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The chemistry of pyrroloindoles

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Abstract. The methods of synthesis of isomeric pyrroloindoles are surveyed. The characteristic features of electrophilic substitution reaction of the pyrroloindole ring and certain side chain reactions are discussed. The bibliography includes 60 references.

I. Introduction

Pyrroloindoles are striking representatives of indole-containing condensed systems. Chemically they are the closest analogues of indole. A wide variety of bifunctional analogues of biologically active indole derivatives have been obtained from pyrroloindoles.

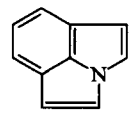
Substances with bactericidal, antimicrobial, and antitumour activities as well as other properties of value for medicine and the national economy have been found among pyrroloindole derivatives.[1–3] The highly active antitumour antibiotic CC-1065, the principal structural fragment of which is the pyrroloindole system, was isolated in 1987 from *Streptomyces zebensis*. Its antitumour activity in vitro is many times greater than that of other known preparations.[4] This stimulated further development of synthetic methods for the preparation of pyrroloindoles. Research on these lines is being continued.

Pyrroloindole is a typical representative of heteroaromatic systems. Its molecule consists of three conjugated rings with 14π electrons which satisfy the aromaticity rule ($4n + 2$) in Dewar's treatment. Like indole itself, the pyrroloindoles **1–4** belong to systems with an excess of π electrons, since the total number of π electrons of the aromatic system exceeds the number of atoms in the ring.[35] In contrast to indole, there are two nitrogen atoms in the molecules of the pyrroloindoles **1–4** which contribute four π electrons to the aromatic system. Simple calculations have shown that the number of π electrons corresponding to each ring atom is 1.17 in the pyrroloindoles **1–4** and 1.11 in indole. Thus the excess of π electrons in pyrroloindoles is greater than in indole. Approximately the same relation between their reactivities with respect to weak electrophiles may be expected.

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The pyrroloindoles described in the literature can be divided into three groups. Those in the molecules of which pyrrole is condensed with indole via the benzene ring (type I) or the carbon atoms in the pyrrole ring (type II) and also pyrroloindoles in the molecules of which there is one common nitrogen atom and all three rings are linked directly to one another (type III), for example as in the following formula:

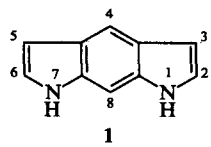


The properties of type I pyrroloindoles differ from those of type II and III compounds, which will not be considered in the present review.

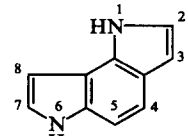
Type I pyrroloindoles are particularly interesting because they contain two reactive centres in the β-positions in the pyrrole rings. This makes it possible to obtain bifunctional analogues of the known physiologically active indole compounds.

II. Methods of synthesis of pyrroloindoles

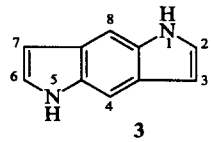
The following pyrroloindole systems are known at present:



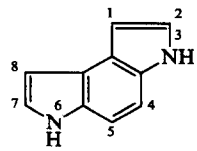
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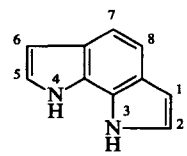
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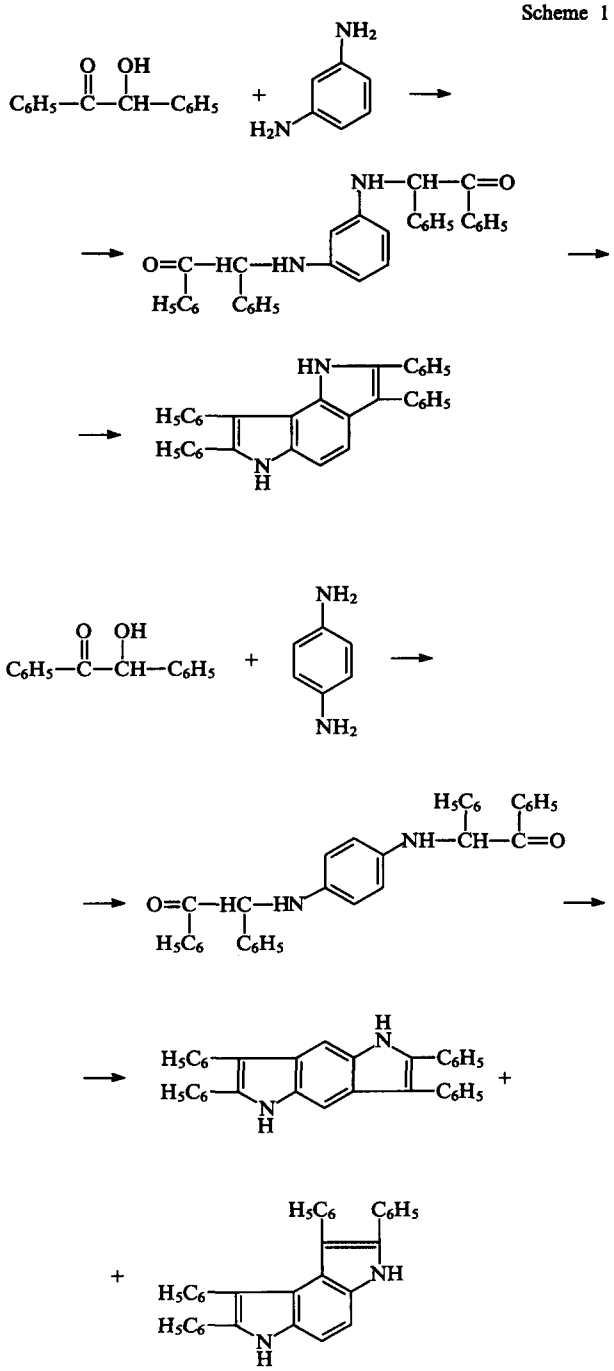


5

Pyrroloindoles may be synthesised in two ways: the first procedure involves simultaneous closure of both pyrrole rings, the second involves the attachment of a pyrrole ring to the benzene ring of indoline or indole.

The first pyrroloindoles were obtained as early as the past century. Thus Japp and Meldrum[5] synthesised tetraphenylpyrroloindoles from *m*- and *p*-phenylenediamines and benzoin by the Bischler reaction (the yields are not indicated) (Scheme 1).

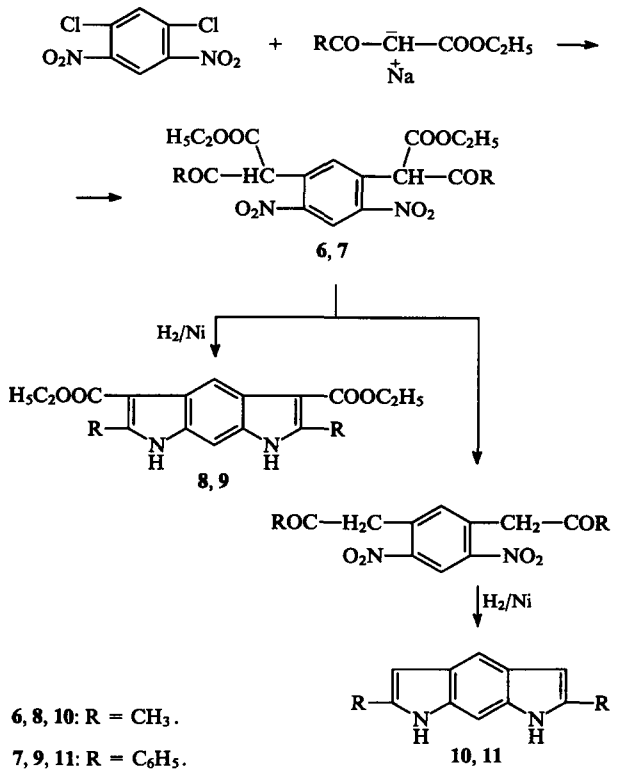
Scheme 1



Another scheme for the synthesis of pyrroloindoles using the Bischler method involves the condensation of 4-, 5-, 6-, and 7-aminoindoles with benzoin and subsequent cyclisation. Various isomeric pyrroloindoles obtained in accordance with this scheme are listed in Table 1.

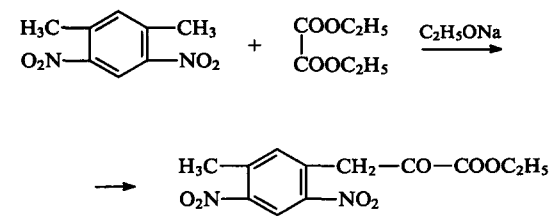
However, these reactions are only of historical significance: they are restricted because only aryl- or arylalkyl-substituted derivatives can be obtained and the yields of the cyclisation products are low.

The German investigator Ruggli and his students[7,8] used a different method for the synthesis of pyrroloindoles, which is based on a modified Reissert reaction.



The condensation of 2,4-dichloro-1,5-dinitrobenzene with the enolates of certain ketoacid esters takes place stepwise; the substitution of the second chlorine atom is difficult. The reductive cyclisation of the diketones **6** and **7** in the presence of 'Ni Rupe' (a mixture of the crude catalyst with clay powder) under a hydrogen atmosphere leads to the pyrroloindoles **8** and **9**. Ketonic cleavage of compounds **6** and **7** and subsequent reduction afford the pyrroloindoles **10** and **11**. It is noteworthy that the target products were obtained in low yields owing to the considerable losses of these compounds during isolation and purification.

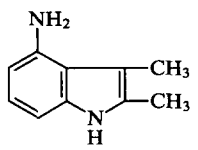
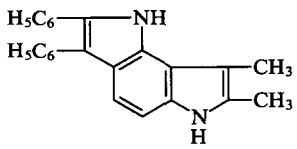
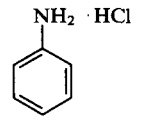
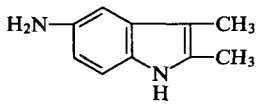
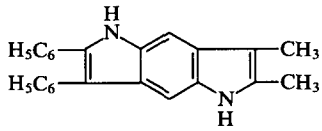
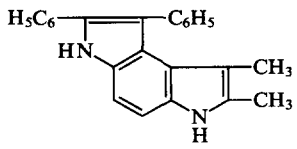
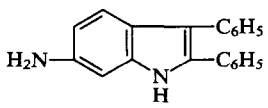
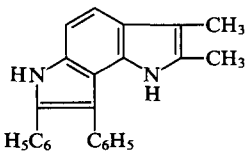
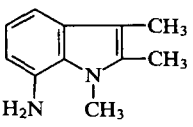
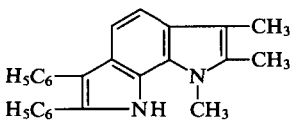
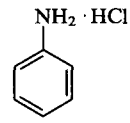
A disadvantage of the synthesis of pyrroloindoles by the Reissert reaction is also the fact that it cannot be used to obtain the unsubstituted pyrroloindole with a linear structure, since it has been established that in the condensation of diethyl oxalate with 4,6-dinitro-*m*-xylene only one methyl group reacts.

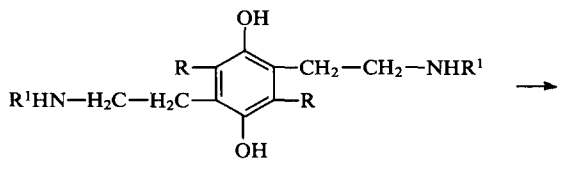


In 1973, Baird, Baxter, and coworkers[9] discovered a new method of synthesis of pyrroloindoles. It was found that the dihydrobromide of 2,5-bis(β-aminoethyl)hydroquinone **12a** is converted spontaneously into the dihydropyrroloindole **13a** in aqueous solution in air. The synthesis of compound **13a** was not the authors' aim, but they nevertheless investigated this process and put forward an hypothesis concerning the reaction mechanism. They also dehydrogenate compound **13a** to give the fully aromatised pyrroloindole **3**.

It was established subsequently[9] that the hydroquinones **12b** and **12c** undergo bicyclisation under similar conditions, forming respectively the dihydropyrroloindoles **13b** and **13c**. Compound **13c** was dehydrogenated to compound **14c**.

