162. Y. Kitahara and M. Funamizu, Jap. P. 11 122 (1962); Chem. Abs,, 59, 100 126 (1963).

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SYNTHESIS OF SUBSTITUTED INDOLES VIA INDOLINES

M. N. Preobrazhenskaya

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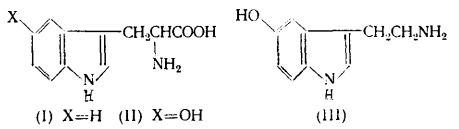
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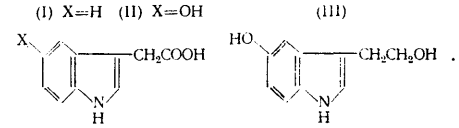
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I. INTRODUCTION

Indole derivatives play an important role in vital processes [1,2]. Of special importance are the essential amino-acid tryptophan (I) and the products of its metabolism, for example, 5-hydroxytryptophan (II), serotonin (III), 3-indolylacetic (IV) and 5-hydroxy-3-indolylacetic (V) acids, 5-hydroxytryptophol (VI) and a number of other substances:

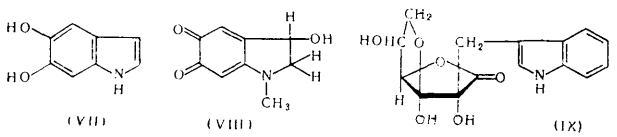


(I) X=H (II) X=OH (III)



(IV) X=H (V) X=OH (VI)

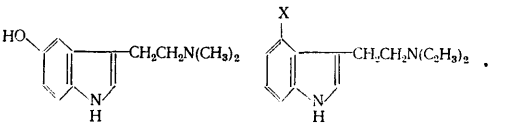
The structure of 5,6-dihydroxyindole (VII) is the basis of the animal pigment melanin [3]. The processes involved in the biosynthesis of melanin are closely related to the metabolism of aminocatechols, including adrenalin and tyrosine. One of the products of adrenalin metabolism is adrenochrome (VIII) [4]. It has been shown recently [5] that ascorbic acid in plants exists in a bound form as two diastereoisomeric ascorbigens A and B (IX):



(VII) (VIII) (IX)

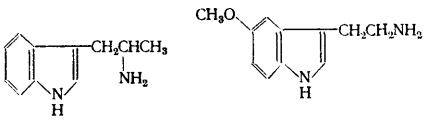
ascorbigen B

Many compounds containing the indole ring exhibit high pharmacological activity. It is sufficient to recall reserpine and other Rauwolfia alkaloids, lysergic acid, brucine, yohimbine, eserine, and other alkaloids, and also halucinogenic compounds such as bufotenin (X) (a component of frog venom), psilocin (XI), psilocybin (XII), and others [1].



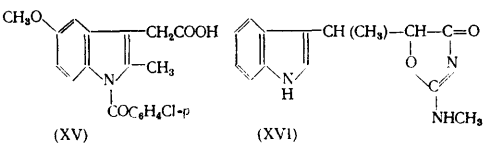
(X) (XI) X=OH (XII) X=OPO_3H_2

The synthetic research on pharmacologically active compounds in the indole series has proved extremely fruitful. In particular, valuable medicinal substances have been found—indopane [6] (3-indolylisopropylamine) (XIII), used as a stimulating antidepressant in psychiatry and mexamine (5-methoxytryptamine) (XIV) [7], used in the prophylaxis of radiation damage:



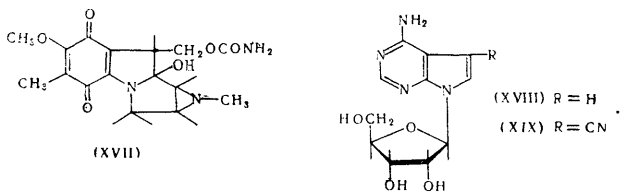
(XIII) (XIV)

Considerable interest was aroused by the discovery of indole derivatives with high anti-inflammatory activity, among which the most important is indomethacin—1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (XV) [8]:



(XV) (XVI)

Until recently indole derivatives with high antimicrobial activity were unknown. However, the first communication dealing with the antibiotic indolmycin (XVI), which inhibits the development of strains of *Staphylococcus aureus*, a micro-organism resistant to the most widely used antibiotics, appeared in 1961. [9,10] Vigorous studies are being made on the synthesis of the antibiotic mitomycin (XVII) and related compounds which exhibit high cytostatic, bacteriostatic, and fungicidal activity [11,12]:



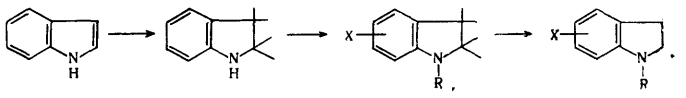
(XVII) (XVIII) R = H (XIX) R = CN

The reports of the discovery of a new group of antibiotics, tubercidin (XVIII) and toyokamycin (XIX) [13], are extremely interesting. These compounds are based on the 5,7-diazaindole (pyrimidinopyrrole) structure.

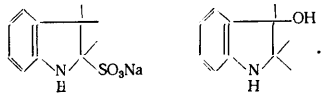
The structure of many indole compounds is based on tryptophan, indole-3-acetic acid, or tryptamine (3-indolylethylamine). In this connection methods of synthesising the side-chain in position 3 of the indole ring have been developed in special detail. The method of introducing substituents in position 1 have been investigated much less,

although many 1-substituted indoles are of great interest—for example, indomethacin (XV), tubercidin (XVIII), and others. The reason for the difficulty of introducing substituents in position 1 of the indole system is that the NH group exhibits acid rather than basic properties, as a result of which direct *N*-alkylation or *N*-acylation of indole frequently cannot be achieved. Mercury or silver salts (with one organic anion) of the type N–M, which are widely used for synthetic purposes, for example in the purine series, have not been described for indoles. Magnesium, sodium, and lithium derivatives of indole usually react with the formation of C_2 or C_3 derivatives. Serious difficulties are also encountered in attempts to introduce substituents into the benzene ring of the indole system. Under the conditions of an electrophilic substitution reaction, most indole derivatives decompose or react in different ways simultaneously. The classical methods of synthesis (the Fischer, Reissert, and other syntheses), in which the molecule is synthesised from components already containing definite substituents, frequently prove cumbersome or altogether inapplicable to indoles with substituents in the benzene ring.

A method based on temporary exclusion of the pyrrole ring has been proposed for the introduction of substituents into the indole ring[14–16]. Indole is converted into 2,3-dihydroindole (indoline), which is an aromatic amine and can be made to undergo various electrophilic reactions with formation of indoline derivatives substituted both in the benzene ring and at the nitrogen atom. Dehydrogenation of these derivatives yields the substituted indole. Thus instead of using unstable, readily decomposed, and difficult to isolate indole derivatives, the experiments are performed with indolines, which are aliphatic-aromatic amines:



Instead of dihydroindole, one can use in this reaction also the unstable adduct of indole and sodium bisulphite, the sodium salt of indoline-2-sulphonic acid (XX), which also exhibits the properties of an aromatic amine[17]. Conversion into indole derivatives is achieved by treatment with alkali:



(XX) (XXI)

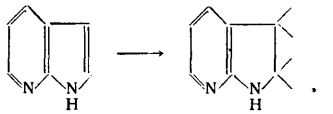
In many cases indolines cannot be obtained from the corresponding indole derivatives and they are synthesised in other ways. This applies, for example, to 2,3-dihydro-3-hydroxyindole, 3-indolinol (XXI), which is readily substituted and forms indole derivatives on dehydration[18]. In this connection, intensive studies have been made in recent years on the methods of synthesis of various indoline derivatives from hydroxyindoles, isatins, and various aromatic compounds.

This review deals with the methods of synthesis of indolines, the substitution reactions in the indoline series, and methods of conversion into the corresponding substituted indoles.

II. METHODS OF PREPARATION OF INDOLINES†

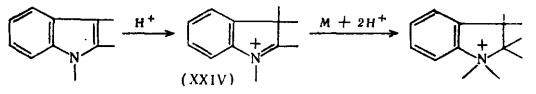
1. Preparation of Indolines by the Reduction of the Corresponding Indoles

The most convenient method for the preparation of indoline is hydrogenation of indole over Raney nickel at 80–100 atm and 75–150°C in an alcoholic or dioxan solution[19]. Further temperature rise leads to the formation of octahydroindole; in alcoholic solution the process is accompanied by *N*-alkylation[20,21]. The method is suitable for the preparation of substituted indolines[22,23]. A series of indolines were obtained by hydrogenation over copper chromite at 250–300 atm and 170–190°C.[24–26] The hydrogenation of indole derivatives over PtO_2 in an alcohol–HBF_4 mixture at 1 atm and room temperature has also been described[27]. The hydrogenation of pyridinopyrrole, 7-azaindole (XXII), to the 2,3-dihydro-derivative (XXIII) is carried out over a nickel catalyst at 200°C and 100 atm. An increase of temperature results in cleavage of the pyrrole ring[28,29]:



(XXII) (XXIII)

1-, 2-, or 3-alkylindoles can be reduced to the corresponding dihydro-derivatives under the action of zinc or tin in hydrochloric acid[30–35]. The ease of reduction of indoles to 2,3-dihydro-derivatives in an acid medium, associated with the formation of the indolenine structure (XXIV) as a result of the protonation of indoles in position 3, is striking[36,37].



