formyl-7-azaindoles with zinc in hydrochloric acid[140]. The most convenient method for the synthesis of 3-2'-aminoalkyl-7-azaindoles is to condense the 3-formyl derivatives with the nitroalkanes and then reduce with lithium tetrahydroaluminate in boiling tetrahydrofuran[66,101,107,140,149,150]. Other methods of synthesis, investigated by analogy with indole compounds (from 7-azagramines or 3-chloromethyl-7-azaindoles via the nitriles, cyanomethylation of azaindoles followed by reduction, from 3-formyl-7-azaindoles via the azlactones and amides of 7-azaindol-3-ylacetic acids), gave no advantages over these methods[66,151].



The course of the reaction of 6-chloro-4-methyl-3(2'-nitrovinyl)7-azaindole (LXIV) with lithium tetrahydroaluminate is unexpected: unlike the normal reduction of the dehalogenated compound (LXV), the reaction is accompanied by rupture of a carbon–carbon bond with formation of 4-methyl-7-azaskatole (LXVI)[150]:



The conversion of 3-formyl-7-azaindole into 3-cyano-7-azaindole by the action of nitropropane, ammonium phosphate, and acetic anhydride is interesting[152]. The mechanism of these reactions has not yet been studied.

The best method for obtaining 7-azaindol-3-ylacetic acids has proved to be from 3-formyl-7-azaindoles via the corresponding azalactones[66], for 7-azaindole-3-carboxylic acid from 3-formyl-7-azaindole via its oxime and 1-acetyl-3-cyano-7-azaindole[146], for 7-azaindol-3-ylacrylic acids from 3-formyl-7-azaindoles by the Knoevenagel and Wittig–Horner reactions[145], and for 7-azatryptophan derivatives by reducing the azlactones with hydriodic acid in the presence of phosphorus[66].

The reduction of 3-formyl-7-azaindoles and of 7-azaindol-3-yl-acetic and -pyruvic esters with complex metal hydrides provides a route for obtaining 3-hydroxymethyl[145], 3-2′-hydroxyethyl[66], and 3-(2,3-dihydroxypropyl)[145] derivatives of 7-azaindoles.

Acylation of 3-aminoalkyl-7-azaindoles followed by cyclodehydration yields derivatives of the new tricyclic system 1,7,9-triazafluorene[153]. Besides the fully aromatic triazafluorenes, the corresponding dihydro- and tetrahydro-derivatives have also been described[153].

## IV. BIOLOGICAL ACTIVITY OF AZAINDOLE COMPOUNDS

Published information on the biological activity of azaindole compounds is still very sparse, and relates mainly to derivatives of 7-azaindole. It is interesting to note that the study of unsubstituted azaindoles led to the conclusion that there was no correlation between their pharmacological properties and such physicochemical characteristics as their ionisation constants, percentage ionisation at pH 7.4, or distribution in the ether–water system[18].

The examination of biological activity showed that in several properties competitive relations existed between indole and azaindole derivatives. For example, experiments with *Neurospora crassa* established that 7-azaindole inhibited the conversion of indole into tryptophan[154]. 7-Azatryptophan retards the assimilation of tryptophan by *Tetrahymena pyriformis*[155], and replaces tryptophan in reaction with the protein of the bacterium *Escherichia coli* and the bacteriophage T2,[156] by blocking the formation of carbamoyl-transferase and D-serine-deaminase[157]. It has been reported[18] that unsubstituted 7-azaindole, unlike indole, causes depression of the central nervous system, adynamia, and weakening of the smooth musculature in small laboratory animals. Another series of parameters established the similarity in the biological action of indole and azaindole compounds. For example, 7-azaindol-3-ylacetic acid proved to be a powerful plant growth hormone[158], similar to heteroauxin, and *laevo*-12-azadeserpidine[159] exhibited reserpinelike activity characteristic of natural deserpidine.

Nevertheless, as the investigations of S. S. Liberman (in M. D. Mashkovskii's laboratory in the All-Union Chemical–Pharmaceutical Scientific Research Institute) have shown[66], in several cases more complicated relationships than competing or similar activities were exhibited in the biological actions of indole and azaindole compounds. For example, in an experiment substituted 3-aminomethyl derivatives of 7-azaindole act similarly to tryptamine, and substituted aza-analogues of tryptamine exert a central depressive effect on the tone of the skeletal musculature, slow down motor activity, and produce a prolonged hypothermic effect. A pronounced hypotensive action, associated with the effect on the central nervous system, is possessed by aminoalkyl derivatives of 7-azaindole containing a longer aminoalkyl chain. Thus replacement of the 7-methine group in the indole ring by a nitrogen atom leads in several cases to the appearance of new pharmacological characteristics, sharply distinguishing azaindoles from analogous derivatives of indole.

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# Chromatographic Resolution of Racemates on Dissymmetric† Sorbents

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The review discusses the use of natural sorbents (proteins, carbohydrates, and optically active quartz) and also artificial dissymmetric sorbents (based on silica gel and activated carbon) for the chromatography of racemates. Gas chromatography is very effective for the separation of diastereomers, but is less suitable for the direct separation of optical isomers. On the other hand, dissymmetric ion-exchange sorbents, which are considered in detail in the review, may find wider practical application. The list of references contains 197 items.

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## I. INTRODUCTION

In connection with the vigorous development of research on the production of synthetic medicines, animal feeds, and food products, the problem of resolving various racemic compounds into optically active components has now become urgent. Chemical synthesis produces a racemic mixture of enantiomorphs, but usually only one form can be used for biological purposes.

A foreign dissymmetric agent is necessary for the resolution of a racemic compound‡. Use can be made of differences between the enantiomorphs in—(1) interaction with a dissymmetric environment (sorption on dissymmetric phases, diffusion through a medium containing dissymmetric centres, dissolution in optically active solvents, interaction with circularly polarised radiation or with polarised elementary particles, etc.); (2) rate of chemical interaction with optically active substances, and physical and chemical properties of pairs of diastereomers formed as a result of such interaction; and (3) interaction with a

† The term dissymmetric is to be applied to sorbents containing dissymmetric structural units possessing optical activity of definite sign (positive or negative). We recall that a structure is said to be dissymmetric if it contains no rotation-reflection axis of symmetry (an axis rotation about which, followed by reflection in a plane perpendicular to the axis, yields a structure identical with the original structure). Dissymmetry of structure is the necessary and sufficient condition for the appearance of optical activity in a substance. In determining the dissymmetric character of a molecule it is necessary to take into account all the conformations which the molecule can adopt under the given conditions. The selective absorption by a dissymmetric sorbent of one of the enantiomorphs of a racemate is to be termed stereoselective sorption.

‡ The "spontaneous" resolution of racemates during crystallisation generally requires the introduction of a seed of an optically active substance.