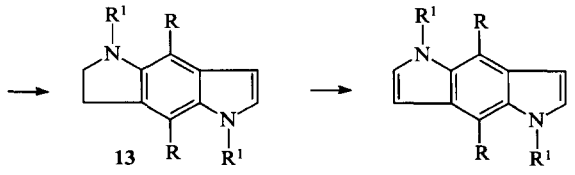
Table 1. Pyrroloindoles obtained from the products of the condensation of aminoindoles with benzoin.[6]

Initial aminoindole	Pyrroloindole	Cyclising agent	Yield (%)
			4
		HCl, H_2SO_4	6
		HCl, H_2SO_4	3
		HCl	7
			8



12a–c

R = R^1 = H (**a**);
R = Br, R^1 = H (**b**);
R = H, R^1 = CH_3 (**c**).

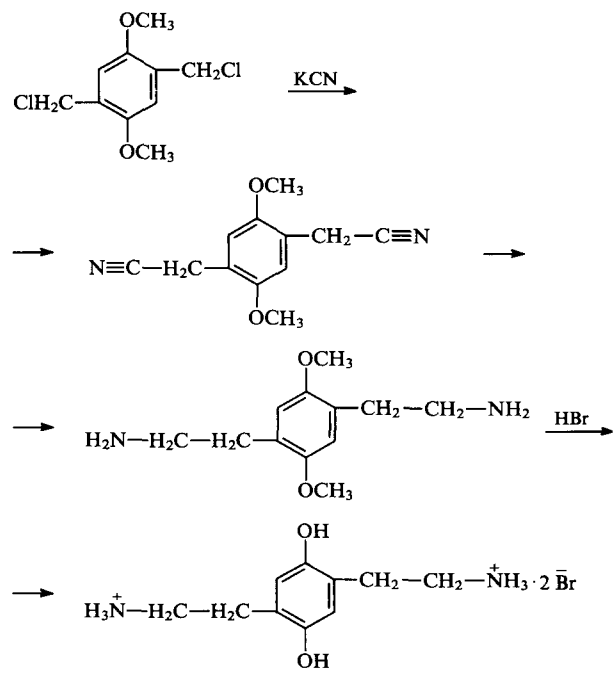


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R = R^1 = H (**a**);
R = Br, R^1 = H (**b**);
R = H; R^1 = CH_3 (**c**).

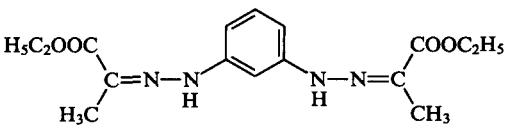
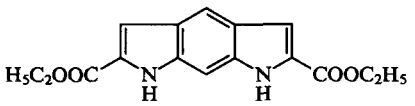
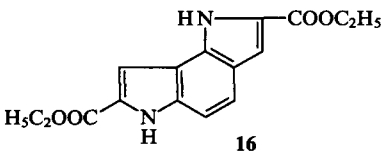
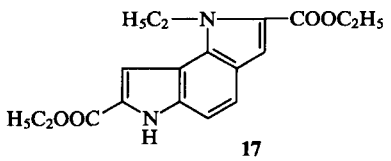
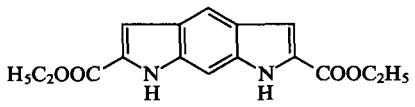
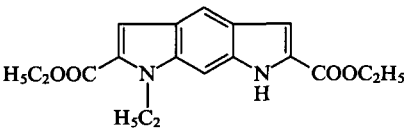
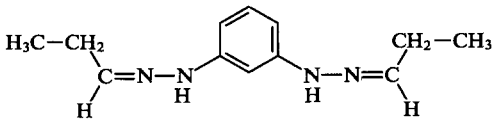
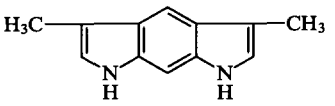
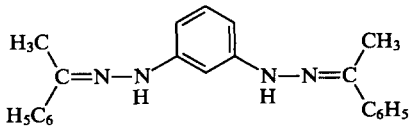
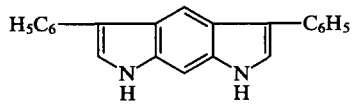
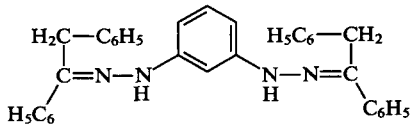
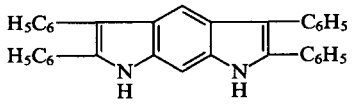
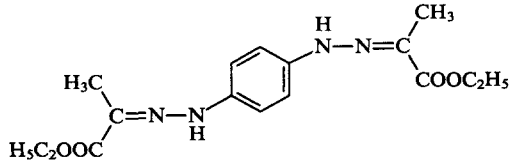
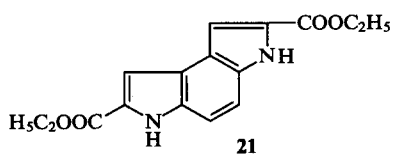
3: R = R^1 = H;

14c: R = H, R^1 = CH_3.



The initial hydroquinone **12a** was synthesised from 1,4-di(chloromethyl)-2,5-dimethoxybenzene.

Table 2. Pyrroloindoles obtained by cyclising certain *m*- and *p*-phenylhydrazones.

Hydrazone	Pyrroloindole	Cyclising agent	Yield (%)	Ref.
 **15**		12% H_2SO_4/C_2H_5OH	—	10
	 **16**	—	65	11–13
	 **17**	—	1	11–13
	 **18**	—	8	11–13
	 **19**	—	1	11–13
		5% H_2SO_4/C_2H_5OH	—	10
		12% H_2SO_4/C_2H_5OH	3	14
		H_2SO_4/ C_2H_5OH	50	14
 **20**	 **21**	EEPPA	6–9	15

Compound **12b** was obtained by brominating the hydroquinone **12a** and compound **12c** was synthesised by methylating it.[9]

However, in view of the low availability and instability of the initial compound and the large number of stages, this method cannot be regarded as preparative for the synthesis and further study of unsubstituted pyrroloindoles.[3]

The Fischer reaction has also been used in the synthesis of pyrroloindoles. The pyrroloindoles obtained by the cyclisation of certain *m*- and *p*-phenylenedihydrazones by the Fischer reaction are presented in Table 2.

It was found subsequently[11] that the first syntheses[10,14] suffered from significant disadvantages: the optimum reaction conditions were not selected (certain dihydrazones did not react even on prolonged refluxing, which indicated the low effectiveness of the catalyst employed); the cyclisation process was accompanied by appreciable charring and the reaction products were difficult to purify; the yield of the reaction products was very low. Furthermore, the cyclisation products were not characterised either by further reactions or by spectroscopic methods and a linear structure was attributed to them without proof. For example, when the cyclisation reaction of the dihydrazone **15** was reproduced under the conditions described by Giuliano and Leonardi[10] and the reaction product was investigated spectroscopically, it was found that it had an angular structure.[11]

For these reasons, there was a need for a detailed investigation of the Fischer reaction of phenylenedihydrazones, since this reaction was and remains the most convenient method of synthesis of indole and its analogues.

Studies were carried out on the cyclisation of ethyl pyruvates and *p*-phenylenedihydrazones and the optimum reaction conditions were selected.[11-13,15]

In the bicyclisation of *m*-phenylenedihydrazones, the formation of pyrroloindoles of two types, differing in the condensation of the rings, is theoretically possible. The cyclisation described above gives a mixture of the pyrroloindoles **16** and **18** having angular and linear structures, the angular isomer **16** predominating (yield 65%).[12,13] This can be explained by the fact that the angular structure is energetically more favourable than the linear structure in the formation of polynuclear condensed aromatic systems.[16] The *N*-ethyl derivatives **17** and **19** were also isolated from the cyclisation products in yields less than 1%.[13]

The conversion of various stereoisomers of the *m*-phenylenedihydrazone of ethyl pyruvate into indole derivatives takes place in virtually identical yields.

It is noteworthy that the development of convenient methods of synthesis of 2,7-diethoxycarbonyl-1*H*,6*H*-pyrrolo[2,3-*e*]indole **16** in high yields is a very important task, since this compound opens the way to the subsequent synthesis of the unsubstituted heterocycle.

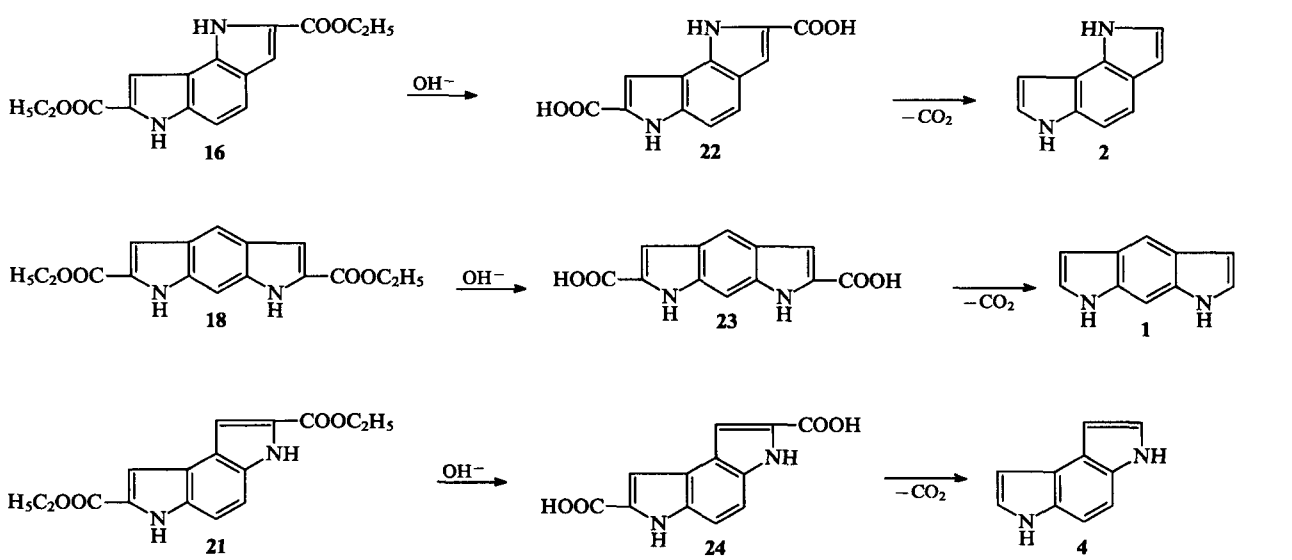
The ethyl ester of polyphosphoric acid (EEPPA) proved to be the most effective cyclising agent for the conversion of the *p*-phenylenehydrazone of ethyl pyruvate **20** into an indole derivative. However, in this case the yield of 2,7-diethoxycarbonyl-3*H*,6*H*-pyrrolo[3,2-*e*]indole **21** was only 6%–9%. In the remaining cases, charring of the reaction mass was observed.[15] The low yield of products in the cyclisation reaction can probably be explained by the fact that a crude dihydrazone **20** was employed, its purification involving considerable difficulties.[15]

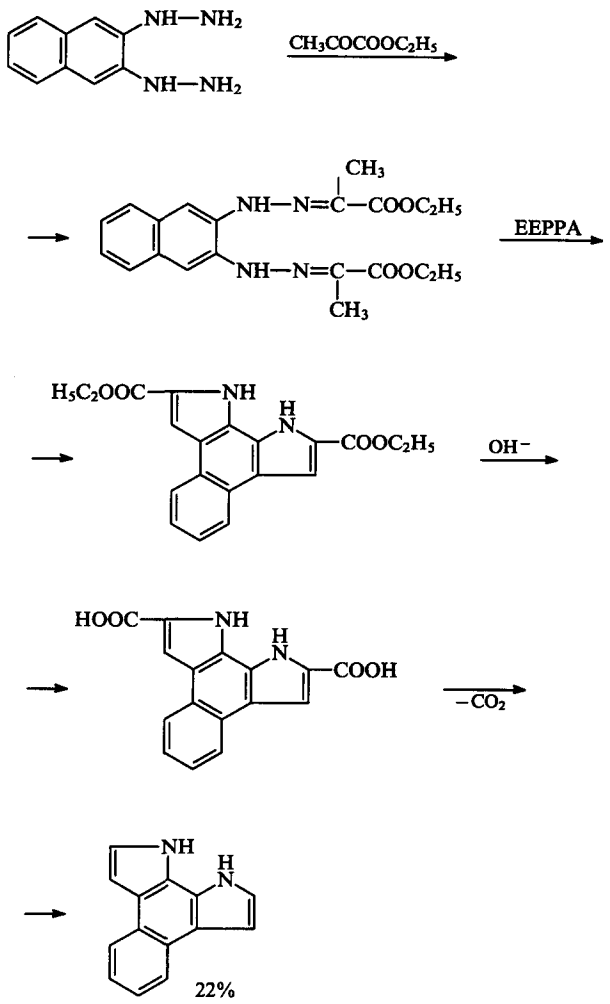
The hydrolysis of the diesters **16**, **18**, and **21** afforded high yields of the corresponding dicarboxylic acids **22–24** (Scheme 2).[11,12,15]

However, the methods for the bisdecarboxylation of dicarboxylic acids described in the literature (heating in quinoline or in dimethylacetamide in the presence of powdered copper[17] or copper salts[18]) proved unsuitable. The desired results were achieved only on thermal decarboxylation of the dicarboxylic acids **22–24** in a stream of an inert gas. The unsubstituted pyrroloindoles **1**, **2**, and **4** corresponding to compounds **22–24** were then obtained in 20%, 30%, and 25% yields respectively.[11,12,15]

The cyclisation of 2,3-naphthylenedihydrazone to 2,9-diethoxycarbonyl-1*H*,10*H*-benzo[*e*]pyrrolo[3,2-*g*]indole was achieved in 1984. Hydrolysis and subsequent decarboxylation of the dicarboxylic acid afforded the unsubstituted 1*H*,10*H*-benzo[*e*]-pyrrolo[3,2-*g*]indole.[19] The yields of the products were high in all the stages of the synthesis except the last.