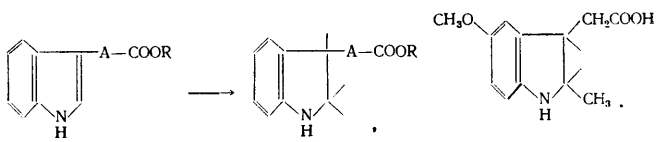
(XXIV)

However, in the reduction of unsubstituted indole in hydrochloric acid it is impossible to isolate indoline, because dimerisation and trimerisation products form under these conditions. In the reduction of indole with zinc in 85% phosphoric acid at 70–80°C in a stream of nitrogen it is possible to avoid the polymerisation of indole and to obtain indoline in 64–69% yield[38]. 2,3-Dimethylindole, 1,2,3,4-tetrahydrocarbazole, and its *N*-methyl derivatives have been synthesised under the same conditions. It has been shown that in the reduction of 2,3-dimethylindole with tin in hydrochloric acid the *cis*- and *trans*-isomers‡ are formed in proportions of 3 : 2,[25] and in the reduction with zinc in 85% phosphoric acid the proportions are 65 : 35.[38] In hydrogenation over copper chromite only the *trans*-isomer is formed[25]. In many cases it is possible to reduce the 1-substituted indoles to indolines under the action of lithium aluminium hydride in tetrahydrofuran[40,41]. Electrochemical reduction of indole[42] and reduction of indole with diborane[43] have been described.

† The synthesis and properties of 2,2- or 3,3-disubstituted indolines, which cannot be converted into the corresponding indoles without the rupture of a C–C bond, will not be considered.

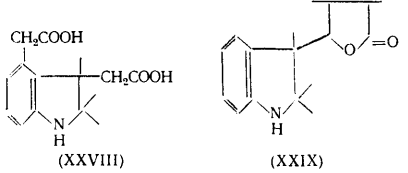
‡ Studies on the *cis-trans*-isomers of 2,3-dimethylindoline have been described by Anet and Muchowski[39].

It is of very great interest to carry out the conversion indole → indoline → substituted indoline → substituted indole using compounds containing the $CH_2CH_2NR_2$ or $(CH_2)_nCOOH$ residue in position 3 of the indole ring. Such conversions have been achieved for indole-3-alkanoic acids[44,45]. 2,3-Dihydroindole-3-propionic (XXVI, A = CH_2CH_2) acid was obtained by dehydrogenation of a salt of indole-3-propionic acid (XXV, A = CH_2CH_2) over Raney nickel at room temperature and 250 atm.[14] Esters of 2,3-dihydroindole-3-propionic [and -3-butyric? (Ed. of Translation)] acids (XXVI, A = CH_2CH_2 or CH_2CHCH_3) have also been obtained under these conditions[46]. The potassium salt of indole-3-acetic acid (XXV, A = CH_2) has been hydrogenated over Raney nickel at 100°C and 70 atm in order to obtain the dihydro-derivative[44]. 5-Methoxy-2-methylindole-3-acetic acid (XXVII), the starting material for the synthesis of indomethacin (XV), has been obtained under the same conditions[47]:



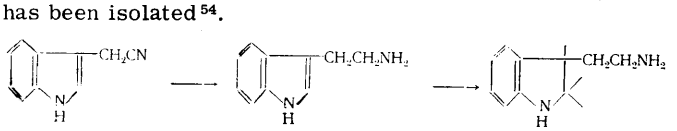
(XXV) (XXVI) (XXVII)

The disodium salt of indole-3,4-diacetic acid has been hydrogenated over Raney nickel at 80°C and 100 atm and the corresponding indoline diacid (XXVIII) has been obtained[48]:



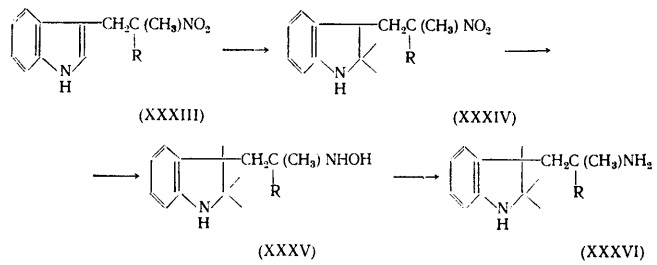
(XXVIII) (XXIX)

The conversion of esters of indole-3-alkanoic acids into the 2,3-dihydro-derivatives by hydrogenation over platinum oxide at the normal pressure and room temperature has been described[49,50]. The ester of 5-methoxy-2-methylindoline-3-acetic acid (XXVII) has been obtained under the action of tin in hydrochloric acid[51]. There is no information about the reduction of amino- and hydroxy-acids of the indole series, with the exception of the reduction of γ-(indol-3-yl)-γ-oxobutyric acid into indolinylbutyrolactone (XXIX)[52]. The data on 2,3-dihydro-5-hydroxytryptophan as well as the information on 2,3-dihydro-5-hydroxytryptamine (dihydroserotonin) appears to be unreliable[53]. The reduction of tryptamines to 2,3-dihydrotryptamines has been almost not investigated. Tryptamine (XXXI) forms in the hydrogenation of indole-3-acetonitrile (XXX) over Raney nickel at room temperature and 90 atm, an increase of temperature to 100°C resulting in partial conversion of tryptamine into dihydrotryptamine (XXXII), whose dipicrate has been isolated[54].



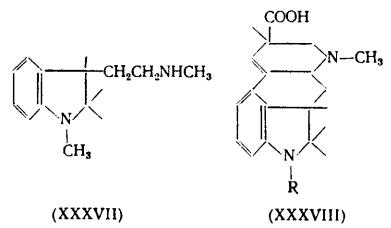
(XXX) (XXXI) (XXXII)

In the hydrogenation of 3-nitroisopropylindole (XXXIII, R = H) over PtO_2 in alcoholic hydrochloric acid it proved possible to obtain the dihydro-derivatives (XXXIV, R = H) and (XXXV, R = H) and on further hydrogenation 3-amino-isopropyl-2,3-dihydroindole (XXXVI, R = H)[55]:



(XXXIII) (XXXIV) (XXXV) (XXXVI)

3-Nitroisobutylindoline (XXXIV, R = CH_3) has been obtained similarly from 3-nitroisobutylindole (XXXIII, R = CH_3). Octahydroindole derivatives are formed together with these substances[55]. The pyrrole ring is reduced more readily than the nitro-group as a result of the easier reduction of the corresponding indolenine structure formed in an acid medium. The introduction of a methyl group into the pyrrole ring of the tryptamine molecule facilitates, as for indolealkanoic acids, the reduction of the double bond in the pyrrole ring. *NN'*-dimethyltryptamine can be converted into the dihydro-derivative (XXXVII) by zinc in hydrochloric acid[56]:

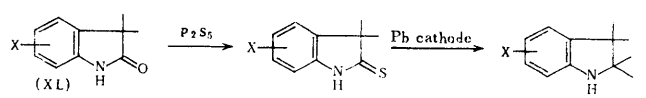


(XXXVII) (XXXVIII)

The conversion of lysergic acid derivatives into dihydrolysergic acid derivatives (XXXVIII) has been achieved similarly[57].

2. Syntheses of Indoline Derivatives Based on Isatins, Indoxyls, and Hydroxyindoles

The direct electrolytic reduction of isatin and hydroxyindole into indoline has been described[58]. It is more convenient to obtain indoline (XXXIX) from hydroxyindoles (XL) via mercaptoindoles (XLI)[59,60]:

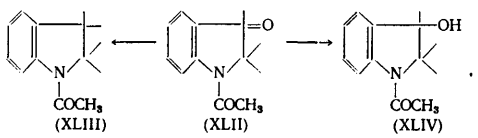


(XL)

where X = H, 4-CH_3O, and 6-CH_3O.

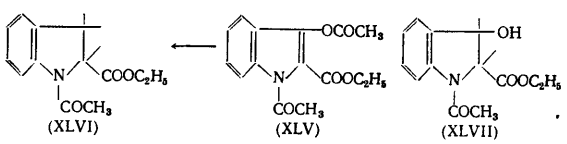
A mixture of indoles and indolines (with the indoles predominating) is usually formed in the reduction of *N*-substituted hydroxyindoles with lithium aluminium hydride[40,61-65]. The hydroxyindole unsubstituted at the nitrogen atom cannot be converted either into indole or indoline by the action of lithium aluminium hydride[40]. The formation of a certain amount of 1-alkylindolines in the reduction of 1-alkylhydroxyindoles with lithium aluminium hydride can probably be accounted for by further reduction of the 1-alkylindoles formed. The reduction of hydroxyindole derivatives with diborane leads to a mixture of the corresponding indoles and indolines[43], but this reaction does not appear to be of preparative value.

Depending on the reaction conditions, 1-acetylindoline (XLIII) or 1-acetyl-3-hydroxyindoline (XLIV) are formed in the catalytic reduction of 1-acetylindoxyl (XLII)[66,67]:



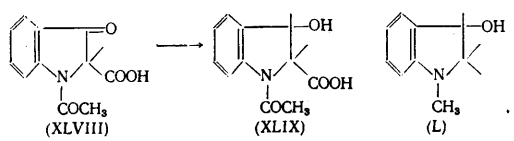
(XLIII) (XLII) (XLIV)

The hydrogenation of *ON*-diacetylindoxyl at 100 atm and 90°C over a nickel catalyst results in the formation of 1-acetylindoline in 90% yield, and from the reaction performed under milder conditions it is possible to isolate 1-acetyl-3-hydroxyindoline (10% yield). In the hydrogenation of 3-acetoxy-1-acetyl-2-ethoxycarbonyl indole (XLV) over Raney nickel at 85 atm and 110°C the product was an ester of 1-acetylindoline-2-carboxylic acid (XLVI) and at 60 atm and 60°C an ester of 1-acetyl-3-hydroxyindoline-2-carboxylic acid (XLVII)[68]:



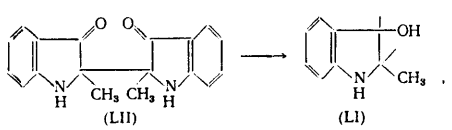
(XLVI) (XLV) (XLVII)

It proved possible to achieve the same reaction in the hydrogenation of an ester of 1-acetylindoxyl-2-carboxylic acid (XLVIII) over nickel chromite at room temperature and a lower pressure[68]:



(XLVIII) (XLIX) (L)

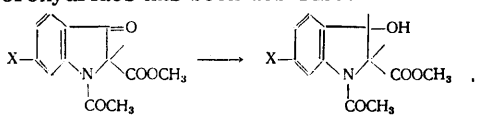
The most convenient method for the preparation of 3-hydroxyindoline is the reduction of isatin with lithium aluminium hydride (yields of 21%[70] and 14%[18]). 3-Hydroxy-1-methylindoline cannot be obtained by the reduction of 1-methylisatin. 3-Hydroxy-1-methylindoline (L) has been obtained by the methylation of 3-hydroxyindoline[71]. In the reduction of dihydroxyindole 3-hydroxyindoline is formed in 15% yield and in the reduction of indoxyl in 5% yield[72]. 3-Hydroxy-2-methylindoline (LI) has been obtained in good yield by the reduction of 2,2′-dimethyl-2,2′-di-indoxyl (LII) with $NaBH_4$ in methanol[73]:



(LII) (LI)

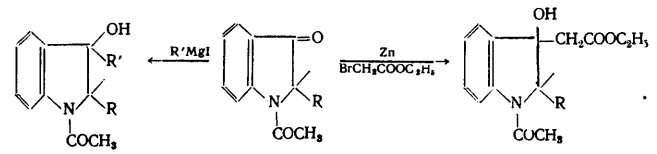
Analysis of the NMR spectrum showed that compound (LI) is a mixture of the *cis*- and *trans*-isomers in proportions of 1:4.[73]

Another example of the conversion of indoxyl derivatives (LIII) into 3-hydroxyindoline derivatives (LIV) with the aid of metal borohydrides has been described[74]:



(LIII) (LIV)

Hydroxyindoline derivatives (LVI) and (LV) have also been obtained from 1-acetyl-2-alkylindoxyls (LVII) by the Grignard and Reformatskii reactions[75]:

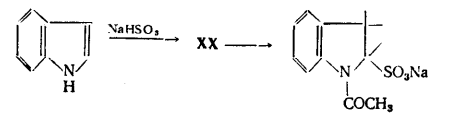


(LVI) (LVII) (LV)

In the synthesis of various indole derivatives from indoxyl, compounds whose structure is based on 3-hydroxyindoline (see, for example, Nenitzescu and Dan Raileanu[76]) are often formed as intermediates. Here only those cases are considered where these compounds have been isolated and identified.

3. Adducts of Indoles and Sodium Bisulphite and Indole Dimers

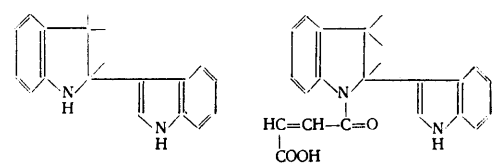
The "exclusion of the pyrrole ring" of indole can also be achieved by the conversion of indole into the sodium salt of indoline-2-sulphonic acid (XX)[17,77]:



(LVIII)

The product of the acetylation of a salt of indoline-2-sulphonic acid (LVIII) is used in electrophilic substitution reactions. The advantage of this method is the ease of preparation of the adduct (the yields are quantitative) and the ease of reconversion into indole derivatives. However, the instability of the reaction products and the impossibility of purifying and identifying the intermediates greatly reduce the value of this method.

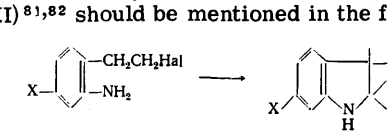
Indole dimers, which have the structure of indolinylindoles (LIX)[78,79] and the adduct of indole and maleic anhydride (LX)[80] should also be mentioned.



(LIX) (LX)

4. Synthesis of Indolines by the Closure of the Pyrroline Ring

The studies on the cyclisation of *o*-aminophenylethyl halides (LXI)[81,82] should be mentioned in the first place:

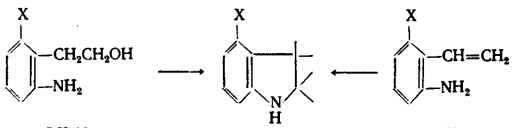


(LXI) (LXII)

where X = H, $RHNSO_2$.

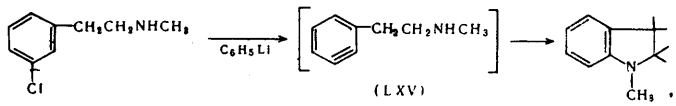
The mechanism of this reaction has not been investigated. The method has been used to prepare indoline-6-sulphonamides (LXII, X = $RHNSO_2$)[83,84]. It is particularly

valuable, since direct sulphonyl chlorination of indolines leads to 5-derivatives (see Section III). The cyclisation is achieved under the action of aqueous alkali. Indoline and its derivatives have also been obtained from *o*-aminostyrene (LXIII)[85] or *o*-aminophenylethanol (LXIV)[65,86,87]:



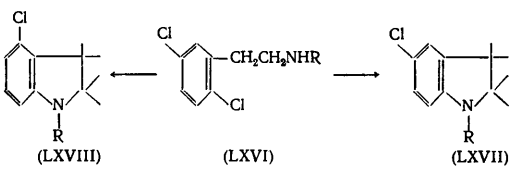
(LXIV) (LXIII)

Indolines are formed when halogeno-derivatives of β-phenylethylamine are acted upon by reagents such as C_6H_5Li, $(C_2H_5)_2NLi$, $NaNH_2$, and others. The intermediate aryne structure (LXV) is formed, this being followed by intramolecular nucleophilic addition to the triple bond of the dehydrobenzene ring[65,88,89].



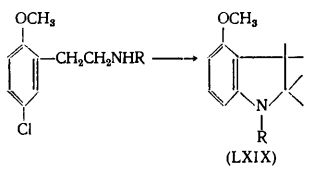
(LXV)

A halogen in a position *meta* to the side-chain forms the aryne more readily than the halogen in the *ortho*-position, which leads to higher yields of indolines when *meta*-derivatives are used. However, it proved possible to obtain 1-methylindoline from β-(*o*-chlorobenzyl)ethylmethylamine in 50% yield[90]. When the benzene ring contains halogens in positions *ortho* and *meta* to the side-chain (LXVI), a mixture of 4- and 5-halogeno-derivatives (LXVIII) and (LXVII) is formed, 4-chloroindoline (the product of the cyclisation of *m*-chlorophenylethylamine) (LXVIII) predominating considerably:



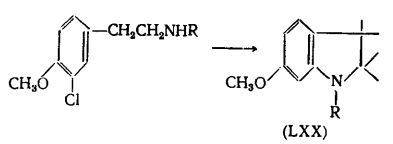
(LXVIII) (LXVI) (LXVII)

This method has been used to prepare 4-methoxyindolines (LXIX) and 6-methoxyindolines (LXX)[91]:



(LXIX)

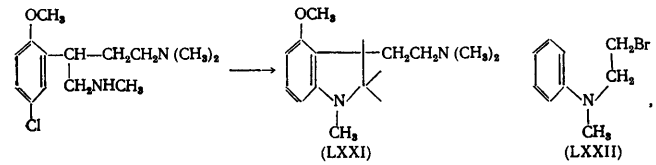
where R = H, CH_3, and $CH_2C_6H_5$;



(LXX)

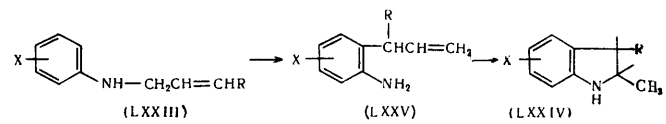
where R = H, CH_3, and C_2H_5.

4- and 6-methoxyindolines have been converted into 4- and 6-hydroxyindolines. 3-(β-Dimethylaminoethyl)-4-methoxy-1-methyl-2,3-dihydroindoline (LXXI) has also been obtained[91]:



(LXXI) (LXXII)

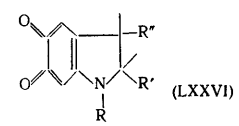
1-Methylindoline has been isolated after the reaction between aluminium chloride and (β-bromoethyl)methylaniline (LXXII)[92]. 2-Methylindolines (LXXIV) are formed (together with small amounts of 2-methylindoles) when *N*-allylanilines (LXXIII) are cyclised under the action of acid reagents[25,93]:



(LXXIII) (LXXV) (LXXIV)

where R = H and CH_3 and X = H, 7-CH_3, 5-CH_3, and 5-F. *o*-Allylaniline (LXXV) is an intermediate in this reaction[25].

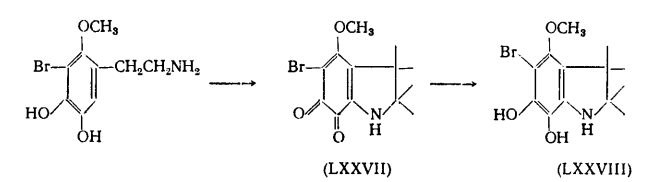
The possibility of obtaining indoline systems by the oxidation of aminocatechols should be recalled. Adrenochrome (VIII), which was isolated after adrenalin had been subjected to the action of catechol oxidase, silver oxide, and other agents[94], has already been mentioned. Aminochromes (LXXVI), analogues and derivatives of adrenochromes, have also been prepared:



(LXXVI)

Among the ether derivatives of adrenalin, the aminochromes (LXXVI, R = CH_3, R′ = H, R″ = alkoxy-group) have been obtained[95].