Scheme 2



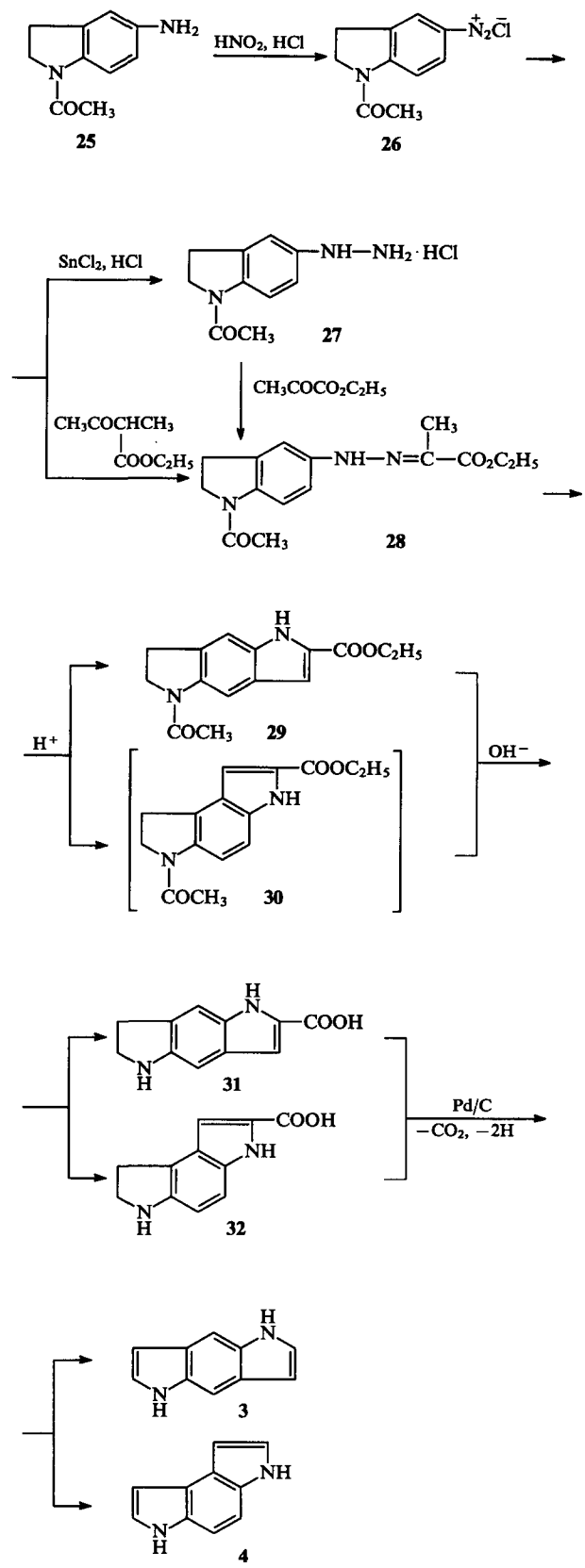


Thus it is seen that the unsubstituted pyrroloindoles **1**–**4** may be obtained with the aid of the Fischer reaction and the reaction of Baird and Baxter. However, these methods enable only 1*H*,6*H*-pyrrolo-[2,3-*e*]indole **2** to be synthesised in an amount sufficient for further study. The remaining three heterocycles **1**, **3**, and **4** are obtained in very low overall yields. Furthermore, the synthesis of the pyrroloindole **3** is complicated by the low availability and instability of the initial compound.

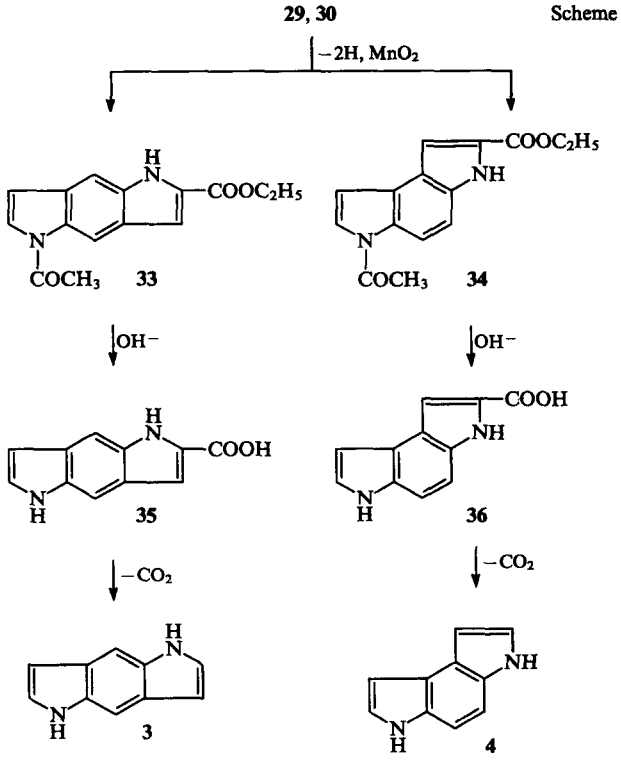
Continuing the search for convenient methods of synthesis of pyrroloindoles, Samsoniya, Suvorov, Kadzhrishvili, and coworkers[20] used a new procedure for the construction of the pyrroloindole system — the addition of the pyrrole ring to the benzene ring of the indoline system. The initial compounds chosen were 5- and 6-aminoindolines. The first of these was synthesised from indoline by the method of Terent'ev and Preobrazhenskaya[21] in acetic anhydride using nitric acid as the nitrating agent (yield 70%), while the second was obtained by nitration with a mixture of nitric and sulfuric acids (quantitative yield). The nitroindolines were acetylated with acetic anhydride and were reduced with hydrazine hydrate in the presence of Raney nickel (yield 95%) by the general method recommended for aromatic nitro-compounds.

The syntheses of 1*H*,5*H*-pyrrolo[2,3-*e*]indole **3**, 3*H*,6*H*-pyrrolo[2,3-*e*]indole **4**, and 1*H*,6*H*-pyrrolo[2,3-*e*]indole **2** are presented in Schemes 3–5.[20]

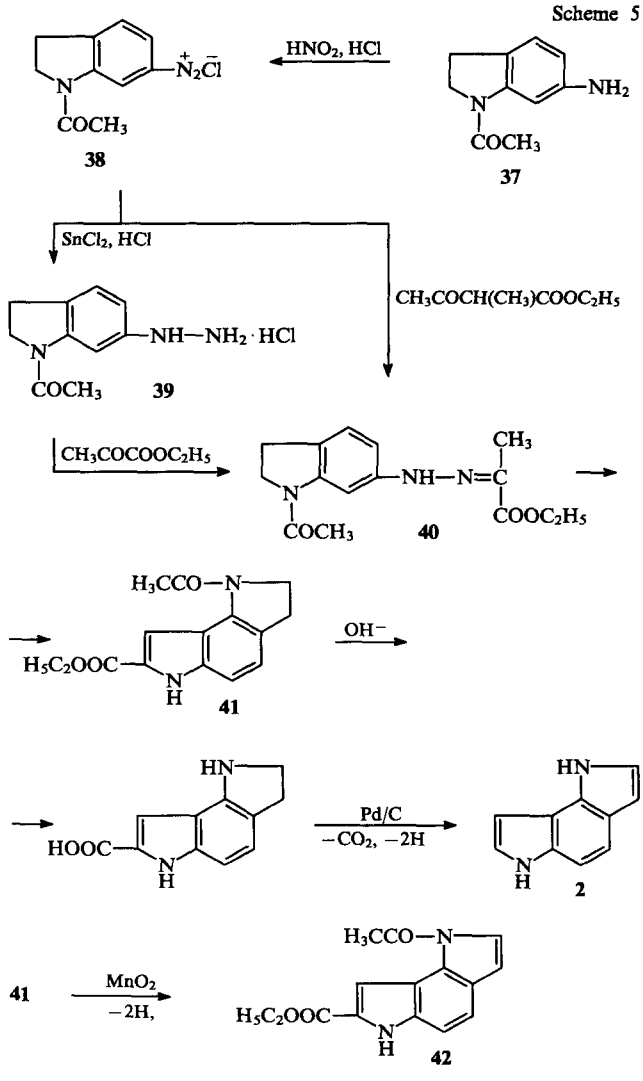
Scheme 3



Scheme 4



Scheme 5



Different compounds were tried as cyclising agents in the conversion of the hydrazones **28** (Scheme 3) and **40** (Scheme 5) into indole derivatives. The best results were obtained when EEPPA was used.

The cyclisation of the hydrazone **28** results in the formation of a mixture of pyrroloindolines having linear (compound **29**) and angular (compound **30**) structures (yield 74%). The main reaction product is the linear isomer. The attempts to separate the mixture of the isomers **29** and **30** were unsuccessful, but compound **29** can be isolated and characterised by means of column chromatography.

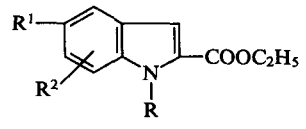
Hydrolysis of the mixture of esters **29** and **30** with aqueous alkali is very rapid and leads to a mixture of the acids **31** and **32** in 93% yield. The decarboxylation and simultaneous dehydrogenation of the acids in the presence of 10% Pd/C afforded a mixture of the isomeric pyrroloindoles **3** and **4** (yield 20%). The latter were separated by column chromatography.

The dehydrogenation of a mixture of the isomeric esters **29** and **30** by manganese dioxide in boiling xylene was also achieved (Scheme 4); compounds **33** and **34** were obtained in 75% yield. Separation of this mixture by column chromatography affords the angular ester **34** and the linear ester **33** in proportions of 1 : 6.

Hydrolysis of the esters **33** and **34** with aqueous alkali leads to high yields of the corresponding acids **35** and **36**, the thermal decarboxylation of which afforded the unsubstituted pyrroloindoles **3** and **4** in 20% and 26% yields respectively.[20]

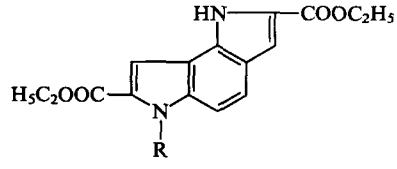
The unsubstituted pyrroloindole **2** was obtained similarly from the hydrazone **40** (Scheme 5) after the corresponding transformations. The dehydrogenation of the ester **41** gives the pyrroloindole **42**. The yields of the products of these reactions are approximately the same as in the previous syntheses.

Later (in 1983) Katti and Siddappa[22] achieved the synthesis of various pyrroloindole systems from *o*-, *m*-, and *p*-nitroanilines by the stepwise closure of one and then the other pyrrole rings using the familiar Fischer scheme. The 4-, 5-, 6-, and 7-nitroindoles obtained in this way are reduced with Raney nickel, diazotised under mild conditions, and coupled with methylacetoacetic ester. The diesters of the isomeric pyrroloindoles are obtained by cyclising the corresponding hydrazones. The overall yields of the pyrroloindoles are low. The subsequent reactions of the heterocycles were not described by the authors.