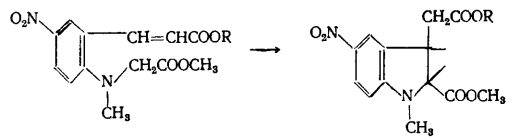
Adrenalin analogues have been prepared from 3-hydroxyindolinequinones (LXXVI, R = R′ = alkyl residues and R″ = OH)[96]. By oxidising dihydroxyphenylalanine derivatives, indolinequinonecarboxylic acids (LXXVI, R = CH_3, C_2H_5, etc., R′ = COOH, and R″ = H) were synthesised[96]. Among the phenylethylamine derivatives, the indolinequinones (LXXVI, R = CH_3, C_2H_5, etc. and R′ = R″ = H) were prepared[96]. Other compounds synthesised are aminochromes, which are indoline-6,7-*o*-quinones (LXXVII), some of which have been used in the synthesis of polyhydroxylated indolines (LXXVIII)[97]:



(LXXVII) (LXXVIII)

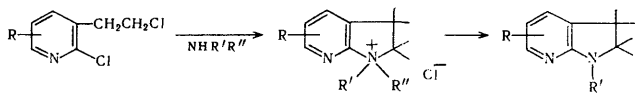
It has been shown that the action of potassiun iodate and other halogen-containing oxidising agents on adrenalin and its analogues leads to the preparation of 7-halogeno-derivatives of adrenochrome[98-100]. Adrenochrome derivatives have been used as the starting materials in the synthesis of certain indole systems.

It proved possible to close the indoline ring (LXXIX) by cyclisation under the conditions of the Michael reaction[101]:



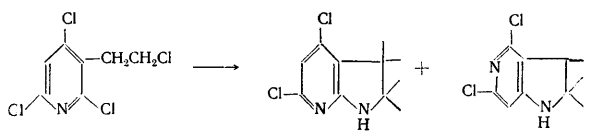
(LXXIX)

In recent years an increasing number of studies have been devoted to the methods of synthesis of pyridino- or pyrimidino-pyrroles (aza- or diaza-indolines)§. These investigations were stimulated by the discovery of the high biological activity of the aza-analogues of nucleosides and nucleotides and the discovery of new antibiotics of the type of tubercidin and toyokamycin. An especially large number of studies are concerned with the development of methods of synthesis of pyridinopyrrolines (azaindolines). It has been established that, when 3-(β-chloroethyl)pyridines containing halogen atoms in positions 2 or 4 (LXXX) are condensed at a high temperature with ammonia and primary or secondary amines, indolines (LXXXI) are formed. Using various chloropyridines and amines, it proved possible to prepare by this method more than 30 substituted 7- and 5-azaindolines[102-114]. The first stage of the reaction[105,109] is the replacement of the aromatic chlorine by the NH_2 residue, this being followed by the formation of the quaternary salt (LXXXII) and the removal of an alkyl halide:



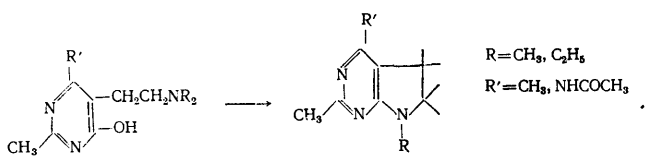
(LXXX) (LXXXII) (LXXXI)

The reaction of 2,4,6-trichloro-3-(β-chloroethyl)pyridine (LXXXIII) with amines takes place with the formation of a mixture of 5- and 7-azaindolines, (LXXXIV) and (LXXXV) respectively, in proportions of 34.6 : 42.2.[109,112] 5- and 7-indolines were obtained by the dechlorination of these compounds.



(LXXXIII) (LXXXV) (LXXXIV)

The formation of pyrimidinopyrrolines (5,7-diazaindolines) (LXXXVI) by the action of phosphorus pentachloride and then alkali on pyrimidines containing β-dialkylamino- and hydroxy-groups in the *ortho*-position (LXXXVII) has been described[115,116]:

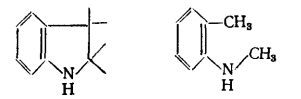


(LXXXVII) (LXXXVI)

§ The present review deals only with pyridino- and pyrimidino-pyrroles and -pyrrolines, which can be regarded as 4-, 5-, 6-, or 7-aza-analogues of indole or indoline.

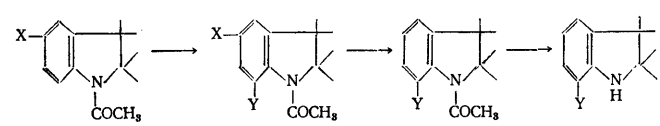
III. INTRODUCTION OF SUBSTITUENTS INTO THE BENZENE RING OF THE INDOLINE MOLECULE

The behaviour of indolines in electrophilic substitution reactions has been investigated with the aim of introducing substituents into the benzene ring of the indoline molecule. The question of the site of substitution in these reactions could not be solved by analogy between indoline (LXXXVIII) and *N*-methyl-*o*-toluidine (LXXXIX):



(LXXXVIII) (LXXXIX)

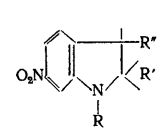
It has been established that these compounds and their *N*-acyl and *N*-alkyl derivatives behave in different ways in electrophilic substitution reactions[117]. The different behaviour of these systems was accounted for by the fact that in *NN*-disubstituted *o*-toluidine the CH_3 and NR_2 groups cannot lie in the plane of the benzene ring due to steric hindrance[117]. This leads to weakening of the conjugation between the NR_2 group and the benzene ring. In disubstituted *o*-toluidine electrophilic substitution takes place in the *para*-position with respect to the methyl group. As a result of the formation of the ring, the indoline molecule is coplanar and there is no weakening of the conjugation between the *p*-electrons of the nitrogen and the π-electrons of the benzene ring. Therefore electrophilic substitution takes place in the *para*-position with respect to the amino- (or acetamido-) group (i.e. position 5), since these groups have a more powerful directing effect. When reactions are carried out in a strongly acid medium, indoline is converted into the indolinium cation, as a result of which the substituents enter the *meta*-position with respect to the ammonium group, i.e. position 6. In the synthesis of 7-substituted indolines, position 5 is blocked by substituents which are readily eliminated and 1-acetylindoline is used as the starting material[118]:



The introduction of substituents into position 4 of the indoline ring, after protection of position 6, was not investigated.

1. Nitration, Nitrosation, and Azo-Coupling of Indolines

When indolines are nitrated with the nitrating mixture in sulphuric acid, the nitro-group enters into position 6. A number of 6-nitroindolines (XC) have been obtained in high yields[15,16,119-122]:

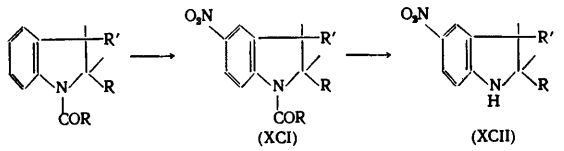


(XC)

R=R′=R″=H R=R′=H; R″=CH_3.
R=CH_3; R′=R″=H. R=C_2H_5; R′, R″=$(CH_2)_4$.
R=R″=H; R′=CH_3. R=R′=CH_3; R″=H.

A 6-nitro derivative of 2,3-dimethyl-1,7-trimethyleneindoline, which is in all probability a mixture of *cis*- and *trans*-isomers, has also been obtained[123,124]. The nitration of

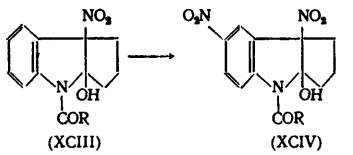
1-acylindolines gave a series of 1-acyl-5-nitroindolines (XCI), which were then converted into 5-nitroindolines (XCII)[16,44,45,119,125-127]:



(XCI) (XCII)

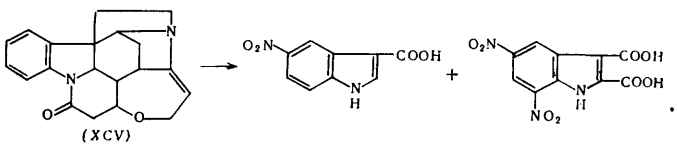
R=R′=H. R=CH_3; R′=H. R, R′=$(CH_2)_4$. R=H; R′=$(CH_2)_nCOOH$.

The nitration of *N*-acylindolines of complex structure (XCIII) has been described[128]:



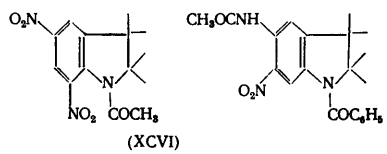
(XCIII) (XCIV)

Strychnine (XCV), which is a complex acylindoline, is nitrated in position 2 which corresponds to position 5 in the indole ring (oxidation and hydrolysis take place simultaneously)[129]:



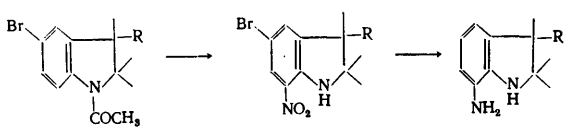
(XCV)

It is interesting to note that 5-nitro-derivatives are formed exclusively; the formation of 7-isomers has not been observed. However, after nitration of 1-acetylindoline, a certain amount of the 5,7-dinitro-derivative (XCVI) was isolated[119]. By further nitration of 1-acetyl-5-nitroindoline, the derivative was obtained in 42% yield[125]:



(XCVI) (XCVII)

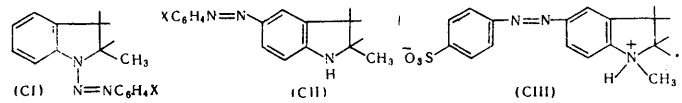
The nitration of 5-acetamido-1-benzoylindoline gave probably the 6-nitro-derivative (XCVII), while the product of the nitration of 1-benzoyl-6-diacetamidoindoline was probably the 4-nitro-derivative. The structure of the products obtained was not proved[16]. 5-Bromo-7-nitroindolines (XCIX), the key substances in the synthesis of 7-aminoindolines (C) and indoles, have been synthesised by the action of nitric acid on 1-acetyl-5-bromoindolines (XCVIII)[44,45,118,126,130]:



(XCVIII) (XCIX) (C)

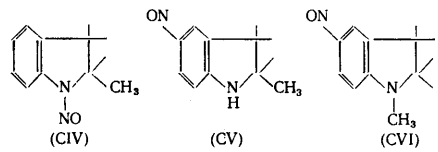
where R = H, CH_2COOH, and CH_2CH_2COOH.

In contrast to 2,3-dihydroindoles, the *N*-acetylated adduct of indole with sodium bisulphite (LVIII) forms on nitration a mixture of 5- and 7-derivatives, which on treatment with alkali yield a readily separated mixture of 5- and 7-nitroindoles[17,77]. On azo-coupling with phenyldiazonium salts in the presence of sodium acetate, 2-methylindoline forms diazoamino-compounds (CI); in a strongly acid medium the products are the diazo compounds (CII)[31]:



(CI) (CII) (CIII)

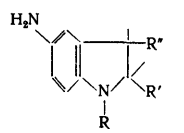
On coupling with diazotised sulphanilic acid, 1-methylindoline also forms the azo-dye (CIII). It proved possible to isolate the sodium salt of the dye from a strongly alkaline medium[131]. The nitrosation of indoline and 2-methylindoline yields *N*-nitroso-derivatives[30,122,132]. 2-Methyl-1-nitrosoindoline (CIV) undergoes the Fischer–Hepp rearrangement with formation of 2-methyl-5-nitrosoindoline (CV). 1-Methyl-5-nitrosoindoline (CVI) was obtained in the reaction between butyl nitrite and 1-methylindoline[122].



(CIV) (CV) (CVI)

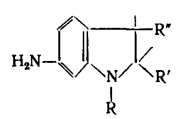
2. Aminoindolines

Aminoindolines have been investigated very thoroughly because, apart from their possible conversion into aminoindoles, they may serve as the starting materials for the preparation of alkoxy-, fluoro-, and other substituted indolines. Elimination of the nitro-group protecting position 5 or 6 also proceeds via the aminoindoline state. 5- and 6-aminoindolines, (CVII) and (CVIII) respectively, have been obtained by the reduction of the corresponding readily available nitroindolines[15,16,44,119,122,133-135]:



(CVII)

R=R′=R″=H;
R=R″=H; R′=CH_3;
R=COC_6H_5; R′=R″=H;
R=R′=H; R″=CH_2COOH.



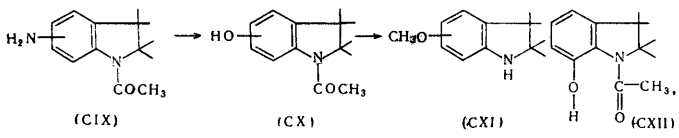
(CVIII)

R=R′=R″=H.
R=R′=H; R″=CH_3.
R=$COCH_3$; R′=R″=H.
R=R″=H; R′=CH_3.
R′=R″=H; R=CH_3.
R′=R″=H; R=COC_6H_5.

Hydrazine hydrate in the presence of Raney nickel[119] and also stannous chloride[15,133] have been used as the reducing agents. Nitroindolines have been hydrogenated over palladium on charcoal[134,135], over the Adams catalyst[16], and over Raney nickel[44]. Certain 5-aminoindolines have been obtained by the reduction of 5-nitroso- or 5-sulphophenylazo-derivatives[31,122]. This method of synthesis is particularly valuable for 5-amino-1-methylindoline, because a method of preparation of 1-methyl-5-nitroindoline has not been described[131]. When bromonitroindolines are

hydrogenated over palladium on charcoal, the bromine atom is eliminated and aminoindolines are produced. The method is suitable for the preparation of 7-aminoindolines.

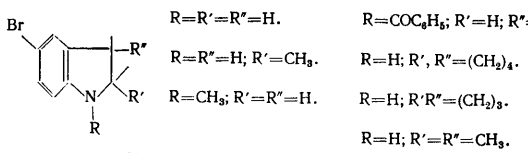
5-Bromo-1-methylindoline [131], 1-acetyl-7-iodoindoline [125], 1-acetyl-6-fluoroindoline [134], 1-acetyl-5-fluoroindoline [134], 1-acetyl-6-chloroindoline [134], and 1-acetyl-5-chloroindoline [134] have been obtained from the corresponding aminoindolines by the Sandmeyer reaction. The replacement of the amino-group by fluorine and chlorine takes place in high yields, the corresponding halogenoindolines being obtained on deacetylation. The conversion of 1-acetyl-5-amino-, 1-acetyl-6-amino-, and 1-acetyl-7-amino-indolines (CIX) into the corresponding hydroxy-derivatives (CX) (in yields of 77, 82, and 42% respectively) has been achieved [133,135]. 5-, 6-, and 7-methoxyindolines (CXI) have been obtained by the methylation of the hydroxy-group. The methylation yield is low in the case of 7-hydroxyindoline (CXII); the authors attribute this to the presence of a hydrogen bond in this compound [135].



(CIX) (CX) (CXI) (CXII)

3. Halogenation of Indolines

5-Bromo-derivatives (CXIII) are formed when indolines are brominated in acetic acid or in the bromination of 1-acetylindolines [44,45,118,119,126,127,131,136,137].

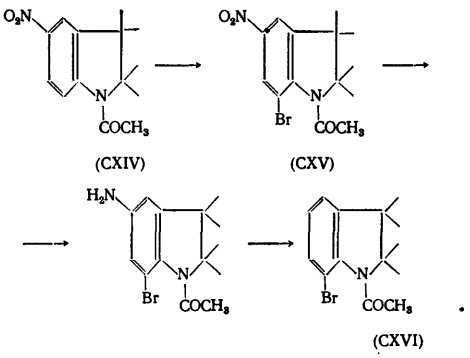


(CXIII)

R=R′=R″=H. R=COC$_6$H$_5$; R′=H; R″=CH$_2$COOH.
R=R″=H; R′=CH$_3$. R=H; R′, R″=(CH$_2$)$_4$.
R=CH$_3$; R′=R″=H. R=H; R′R″=(CH$_2$)$_3$.
R=H; R′=R″=CH$_3$.

The non-protonated indoline species appear to react in the bromination of indolines in a mixture of sulphuric and acetic acids. 6-Bromo-2,3-dimethylindoline has been obtained by the bromination of 2,3-dimethylindoline in a strongly acid medium [137]. The paper describing the synthesis was the first communication about the possibility of a direct synthesis of 6-bromoindolines. It was not stated whether the 5- and 6-bromo-2,3-dimethylindolines were pure substances or mixtures of *cis*- and *trans*-forms [137].

The bromination of the sodium salt of 1-acetylindoline-2-sulphonic acid (LVIII) followed by treatment with alkali gave 5-bromoindole in 70% yield [17,77]. When ICl is allowed to act on compound (LVIII), the 5-iodo-derivative is produced and from the latter 5-iodoindole can be obtained by the action of alkali [17,77]. 5-Iodoindoline has been obtained by the action of ICl on 1-acetylindoline with subsequent hydrolysis of the acetyl group [138]. The attempt to prepare 5-chloroindole by the action of chlorine on the adduct of indole and sodium bisulphite (LVIII) was unsuccessful [17,77]. Chloro- and fluoro-indolines have been obtained, as stated above, from the corresponding 1-acetamidoindolines [134]. The attempt to prepare fluoroindolines from bromoindolines was unsuccessful [134]. The 7-bromo-derivative (CXV) has been obtained by the bromination of 1-acetyl-5-nitroindoline (CXIV). The reduction of the nitro-group and the elimination of the amino-group gave 1-acetyl-7-bromoindoline (CXVI) [126]:

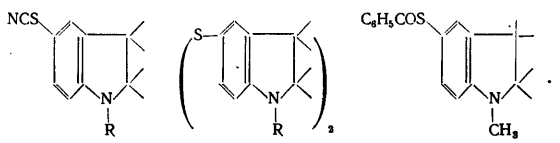


(CXIV) (CXV) (CXVI)

There are data indicating high physiological activity of 1-acyl-5-halogenoindolines [139].

4. Thiocyanato- and Mercapto-Derivatives of Indoline

5-Mercapto-derivatives of indoles and indolines, the thio-analogues of hydroxyindole derivatives which exhibit high pharmacological activity, have been investigated very little so far. 5-Thiocyanato-derivatives (CXVII), which are both of intrinsic interest and are important as key substances for the synthesis of 5-mercaptoindoline or 5-mercaptoindole derivatives, have been obtained by the thiocyanation of indoline derivatives [140]:

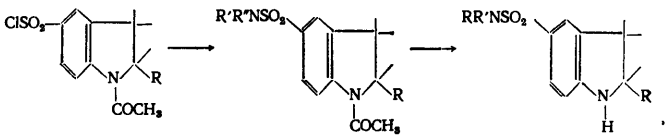


(CXVII, R=H, CH$_3$) (CXVIII, R=H, CH$_3$) (CXIX)

The treatment of 5-thiocyanatoindolines (CXVII) with alkali gave the corresponding disulphides (CXVIII) and the reduction of 1-methyl-5-thiocyanatoindoline with tin in hydrochloric acid led to 5-mercapto-1-methylindoline, which was isolated as the *S*-benzoyl derivative (CXIX) [140].