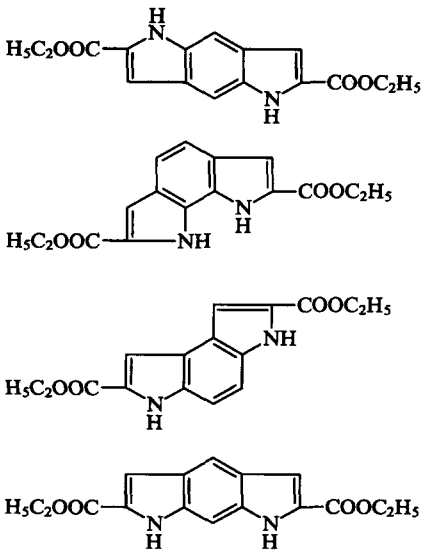
R = H, CH_3; R^1 = H, CH_3;

R^2 = NO_2, NH_2, —NH—N=C(CH3)COOC2H5.

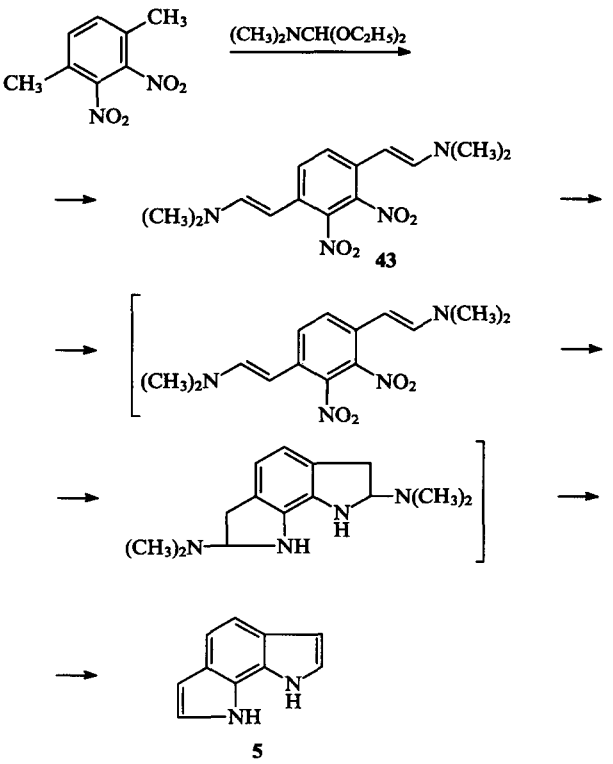


R = H, CH_3.

(continued over)



A convenient method of synthesis of certain pyrroloindoles has been proposed by Berlin et al.[23]



The synthesis was carried out by the Leimgruber – Batcho reaction and involved the following processes: the condensation of dinitro-*p*-xylene with the diethyl acetal of dimethylformamide and subsequent reductive cyclisation of the dinitroenamine **43**, obtained in the condensation reaction (yield 75%), to the unsubstituted pyrroloindole **5** (yield 70%).

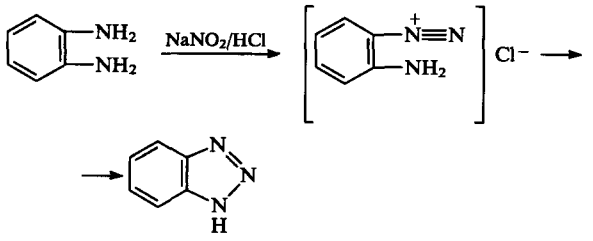
The linear pyrroloindole **1** was obtained similarly from 4,6-dinitro-*m*-xylene (yield 55%), while the isomer **3** was synthesised from 2,5-dinitro-*p*-xylene (yield 39%).

Only pyrroloindoles unsubstituted in the pyrrole rings can be obtained by this method, which limits its applications.

1. Synthesis of the initial hydrazones

The initial compounds for the Fischer reaction (arylhydrazones) are obtained by condensing arylhydrazines with the corresponding carbonyl compounds; the Japp – Klingemann reaction is sometimes used for this purpose. In both cases, it is necessary to have sufficiently pure aryldiazo-compounds.

The synthesis of benzene-1,2-bisdiazonium salts by the usual diazotisation of phenylenediamines is known to involve appreciable complications. Thus the diazotisation of *o*-phenylenediamine results in the initial formation of the *o*-aminobenzenediazonium salt, which is converted into a cyclic azimine (benzotriazole).



The diazotisation of *p*-phenylenediamine is accompanied by appreciable oxidation to quinone or quinone imine, while *m*-phenylenediamine readily couples during the diazotisation process with the mono- and bis-diazonium ions formed, affording the corresponding azo-dyes.[24-26]

Special diazotisation methods are used in the synthesis of the benzene-1,2-diazonium salt. Thus comparatively pure benzene-1,2-diazonium and benzene-1,4-diazonium chlorides are synthesised by diazotising the corresponding diamines with nitrosylsulfuric acid in the presence of concentrated phosphoric acid.[26,27] Since the synthesis of pure benzene-1,4-diazonium involves considerable difficulties, a two-stage process is employed as a rule in the synthesis of dyes — diazotisation and coupling of the amino-groups of *p*-phenylenediamine.[24]

In the diazotisation of *m*-phenylenediamine, the excess HCl and the brief contact between the reactants suppress the coupling reaction indicated above. The yield of benzene-1,3-diazonium chloride then increases.[24,28] The same result was achieved by introducing polyhydric alcohols or carbohydrates into the reaction.[29]

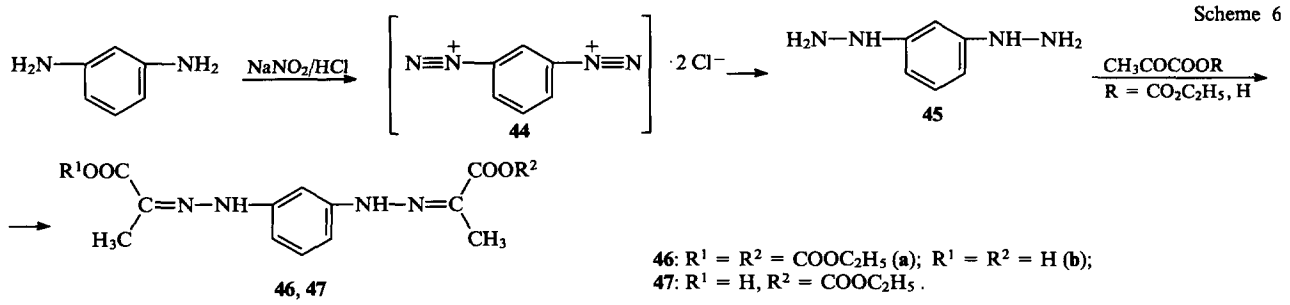
Thus only the *meta*-isomer is obtained in a high yield from all the isomeric benzenebisdiazonium chlorides, which makes it convenient to use it in the synthesis of phenylenedihydrazones.

The reduction of benzene-1,3-bisdiazonium **44** with tin dichloride in an excess of HCl leads to the corresponding dihydrazine **45**. However, the product is highly contaminated by tin salts, which creates difficulties for subsequent reactions. The purification of dihydrazine **45** is also difficult. It is carried out by passing gaseous H_2S through an aqueous solution of the compound.[10] However, the present authors were able to solve this problem by simple recrystallisation of compound **45** from water.[11] The *m*-phenylenedihydrazine purified in this way is entirely suitable for further reactions (Scheme 6).

The condensation of *m*-phenylenedihydrazine **45** with ethyl pyruvate in a weakly acid medium leads to a high yield of the *m*-phenylenedihydrazone of ethyl pyruvate **46a**. The mixed hydrazone **47**, containing both ester and acid groups, is formed as a side product of this reaction. It is apparently obtained as a result of the hydrolysis of the ethoxycarbonyl group of the initial ethyl pyruvate or of the dihydrazone **46b** formed.

p-Phenylenedihydrazine, which is suitable for the synthesis of *p*-phenylenedihydrazone, cannot be obtained in a pure form. It contains an appreciable amount of *p*-phenylenediamine.[15] Owing to the difficulty of separating this mixture and also the instability of *p*-phenylenedihydrazine, the latter could not be identified either in the form of a base or in the form of the dihydrochloride.

Scheme 6



46, 47

46: $R^1 = R^2 = COOC_2H_5$ (a); $R^1 = R^2 = H$ (b);
47: $R^1 = H$, $R^2 = COOC_2H_5$.

The m-phenylenedihydrazone of ethyl pyruvate is formed as a mixture of geometrical isomers having the *syn,syn-*, *syn,anti-*, and *anti,anti*-configurations. These isomers were separated by column chromatography and their structures were established from spectroscopic data. [11]

The usual diazotisation of 1-acetyl-5-aminoindoline **25** and 1-acetyl-6-aminoindoline **37** and the subsequent reduction of the diazonium salts **26** and **38** by tin(II) chloride lead to the hydrochlorides of 1-acetyl-5-hydrazinoindoline **27** and 1-acetyl-6-hydrazinoindoline **39**. The hydrazones **28** and **40** have been obtained in high yields by condensing the hydrazines **27** and **39** with ethyl pyruvate. [20]

The coupling of the diazonium salts **26** and **38** with methylacetoacetic ester via the Japp–Klingemann reaction also affords the hydrazones **28** and **40**.

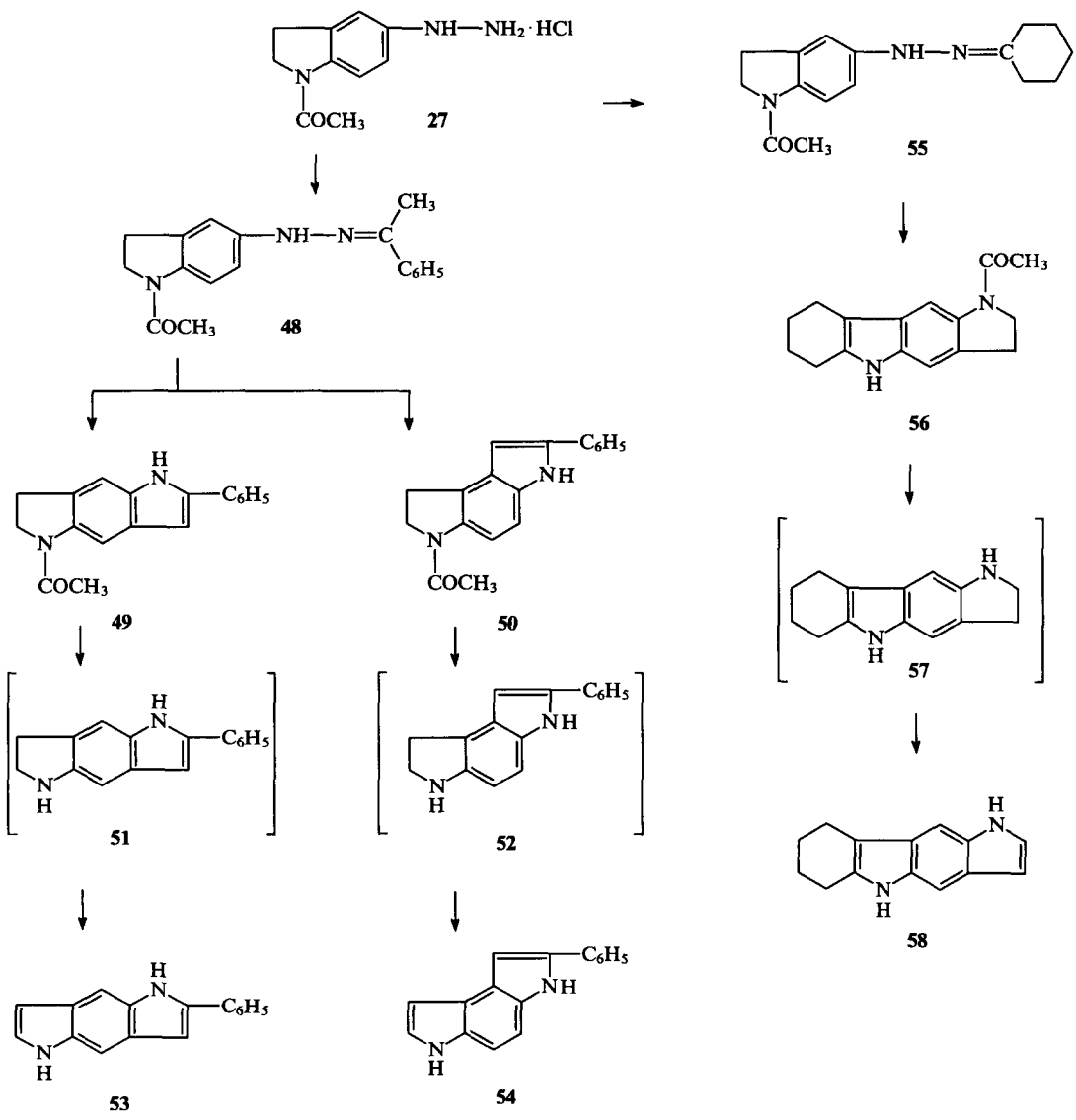
2. Synthesis of substituted pyrroloindoles from acetophenone and cyclohexanone

Apart from the cyclisation of the hydrazones of ethyl pyruvate, the conversion of the hydrazones of acetophenone and cyclohexanone into indole derivatives (Schemes 7 and 8) has been used to obtain pyrroloindole structures. [30]

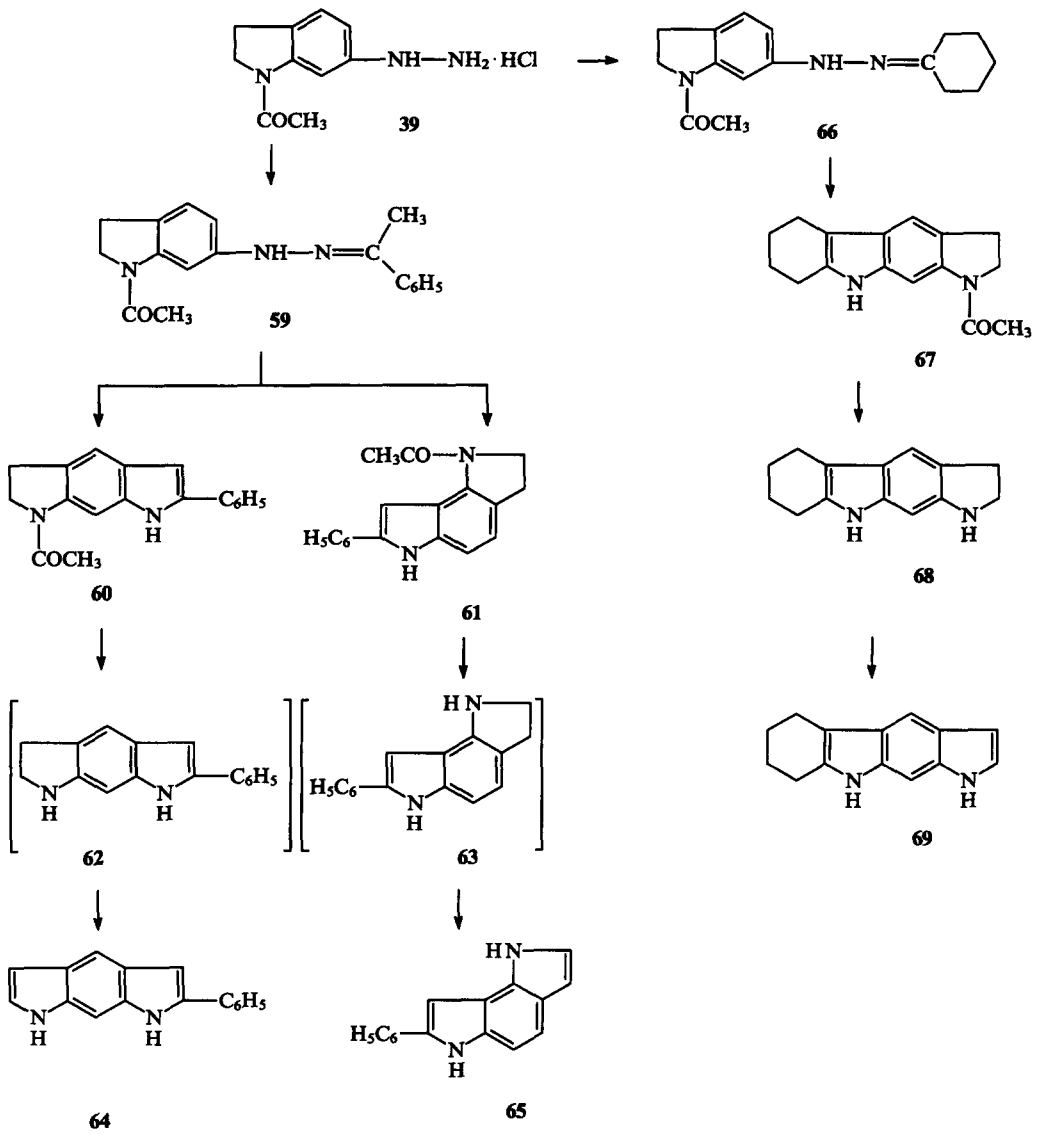
Condensation of compounds **27** and **39** with acetophenone and cyclohexanone yielded the corresponding hydrazones **48**, **55**, **59**, and **66**.

When the hydrazones were converted into indole derivatives, the best results were achieved using EEPPA as the cyclising agent.

Scheme 7



Scheme 8



It was established from spectroscopic data on the cyclisation products that conversion of the acetophenone hydrazones **48** and **59** into indole derivatives gives a mixture of the linear pyrroloindolines **49** and **50** and the angular pyrroloindolines **60** and **61**, while the conversion of the cyclohexanone hydrazones **55** and **66** into indole derivatives afforded only the linear isomers (compounds **56** and **67**). This has been explained by steric factors.[30] Hydrolysis of the pyrroloindolines **49**, **50**, **55**, **60**, **61**, and **66** leads to compounds **51**, **52**, **57**, **62**, **63**, and **68** and their subsequent dehydrogenation gives rise to the pyrroloindoles **53**, **54**, **58**, **64**, **65**, and **69** respectively.

III. Electrophilic substitution reactions of pyrroloindoles

The preparative methods described above have enabled the pyrroloindoles **1**–**4** to be obtained in amounts sufficient for various electrophilic substitution reactions to be studied in this series of compounds. The classical electrophilic substitution reactions characteristic of indoles were investigated: the Mannich, Vilsmeier, azo-coupling, and acetylation reactions.[13,31–34]

The effect of different types of condensation of the pyrrole and indole rings on the specific features of electrophilic substitution was of definite interest. Furthermore, the study of the above reactions was also of practical importance, since some of the pyrroloindole derivatives themselves possess physiological activity or can be used in the syntheses of other physiologically active substances.

The distribution of electron densities in the substrate is known to determine the mode of attack by electrophiles in electrophilic substitution reactions, although the site of preferential substitution depends greatly also on other factors promoting the stabilisation of the corresponding transition state.

In order to predict the most preferable directions of electrophilic attack in pyrroloindole molecules, quantum-chemical calculations were performed for compounds **1**–**4** in accordance with Maslov's program[36] on a BESM-6 computer by the SCF-MO method in the CNDO/2 approximation (Fig. 1).[37]

It is seen from the molecular diagrams that the highest overall ($\sigma + \pi$)- and π-electron densities are observed for atoms in the β-positions in the pyrrole rings. It was postulated that initial attack by electrophiles should take place at these sites. In the molecules of the pyrroloindoles **1**–**4**, there are also other reaction centres having fairly high electron densities. Nor can one rule out also the influence of other factors, especially steric factors, on the site of the initial electrophilic attack in these electrophilic molecules.

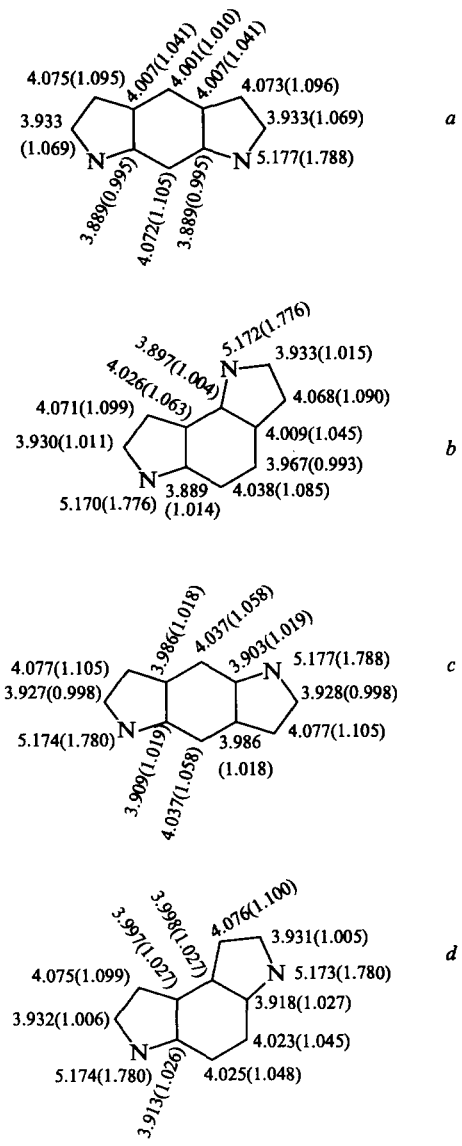


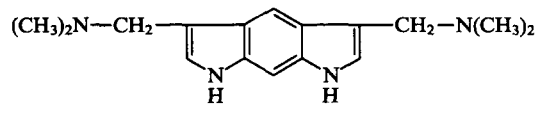
Figure 1. Molecular diagrams for the pyrroloindoles **1**–**4** (*a*–*d*); the overall ($\sigma + \pi$) charges are presented; the (σ^{**}-π)-electron densities are indicated in brackets.

1. The Mannich reaction

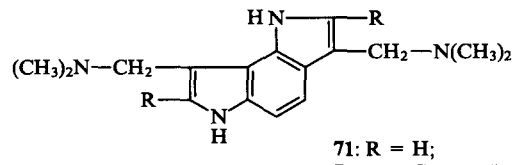
The great importance of the Mannich reaction for compounds of the indole series arises from the possibility of using the products of this reaction in the synthesis of a wide variety of biologically important compounds (tryptophan, heteroauxin, the series of tryptamines, etc.).

Among the indole Mannich bases, the alkaloid gramine (3-dimethylaminomethylindole) and its substituted derivatives have found the most extensive applications. The study of the Mannich reaction for the pyrroloindoles **1**–**4** is therefore of interest both from the standpoint of the possibility of obtaining bifunctional gramine analogues and for the investigation of their biological activity.

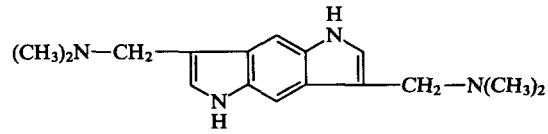
The aminomethylation of the unsubstituted pyrroloindoles **1**–**4** by freshly prepared Mannich bases (dimethylamine, formaldehyde, acetic acid) affords, apart from the bisgramine analogues **70**, **71**, **73**, and **74**, also compounds which are insoluble in the majority of organic solvents, which greatly reduces the yield of the target product.[31–33]



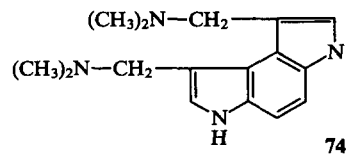
70



71: R = H;
72: R = $COOC_2H_5$.



73



74

The formation of side products can probably be accounted for by the interaction of the heterocycles with formaldehyde, similarly to the situation which obtains in the condensation of indole and its derivatives with formaldehyde in an acid medium with formation of bis(3-indolyl)methanes.[38,39]

This undesirable process is hindered in the case of 2,7-di-(ethoxycarbonyl)-1*H*,6*H*-pyrrolo[2,3-*e*]indole, apparently owing to the presence of the electron-accepting α-ethoxycarbonyl groups and their steric influence. The bisgramine **72** is formed in a high yield.