5. Chlorosulphonation of Indolines and Sulphonamides of the Indoline Series

By the chlorosulphonation of 1-acetylindoline, 1-acetylindoline-5-sulphonyl chlorides (CXX) were obtained, from which a number of indoline-5-sulphonamides (CXXI) [117,138, 141-143] and indoline-5-sulphonic acids were synthesised [117]:



(CXX) (CXXI, R=H, CH$_3$)

As stated above, indoline-6-sulphonamides (LXII) have been obtained by the cyclisation of the indoline ring. The sulphoureides (CXXII) and (CXXIII) have been prepared

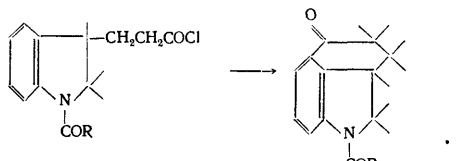
from indoline-5-sulphonamides and indoline-6-sulphonamides [141,143]:



(CXXII) (CXXIII)

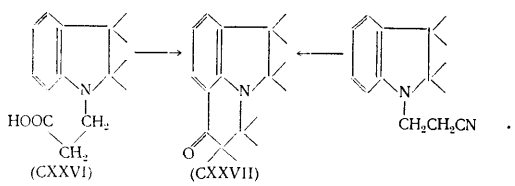
6. Acylation and Alkylation of Indolines

Intramolecular *C*-acylation of derivatives of indolinealkanoic acids has been investigated in connection with studies on the synthesis of indole alkaloids. The first stage in the synthesis of lysergic acid consists in the conversion of 1-acylindoline-3-propionic acid into the acid chloride (CXXIV) which is cyclised under the conditions of the Friedel–Crafts reaction with the formation of the corresponding tricyclic derivative [14,144,145] (CXXV):



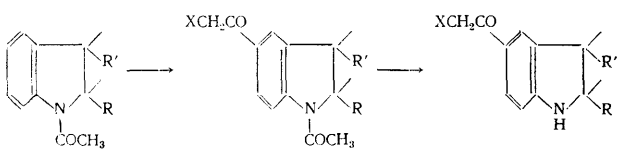
(CXXIV) (CXXV)

The intramolecular cyclisation of indoline-1-propionic acid (CXXVI) by heating with perfluoroacetic anhydride led to the corresponding tricyclic ketone (CXXVII) [146]. The same oxo-derivative (CXXVII) was obtained from *N*-(β-cyanoethyl)indoline (CXXVIII) [147]:



(CXXVI) (CXXVII)

The syntheses of alkyl *C*-indolyl ketones and especially methyl 5-indolyl ketone has been attracting attention in recent years in connection with the discovery of the pharmacological activity of 5-acetyltryptamine and its derivatives [148]. A series of 5-acetyl- and 5-chloroacetyl-indolines (CXXIX) have been obtained by the Friedel–Crafts acylation of 1-acetylindolines [149,150]:

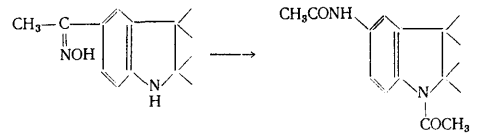


(CXXIX)

R=R′=H; X=H.
R=R′=H; X=Cl.
R=CH$_3$; R″=X=H.
R=CH$_3$; X=Cl; R′=H.
R, R′=(CH$_2$)$_4$; X=H.

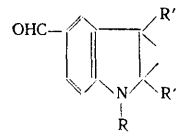
The acylation yields mainly the 5-derivative, but in the chloroacetylation of 1-acetylindoline 3% of a product, which was probably 1-acetyl-7-chloroacetylindoline, was isolated in addition to 83% of the 5-chloroacetyl derivative [149].

Acetamidoindolines have been obtained from the oximes of indolinyl ketones by the Beckmann reaction [149]. For example:



Clemmensen reduction of 5-acetyl- and 5-chloroacetylindolines gives 5-ethylindolines [149].

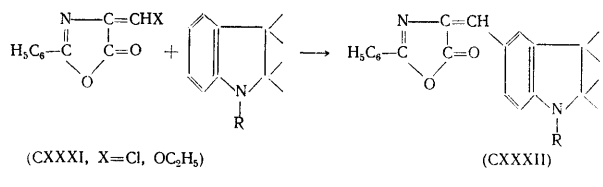
The Vilsmeier reaction has been used to prepare indoline-5-aldehydes. Indoline-5- and indole-5-aldehydes are of interest as key substances in the synthesis of various 5-analogues of tryptamine and tryptophan. A series of 1-alkyl-5-formylindolines (CXXX) have been obtained by the formylation of *N*-alkylindolines with methylformanilide and phosphorus oxychloride [151]:



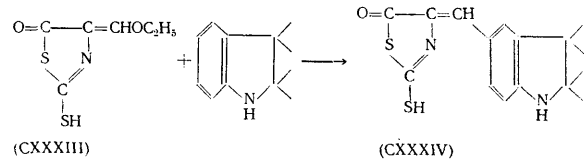
R=n-C$_4$H$_9$; R′=CH$_3$; R″=H. R=CH$_2$CH$_2$CN; R′=CH$_3$; R″=H.
R=R′=CH$_3$; R″=H. R=CH$_2$C$_6$H$_5$; R′=C$_6$H$_5$; R″=H.
R=C$_2$H$_5$; R′=CR$_3$; R″=H. R=H; R′R″=(CH$_2$)$_4$.

(CXXX)

The formylation of indoline and 1-methylindoline with dimethylformamide gives the corresponding 5-formyl derivatives (CXXX, R = R″ = H, R = H or CH$_3$) [152,153]. 1-Methylindoline yields also a certain amount of the 5,7-diformyl derivative [153]. The antitubercular activity of the thiosemicarbazone of 1-methylindoline-5-aldehyde has been described [154]. When phosphorus oxychloride or phosgene are allowed to act on 1-formylindolines, the latter are converted into 5-formylindolines. The authors call this reaction the migration of the formyl group to position 5, although it can be supposed that intermolecular formylation actually takes place. A number of aldehydes [CXXX, R = R″ = H, R′ = CH$_3$; R = R″ = H, R′ = C$_6$H$_5$; R = H and R′, R″ = (CH$_2$)$_4$] have been obtained by this method [155]. 4-(Indolin-5′-ylmethylene)-2-phenyl-5-oxazolone (CXXXII) has been obtained in the reaction of chloro- or ethoxy-methylene-2-phenyl-5-oxazolone (CXXXI) while the reaction of indoline with 4-ethoxymethylene-2-mercapto-1,3-thiazol-5-one (CXXXIII) gave the corresponding derivative of indoline and thiazolone (CXXXIV) [152]:



(CXXXI, X=Cl, OC$_2$H$_5$) (CXXXII)

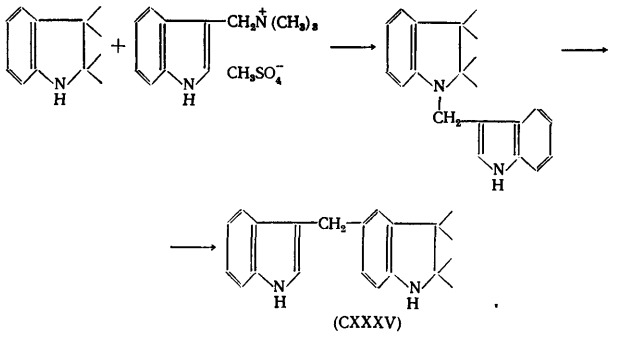


(CXXXIII) (CXXXIV)

Similar *C*-substitution of indoline takes place with high yield on heating in a neutral medium. Indolinylmethylenephenylazlactone (CXXXII, R = H) has been used as the starting material for the synthesis of 5-isotryptophan (5-indolylalanine) [152].

The *C*-alkylation of indolines has been almost not investigated. It has been shown that the reaction of the

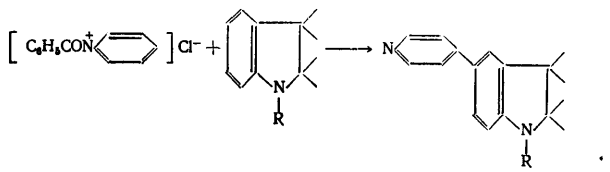
quaternary salt of gramine with indoline yields 5-scatylindoline (CXXXV)[156,157]:



(CXXXV)

Indoline can probably be alkylated also by other ammonium derivatives.

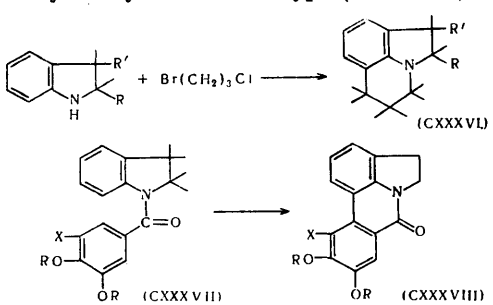
The reaction of 1-alkylindolines with 1-acylpyridinium salts in the presence of Lewis acids leads to 1-alkyl-5-(pyrid-4′-yl)indolines. 1-Alkyl-5-benzoylindolines are formed as side-products[158]:



1-Acylquinolinium salts react with 1-alkylindolines without catalysts with formation of 1-alkyl-5-(1′-benzoyl-1′,2′-dihydroquinolin-2′-yl)indolines, which are converted by alkaline hydrolysis into 1-alkyl-5-(quinolin-2′-yl)indolines[159].