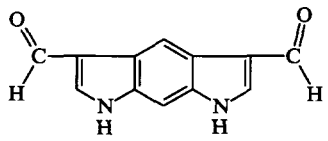
In the syntheses of the unsubstituted bisgramines **70**, **71**, **73**, and **74**, the desired result was achieved using as the electrophile *N*,*N*-dimethylmethyleneammonium chloride [$CH_2=N^+(CH_3)_2 . Cl^-$], synthesised from $[(CH_3)_2N]_2CH_2$ and CH_3COCl.[40] Best results were obtained when acetonitrile was used as the solvent. In this case, side products are not formed and the bisgramines **70**, **71**, **73**, and **74** were isolated in high yields.[31–33]

In order to investigate their physiological activity, the bifunctional gramine analogues synthesised were converted into the corresponding dihydrochlorides.[1]

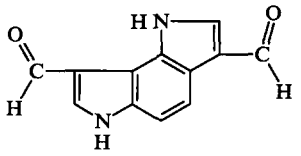
The blocking effect of the bisgramines on neuromuscular transmission was investigated by quaternising the tertiary nitrogen atoms in their molecules, which was achieved by converting them into the corresponding dimethosulfates.[1,2] The synthesis of the dimethosulfates is accompanied by formation of polyadducts as a result of interaction of the quaternary salts with the gramines. In order to suppress side reactions, the process is carried out in an acid medium. In the synthesis of the dimetho-sulfates of the diaminomethyl derivatives of the pyrroloindoles containing ethoxycarbonyl groups in the α-positions in the pyrrole rings, the formation of side products was not observed even in the absence of acetic acid, owing to the presence of electron-accepting groups.

2. The Vilsmeier reaction

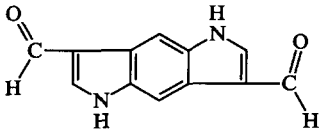
The formylation of the pyrroloindoles **1**–**4** by the dimethylformamide–$POCl_3$ complex proceeds readily at room temperature. When the reaction is carried out in the presence of a threefold excess of the Vilsmeier reagent, the hydrogen atoms in the β-positions in the pyrrole rings are substituted, as expected, and the dialdehydes **75**–**78** are formed in high yields.[31–33,41]



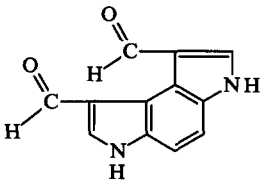
75



76

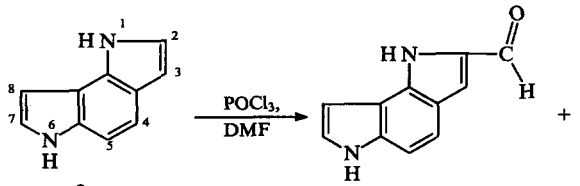


77



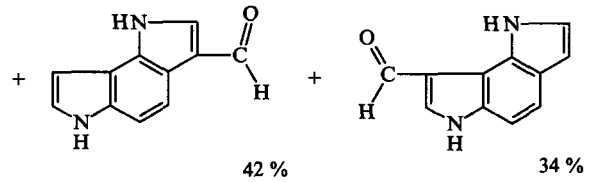
78

In the pyrroloindole **2**, the reactivities of the β-positions in the two different pyrrole rings are not the same. It follows from the model of the molecule of this compound that substitution in the 8-position is difficult owing to shielding by the neighbouring pyrrole ring. It was interesting to elucidate how these factors influence the electrophilic substitution reaction for an equimolar reactant ratio. It was established that three monosubstituted products are formed: 2-, 3-, and 8-formylpyrroloindoles.[42]



2

5 %



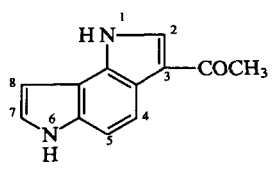
42 % 34 %

The ethoxycarbonyl groups in the α-positions in the pyrrole rings of the pyrroloindole **2** lower its reactivity, as expected. In this case, only the 3-substituted product is formed (yield 41%) and even then a fivefold excess of the Vilsmeier complex is required.[42]

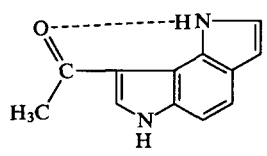
The formylation of 2,6-diethoxycarbonyl-1*H*,7*H*-pyrrolo-[3,2-*f*]indole under these conditions proceeds anomalously. Mainly the hydrogen atoms of the benzene ring are substituted (Scheme 9).[43]

In order to compare the reactivities of the β-positions of 1*H*,6*H*-pyrrolo[2,3-*e*]indole in the Vilsmeier reaction, a more selective electrophile was employed—a complex based on dimethylacetamide and $POCl_3$. This complex is known to react only with highly nucleophilic substrates. Certain indole-containing polynuclear heterocycles altogether fail to react with it,[44] while indole itself does react, affording 3-acetylindole in only 22% yield.[45]

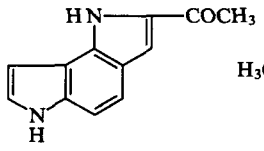
The pyrroloindole **2** has been acylated under the same conditions as those employed in the acetylation of indole. Four reaction products were isolated.[34] The main one is 3-acetyl-pyrroloindole **79**, which is formed at room temperature immediately after mixing the initial compounds. On heating the reaction mixture, the 8- and 2-acetyl-substituted derivatives **80** and **81** were also obtained and after some time 3,8-diacetyl-pyrroloindole **82** was produced. The overall yield of products is ~40%.



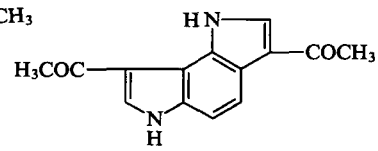
79



80

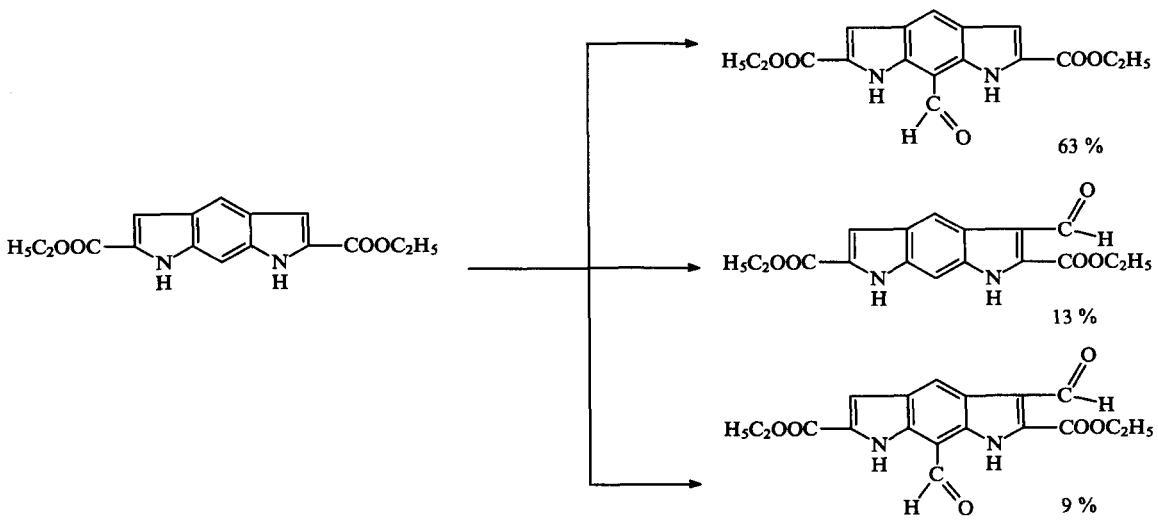


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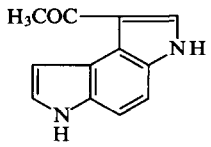


82

Scheme 9



As regards the remaining isomeric pyrroloindoles (compounds **1**, **3**, and **4**), the Vilsmeier reaction could be carried out only for compound **4**. 1-Acetyl-3*H*,6*H*-pyrrolo-[2,3-*e*]indole **83** is formed in 60% yield. In the remaining cases (compounds **1** and **3**), the reaction takes place with charring.[41]



83

Thus the acetylation of pyrroloindoles by the Vilsmeier complex showed that the angular structures are more stable than the linear isomers.

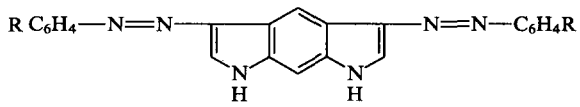
The reduced electrophilicity of the complex based on *N*,*N*-dimethylacetamide and $POCl_3$ compared with the dimethylformamide–$POCl_3$ complex makes it necessary to carry out the reaction at elevated temperatures, which leads to charring of the products of the reaction of linear pyrroloindoles.

3. The azo-coupling reaction

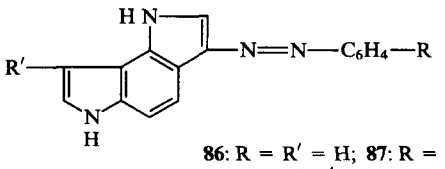
Arenediazonium salts are typical weak electrophiles. They are sensitive to small differences in the reactivities of substrates.

Benzenediazonium and *p*-chloro- and *p*-nitro-benzenediazonium chlorides have been used as the diazo-components in the azo-coupling of pyrroloindoles. Complex mixtures are formed in all cases, from which it has been possible to isolate by preparative column chromatography one product (probably the main one) in each case.

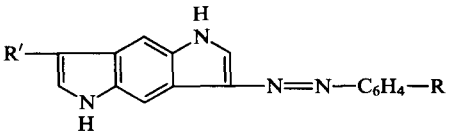
The azopyrroloindoles **83**–**93** are relatively unstable compounds which readily decompose during purification on a chromatographic column and on recrystallisation, which greatly hinders their isolation.



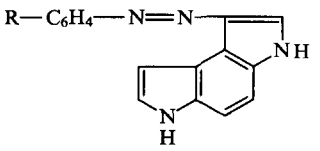
83: R = H; **84**: R = Cl; **85**: R = NO_2.



86: R = R′ = H; **87**: R = Cl, R′ = H;
88: R = Cl, R′ = N=N–C_6H_4–Cl.



89: R = NO_2, R′ = H;
90: R = H, R′ = N=N–C_6H_5;
91: R = Cl, R′ = N=N–C_6H_4–Cl.



92: R = Cl;
93: R = NO_2.

In the azo-coupling of the linear compounds **1**–**3**, mainly the formation of disubstituted products is observed.[32,33]

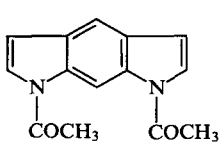
After the azo-coupling of the angular pyrroloindoles **2** and **4**, mainly monosubstituted products were isolated. In this case, the neighbouring pyrrole ring probably exerts a steric influence.[31,32]

4. The acetylation reaction

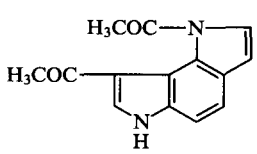
The acetylation of the pyrroloindoles **1**–**4** has been carried out without using the typical Friedel–Crafts catalysts: because these heterocycles are acidophobic, the use of strong catalysts induces the charring of the reaction mixture and lowers the yield of products.

The acetylation of the pyrroloindoles **1**–**4** under the conditions proposed for indole itself[46] leads to the formation of a mixture of the *N*- and *C*,*N*-acetylated derivatives **94**–**102**. The low yield of the reaction products (not more than 40%) can be explained by the partial charring of the reaction mixture.[31–33]

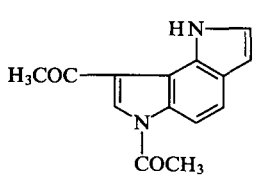
Thus electrophilic substitution reactions in the pyrroloindoles **1**–**4** take place mainly in the β-positions in the pyrrole rings, which agrees with the results of quantum-chemical calculations. In the Vilsmeier acetylation of the pyrroloindole **2**, the formation of 2-substituted products, for which there is no analogous reaction involving indole, is due to the increased excess of π electrons and hence the increased reactivity of the pyrroloindole compared with indole.