7. Synthesis of Tricyclic Systems Based on Indolines

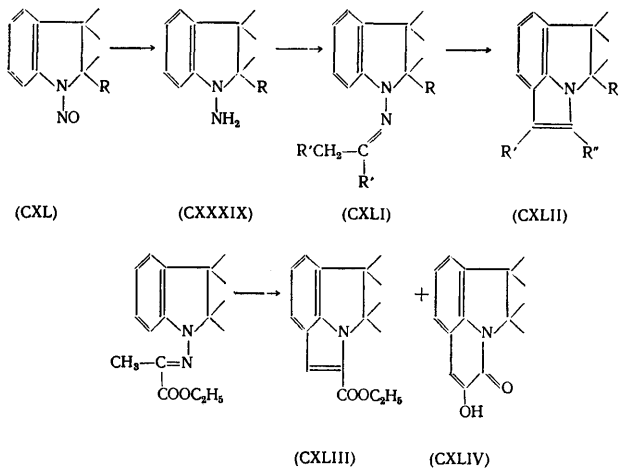
In connection with studies on the structure of indole alkaloids, the possibility of synthesising condensed indole and indoline systems has been investigated. When 1-bromo-3-chloropropane was allowed to react with indoline, lilolidine and its derivatives (CXXXVI) were obtained[160]. Similarly 9,10-dimethyl-lilolidine (CXXXVI, R = R′ = CH_3) is formed from 2,3-dimethylindoline[161]. It is not clear whether the authors dealt with pure substances or with mixtures of *cis*- and *trans*-isomers. The decomposition of diazotised derivatives of *o*-aminobenzoylindoline (CXXXVII) under the conditions of the Pschorr reaction leads to tricyclic systems of the type (CXXXVIII)[118,162]:



(CXXXVI) (CXXXVII) (CXXXVIII)

A similar cyclic system could not be obtained from 7-amino-1-benzoylindoline. The cyclisation can only be achieved in the presence of several alkoxy-groups in the benzene residue.

The use of indoline derivatives for the synthesis of cyclic systems by the Fischer reaction has also been described. 1-Aminoindolines (CXXXIX), prepared by the reduction of 1-nitrosoindolines (CXL), form with carbonyl compounds the hydrazones (CXLI), from which the tricyclic indole derivatives (CXLII), (CXLIII), and (CXLIV) were obtained[163-166]:

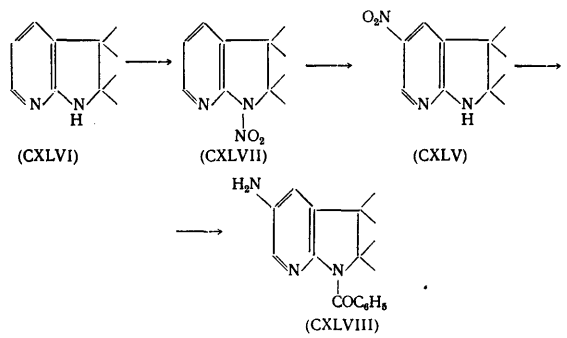


(CXL) (CXXXIX) (CXLI) (CXLII)

(CXLIII) (CXLIV)

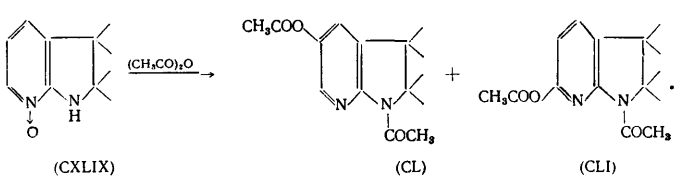
8. Substitution Reactions of Azaindolines

The substitution reactions in the series of pyridinopyrrolines (7-azaindolines) have been investigated with the aim of synthesising 7-azaindole derivatives[167]. 5-Nitro-7-azaindoline (CXLV) has been obtained by the nitration of 7-azaindoline (CXLVI). 1-Nitro-7-azaindoline (CXLVII) forms as an intermediate. 5-Amino-1-benzoyl-7-azaindoline (CXLVIII) has been prepared[167]:



(CXLVI) (CXLVII) (CXLV) (CXLVIII)

By allowing peracetic acid to react with 7-azaindoline, the corresponding *N*-oxide (CXLIX) was obtained and under the action of acetic anhydride the oxide was converted into a readily separated mixture of 5-acetoxy-1-acetyl-7-azaindoline (CL) and 6-acetoxy-1-acetyl-7-azaindoline (CLI). On hydrolysis, these compounds gave 5- and 6-hydroxy-7-azaindolines:



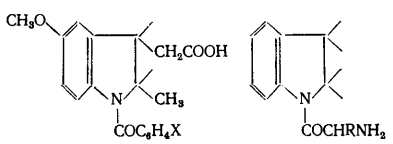
(CXLIX) (CL) (CLI)

It has been shown that 4-methyl-7-azaindoline derivatives are capable of forming 4-styryl derivatives [105]. The halogen in halogeno-7-azaindolines has been replaced by a methoxy-group and iodine [105]. The conditions of the dehalogenation of 6-chloro-7-azaindoline, 2,4-dichloro-7-azaindoline, and 4,6-dichloro-5-azaindoline have been investigated [113].

IV. INTRODUCTION OF SUBSTITUENTS INTO THE PYRROLE RING OF THE INDOLINE MOLECULE

The capacity of indolines to form *N*-derivatives, a property characteristic of all aromatic amines, was used to produce *N*-acyl- and *N*-alkyl-indoles, *N*-glycosylindoles, and also a quaternary indole salt, dimethylindolium perchlorate, which are difficult to obtain.

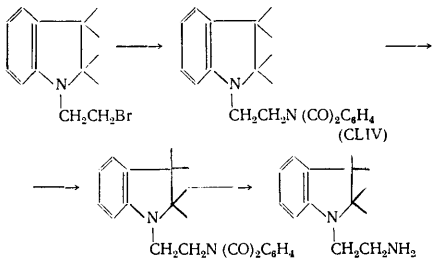
1-Acylindolines. When acted upon by acylating agents, indoline, sodium indoline-2-sulphonate, and 3-hydroxy-indoline form *N*-acyl derivatives. An enormous number of a wide variety of indoline derivatives, obtained by the action of acid anhydrides, arenesulphonyl chlorides, diketen [139], etc., have been described. We shall examine only those *N*-acylindolines which have been converted into the corresponding indole derivatives. In recent years much work has been done on the study of 1-benzoylindoline-3-alkanoic acids [for example, compound (CLII)]. These compounds have been converted into indomethacin (XV) and its analogues. The Merck Co. has published a number of patents dealing with the synthesis of compounds of this type [46,47]:



(CLII) (CLIII)

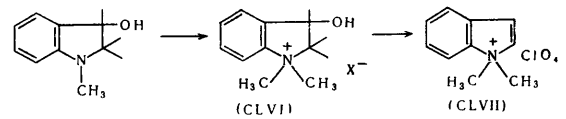
N-Aminoacyl derivatives of indoline (CLIII) have been investigated with the aim of converting them into the amino-acid derivatives of indole [168]. The principal difficulties arising in the preparation of *N*-acylindoles from *N*-acylindolines are encountered in the dehydrogenation stage. Probably the study of the *N*-acylation of the readily dehydrated 3-hydroxyindoline derivatives would prove very useful.

1-Alkylindolines and quaternary indolinium salts. *N*-alkylation of indolines and 3-hydroxyindolines has been investigated in great detail. Particular attention has been devoted to the preparation of derivatives of 1-(β-aminoethyl)indolines (CLIV), used for the synthesis of 1-isotryptamines (CLV) [169-172]:



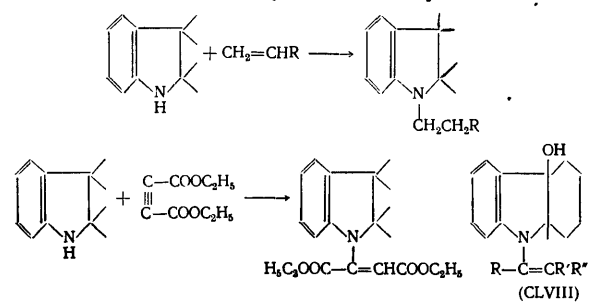
(CLV)

The quaternary 3-hydroxyindolinium salt (CLVI) has served as the starting material for the preparation of the quaternary indolium salt (CLVII) [18]:



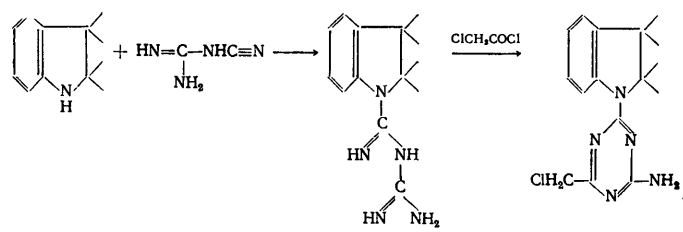
(CLVI) (CLVII)

Like other aromatic amines, indoline is capable of adding to the activated double bond of acrylonitrile [146,173], vinylpyridines [174], and also acetylenedicarboxylic acids [175]:

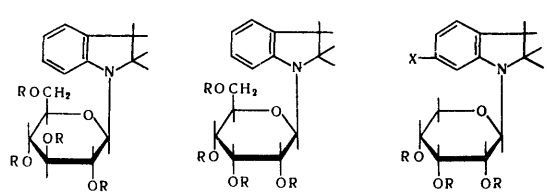


(CLVIII)

However, in the conversion to indole derivatives difficulties are encountered in this case in the dehydrogenation stage. When the corresponding hydroxyindoline derivative (CLVIII) is used, the conversion into indoles presents no difficulties [175]. The addition of indoline to the −C≡N bond has been described [176]:



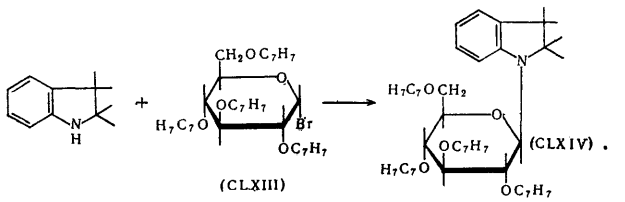
1-Glycosylindolines. In connection with the discovery of the antiviral activity of nucleoside and nucleotide analogues, the study of the properties of 1-glycosylindoles is of great interest. The investigations have acquired special importance after the discovery of the antibiotics tubercidin and toyokamycin. 1-Glycosylindolines have been used as the starting materials for the synthesis of 1-glycosylindoles [177-182]. 1-Glycosylindolines belong to the class of arylaminoglycosides, which have been little investigated. They are formed when indoline reacts with a hexose or pentose. 1-(D-β-Glucopyranosyl)indoline (CLIX, R = H) [177,178], 1-(D-β-galactopyranosyl)indoline (CLX, R = H) [179], 1(D-β-ribopyranosyl)indoline (CLXI, R = H) [180], 1-(D-β-ribopyranosyl)-6-nitroindoline (CLXII, R = H) [181], and their *O*-acetyl derivatives (CLIX, CLX, CLXI, CLXII, R = $COCH_3$) have been obtained.