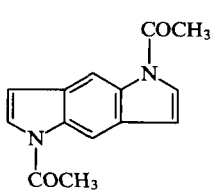
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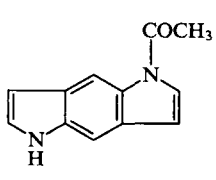
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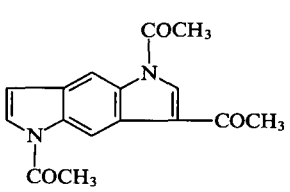
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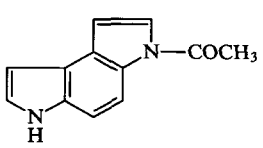
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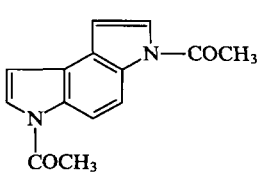
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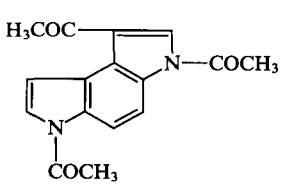
99



100



101



102

It has been established that the β-positions of both pyrrole rings in linear pyrroloindoles are equally reactive, which cannot be said of the angular isomers. In the interaction of the latter with weaker electrophiles (the azo-coupling reaction and the Vilsmeier acetylation), mainly monosubstituted products are formed, probably as a consequence of steric factors and of the reduced reactivity of the system due to the introduction of an electron-accepting substituent.

IV. Side chain reactions of derivatives of 1*H*,6*H*-pyrrolo[2,3-*e*]indole

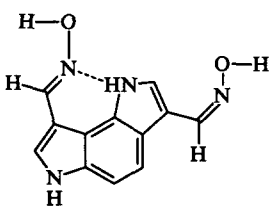
1. The condensation reactions of 3,8-diformyl- and 3-formyl-1*H*,6*H*-pyrrolo[2,3-*e*]indole

Among nucleophilic addition–elimination reactions, the condensation reactions with nitromethane, nitroethane, acetone, malonic and barbituric acids, aniline, and thiosemicarbazide have been investigated (for 3,8-diformyl-1*H*,6*H*-pyrroloindole) (Scheme 10).[47–49]

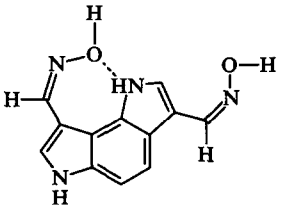
Under the conditions described,[47,48] the dialdehyde **76** reacts with CH acids mainly via one formyl group. The monocondensation products **103, 105**, and **107–110** are formed in high yields. The reduced reactivity of the formyl group in the 8-position can apparently be accounted for by the presence of an intramolecular hydrogen bond and also by steric factors.

In order to develop a convenient method of synthesis of the dinitrovinylpyrroloindoles **104** and **106**, various catalysts were employed (ammonium acetate, liquid ammonia, 50% NaOH solution, pyridine, $KHSO_4$). The desired result was achieved only when dimethylformamide was used as the solvent, in which the dialdehyde **76** is readily soluble.

The disubstituted products **111** and **112** are obtained when the dialdehyde **76** is condensed with hydroxylamine and thiosemicarbazide in a weakly acid medium. The dioxime **111** was formed as a mixture of geometrical isomers which were separated by column chromatography. It has been established by ^1H NMR spectroscopy that these isomers have the *anti,syn*-configuration (compound **111a**) and the *syn,syn*-configuration (compound **111b**) and the cisoid-transoid conformation of the side chains.[49]

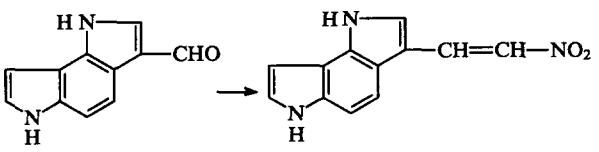


111a

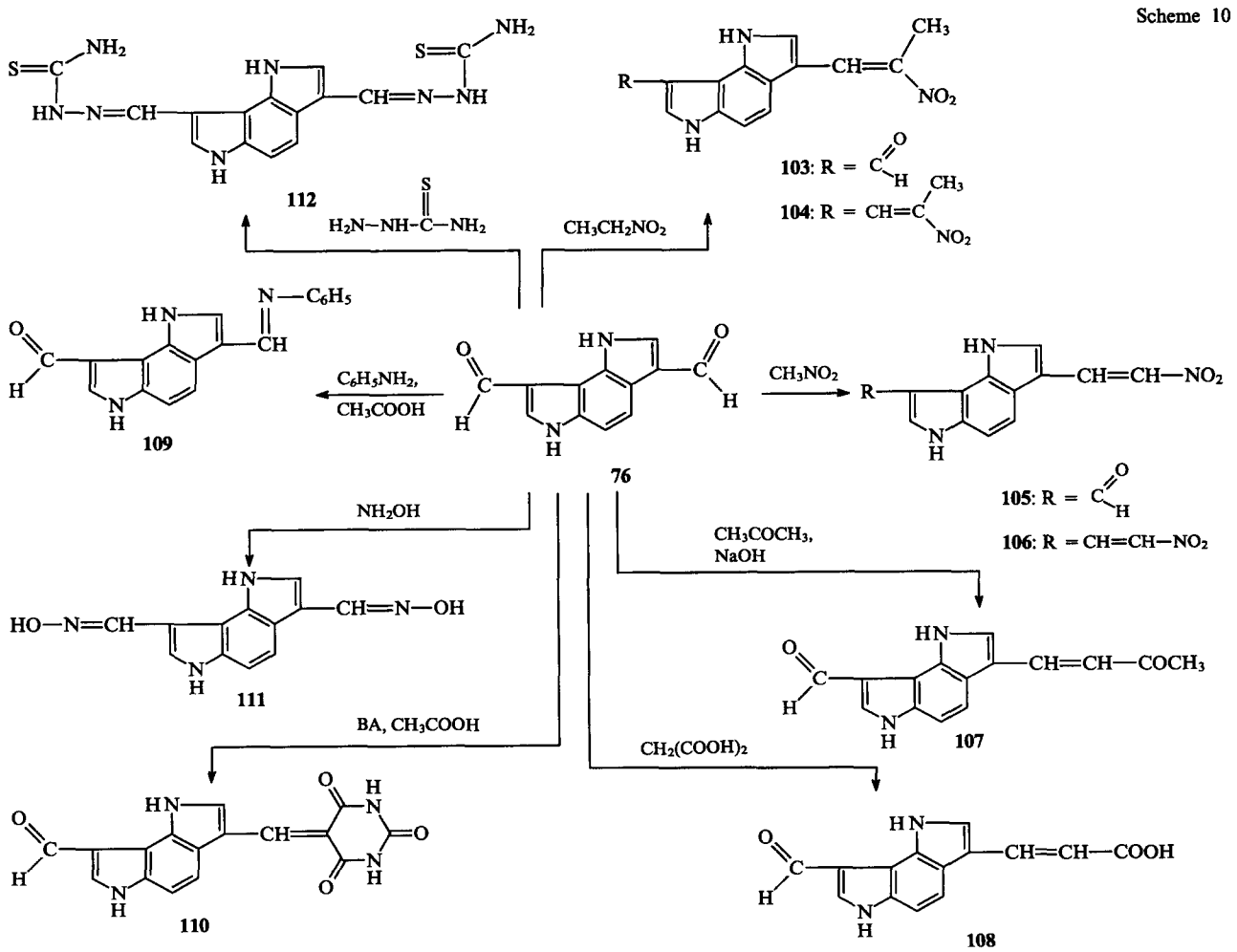


111b

In the reaction of the monosubstituted 3-formyl-1*H*,6*H*-pyrrolo[2,3-*e*]indole with nitromethane in the presence of ammonium acetate, 3-nitrovinyl-1*H*,6*H*-pyrrolo[2,3-*e*]indole is formed in a high yield.



Scheme 10



BA = barbituric acid.

2. Certain syntheses based on 3,8-bis(dimethylaminomethyl)-1*H*,6*H*-pyrrolo[2,3-*e*]indole and its diethoxycarbonyl derivative

3-Indolylacetonitrile (a natural product), is an effective stimulator of plant growth.[50] It has been used successfully in the syntheses of certain physiologically active indole derivatives.

3-Indolylacetonitrile can be conveniently obtained from quaternary salts of gramine and alkali metal cyanides. The use of a quaternised amino-group instead of a free amino-group facilitates the reaction and increases the yield of the target product.[51]

The bisgramines **71** and **72** were converted into the corresponding quaternary salts **113** and **114**. The subsequent reaction of these salts with KCN at 40 °C leads to the corresponding dinitriles **115** and **116**.[52] In the case of the salt **114**, the monosubstituted product **117** is also formed in a low yield. Its yield increases appreciably at high temperatures, accounted for, probably, by the increase in the rate of hydrolysis of KCN.[52]

Further studies showed that the dinitrile **116** can be more conveniently synthesised without the preliminary isolation of the quaternary salt, by adding solutions of KCN and CH_3I to the reaction mixture containing the Mannich base **72**. The application of this method in the synthesis of the dinitrile **115** did not yield positive results.[52]

The tetracarboxylic acid **118** is formed readily in the alkaline hydrolysis of the dinitrile **116**. Its structure was established by spectroscopic methods and by specific synthesis from the corresponding tetraester **119**.

The skatole analogue **120** has been synthesised by decarboxylating the acid **118**; acid alcoholysis of the dinitrile **116** in 33% alcoholic HCl afforded the tetraester **119** (Scheme 11).[52]

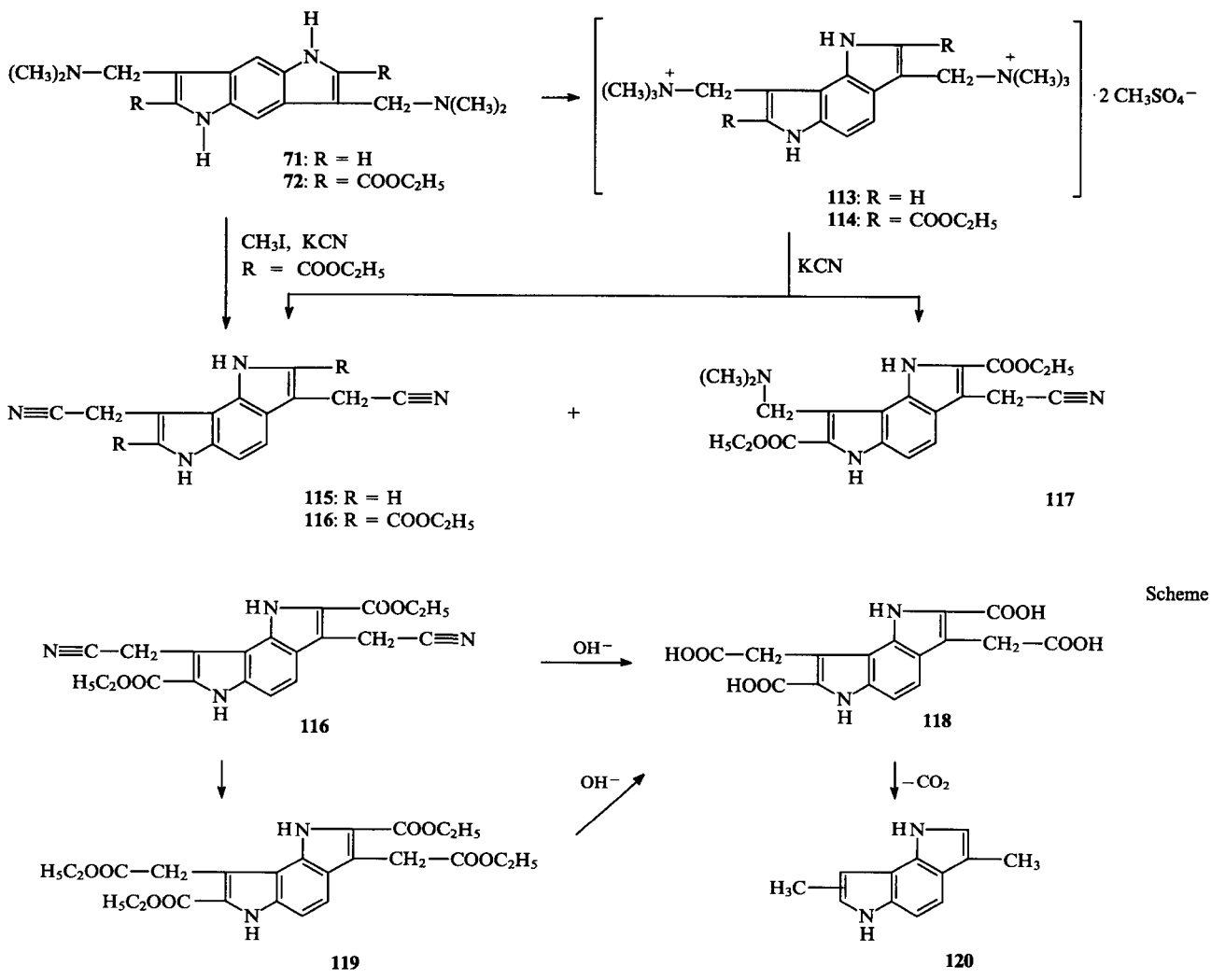
3. Synthesis of a tryptamine analogue from 1*H*,6*H*-pyrrolo[2,3-*e*]indole

It has been shown[48] that the bistryptamine **121** cannot be obtained by the direct reaction of the corresponding Grignard reagent, 1*H*,6*H*-pyrrolo[2,3-*e*]indolebismagnesium halide, and ethyleneimine.[48]

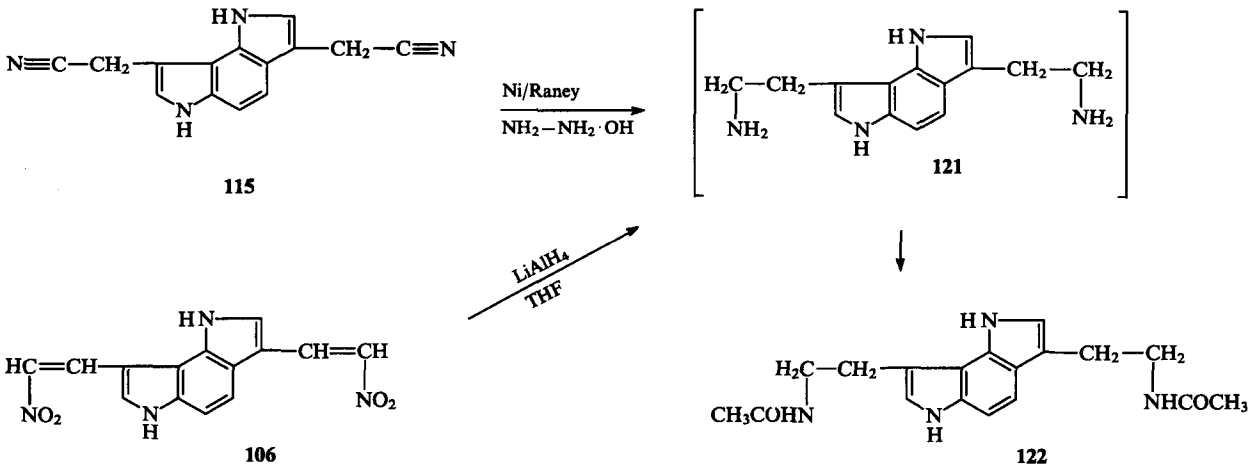
The bistryptamine **121** has been obtained in a high yield by reducing 3,8-di(cyanomethyl)-1*H*,6*H*-pyrrolo[2,3-*e*]indole **115** and 3,8-di(nitrovinyl)-1*H*,6*H*-pyrrolo[2,3-*e*]indole **106**. The product was purified by conversion into the diacetyl derivative **122** and was characterised in this form.[48]

In order to obtain the *N*-unsubstituted tryptamine in a pure form, 8-formyl-3-nitrovinyl-1*H*,6*H*-pyrrolo[2,3-*e*]indole **105** was used as the starting compound. However, the reaction took a completely different route. It was found that the reduction of compound **105** with diimide (hydrazine hydrate and Raney nickel) and subsequent acetylation of the product afford only the 3-*N*-acetylhydrazone of 3,8-diformyl-1*H*,6*H*-pyrrolo[2,3-*e*]indole **123**[48] (see over).

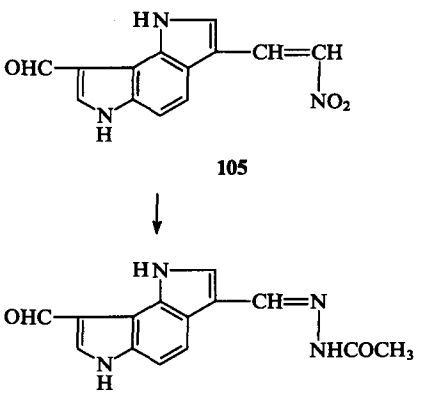
The reduction of the pyrroloindole **105** with lithium tetrahydroaluminate and subsequent acetylation lead to the formation of a gel-like mass, the components of which are difficult to isolate and identify. This is apparently associated with the formation, after the reduction of the aldehyde group, of an analogue of the unstable 3-indolylmethanol,[53] which is capable of both dimerising and of conversion into an oligomer in an acid medium or on standing.[48]



Scheme 11



115 121 106 122



105 123

4. Some syntheses based on 1*H*,10*H*-benzo[*e*]pyrrolo-[3,2-*g*]indole

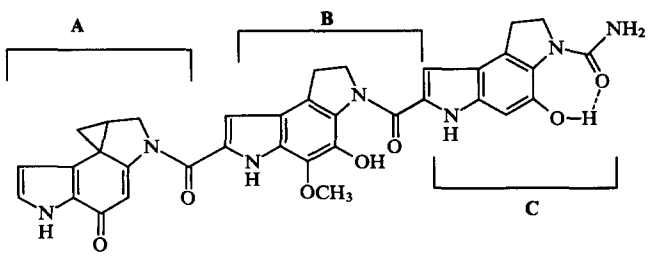
As expected, 1*H*,10*H*-benzo[*e*]pyrrolo[3,2-*g*]indole forms products disubstituted in the β-positions of the pyrrole rings in the Vilsmeier and Mannich reactions. In reactions with weaker electrophiles (azo-coupling reactions), only monosubstituted products are formed.[54]

Certain reactions of 2,9-di(carbohydrazido)-1*H*,10*H*-benzo-[*e*]pyrrolo[3,2-*g*]indole **124** have been described (Scheme 12).[55]

The reactions of the acid dichloride of 2,9-dicarboxy-1*H*,10*H*-benzo[*e*]pyrrolo[3,2-*g*]indole **125** merit attention. It has been obtained in a quantitative yield by refluxing the corresponding dicarboxylic acid with thionyl chloride. The condensation of the acid dichloride **125** with amines and phenols leads to various diamides and diesters.[56] In addition, high-molecular-mass compounds containing benzopyrroloindole fragments have been obtained from the pyrroloindole **125**.[57]

5. The antibiotic CC-1065 and its analogues

In the Introduction, we noted that the molecule of the powerful antitumour antibiotic CC-1065 contains the pyrrolo-indoline fragments **B** and **C**.[4]



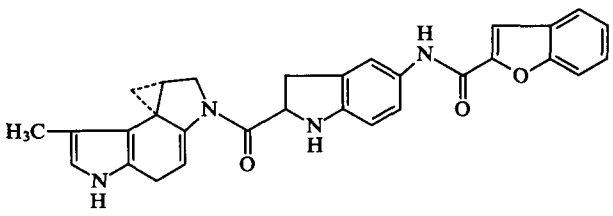
It was shown that this compound is bound covalently via the cyclopropane ring to the *N*(3)-position of adenine in a specific nucleotide sequence and is located within the limits of the small groove of DNA, suppressing selectively its synthesis. On the other hand, the antibiotic is not an intercalator; the cytotoxicity of the compound CC-1065 is approximately 400 times higher than that of adriamycin, which has been used successfully in the treatment of oncological diseases.[4] Unfortunately the antibiotic CC-1065 is also highly toxic, which precludes its clinical application.[58]

The data of Rawal et al.[4] initiated studies, directed towards the synthesis of the individual components (**A**, **B**, and **C**) of compound CC-1065. These investigations have been described in detail in the above review by the American investigators Rawal et al.[4]

A classical strategy was used in the synthesis of the pyrroloindole fragments **B** and **C** of the compound CC-1065. Indoline was obtained from substituted benzene and then the corresponding pyrroloindoline was obtained by the Fischer method or the pyrrole rings were attached stepwise to the benzene ring and the resulting pyrroloindole was hydrogenated to the corresponding pyrroloindoline.

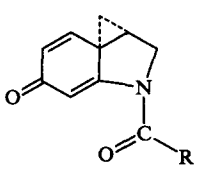
These skillfully performed complex syntheses include 14 stages each and the yields of the target products are < 7%.

An enormous amount of work was carried out on the synthesis of analogues of the antibiotic CC-1065. The benzofuran analogue I-73975 is promising.

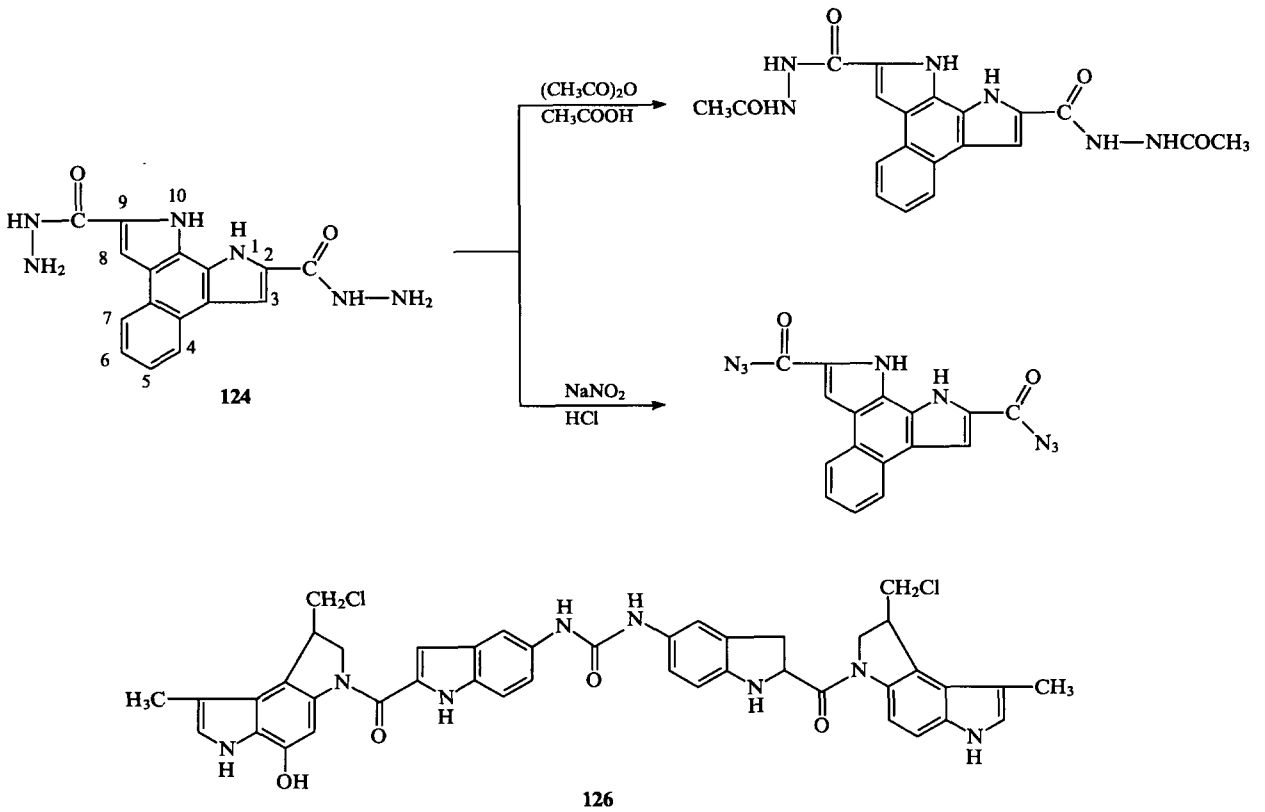


This compound is also a monoalkylating agent containing a cyclopropane ring in its structure. A highly active dialkylating agent, having the structure **126**, has also been synthesised.[59] However, it is not altogether clear whether the mechanism of its action is identical with that of the natural antibiotic.[59]

It was later observed,[60] that a whole class of antibiotics exist—duocarmycins—which are structurally and chemotherapeutically similar to CC-1065. They are all characterised by a common pharmacophore.[60]



Scheme 12



It is evident from the data presented that pyrroloindoles are extremely promising as regards the search for new antitumour preparations and merit further study.

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