(CLIX) (CLX)

(CLXI, X = H); (CLXII, X = NO_2).

The pyranoside structure of the products obtained has been confirmed by the fact that they have also been isolated in the reaction between *O*-acetylated pyranosyl acetates or acetohalogenopyranoses and indoline. Furthermore, in the hydrolysis of *O*-acetylated glycosylindolines it proved possible to isolate the corresponding *O*-acetylated pyranoses. The conclusion that 1-glycosylindolines and their derivatives have the β-configuration is based on the analysis of the molecular rotation and the infrared spectra. The formation of α-anomers could not be observed. Tetra-*O*-benzylglucopyranosyl bromide (CLXIII) has also been allowed to react with indoline, the tetra-*O*-benzyl derivative of glucopyranosylindoline (CLXIV) being obtained[182]:



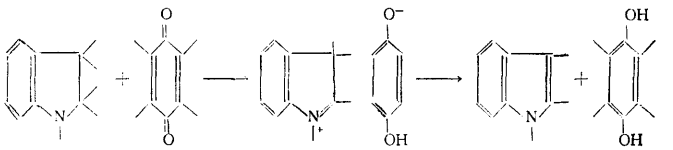
(CLXIII) (CLXIV).

V. CONVERSION OF INDOLINE DERIVATIVES INTO INDOLES

1. Dehydrogenation of Indolines

A wide variety of dehydrogenating agents are used to convert indolines into indoles—quinones with high oxidation potentials (chloranil, 2,3-dichloro-4,5-dicyano-*p*-benzoquinone), the pyridine complex of $CuCl_2$, $Hg(OCOCH_3)_2$, NiO_2, MnO_2, and others. The oxidation of indolines with atmospheric oxygen under various conditions and also catalytic dehydrogenation in the presence of Raney nickel, the Adams catalyst, palladium black or palladium on charcoal, nickel chromite, and other catalysts has also been described. The specific properties of the indole ring preclude the use of dehydrogenating agents such as sulphur and selenium, since indoles react with these substances[183].

The mechanism of the effect of quinones and other dehydrogenating agents on indoline has not been investigated. However, on the basis of general hypotheses[184], one can assume that at the beginning of the dehydrogenation process a hydride ion is removed, this being facilitated by the high-electron-donor capacity of the >NR group. The transition complex (CLXV) thus produced is then converted into indole and hydroquinone.



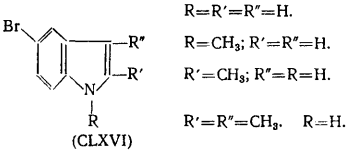
(CLXV)

It can be assumed that in other cases too, for example in heterogeneous catalysis, the initial dehydrogenation step is the removal of a hydride ion and the overall dehydrogenation mechanism is as follows:

$$\text{indoline} + A \rightleftharpoons \text{indole}.\ H^+.AH^- \rightarrow \text{indole} + AH_2,$$

A being the dehydrogenating agent. In the dehydrogenation with chloranil and in catalytic dehydrogenation electron-donor substituents, which favour the removal of a hydride ion, also facilitate the dehydrogenation. In the dehydrogenation with quinones the *trans*-configuration of the hydrogen ion eliminated is not obligatory, since *cis*-2,3-dimethylindoline forms 2,3-dimethylindole in 38% yield[93], which is consistent with the proposed mechanism of dehydrogenation by quinones. In dehydrogenation with palladium on charcoal selective *trans*-dehydrogenation is also not observed[25].

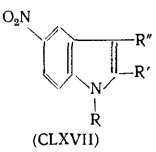
The most widely used dehydrogenating agent is chloranil. Dichlorodicyanoquinone, which has a higher redox potential, is finding increasing application in organic synthesis. Yet another property makes it a valuable dehydrogenating agent—dichlorodicyanohydroquinone formed in the reaction is sparingly soluble in benzene and xylene, which facilitates the isolation of the reaction products. As already mentioned, chloranil has been used to dehydrogenate 2,3-dimethylindoline[93], unsubstituted indoline and other alkylindolines[40], and also 5-ethoxy-1-methylindoline[35]. This agent has been used in the dehydrogenation of halogenoindolines. The following 5-bromoindoles (CLXVI) have been obtained[119,121,127]:



(CLXVI)

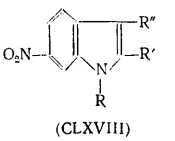
R=R′=R″=H.
R=CH₃; R′=R″=H.
R′=CH₃; R″=R=H.
R′=R″=CH₃. R=H.

6-Bromo-2,3-dimethylindole has also been prepared[137]. The dehydrogenation of 5-iodoindoline[138], 5- and 6-chloroindolines, and fluoroindolines[134] has been described. A number of nitroindoles (CLXVII and CLXVIII) have been synthesised by boiling with chloranil in xylene[15,119,123,124]:



(CLXVII)

R=R′=R″=H.
R=R″=H; R′=CH₃.

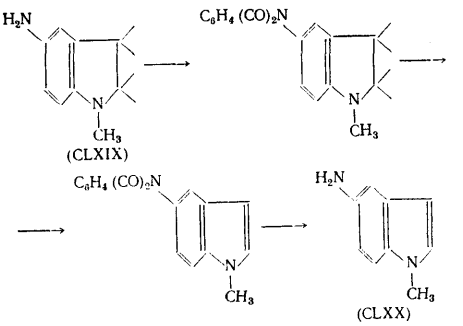


(CLXVIII)

R=R′=R″=R‴=H.
R=R″=R‴=H; R′=CH₃.
R=CH₃; R′=R″=R‴=H.
R, R‴=(CH₂)₃; R′=R″=CH₃.

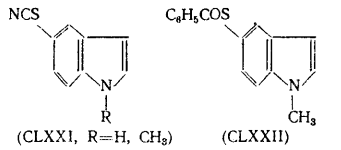
When a second nitro-group is introduced into the indoline molecule, the redox potential of chloranil proves insufficient and dinitroindoline cannot be dehydrogenated by boiling with chloranil in xylene[125].

In the dehydrogenation of aminoindolines with quinones it is necessary to protect the amino-group in order to avoid its undesirable interaction with chloranil. The following method for the conversion of 5-amino-1-methylindoline (CLXIX) into the corresponding indole (CLXX) has been described[131]:



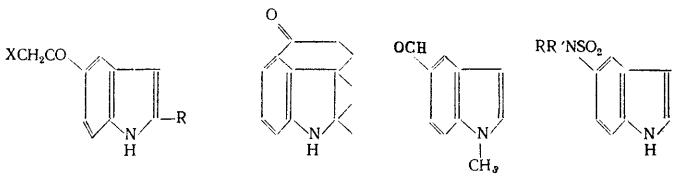
(CLXIX) (CLXX).

5-Thiocyanatoindoles (CLXXI) have been obtained by boiling 5-thiocyanatoindolines with chloranil in xylene. 5-Benzoylmercapto-1-methylindole (CLXXII) has been obtained similarly [140]:



(CLXXI, R=H, CH_3) (CLXXII)

The 5,5′-disulphide of 1-methylindole has been described [140]. Indoles containing an acyl group in the benzene ring have also been synthesised by dehydrogenating the corresponding indolines with chloranil. Chloranil has been used in the synthesis of the ketones (CLXXIII) [149]:

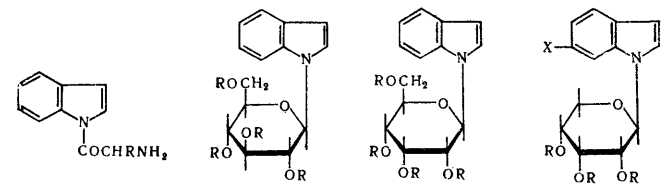


(CLXXIII, R=H; X=H·R=CH_3; X=H. R=H; X=Cl·R=CH_3; X=Cl) (CLXXIV) (CLXXV) (CLXXVI)

Heat is used in the dehydrogenation with quinones. At room temperature the ketone (CLXXIV) could not be dehydrogenated with chloranil and dichlorodicyanoquinone gave the corresponding indole in 5% yield only [185]. In contrast to 4-(indolin-5′-yl)methylene-5-oxo-2-phenyloxazole (CXXXII, R = H), 1-methylindoline-5-aldehyde was converted into 1-methylindole-5-aldehyde (CLXXV) on boiling with chloranil in xylene. The dehydrogenation of indoline-5-sulphonamides yielded a series of indole-5-sulphonamides (CLXXVI) [117,138,141]. Convenient solvents for the dehydrogenation of indolinesulphonamides and other indoline derivatives which are sparingly soluble in xylene are 1,2-dimethoxyethane [141], diglyme, and dimethylformamide [181].

The reaction with chloranil or dichlorodicyanoquinone also constitutes a general method for the dehydrogenation of 1-alkyl(aryl)-7-azaindolines [103,105,106]. A large number of 7-azaindole derivatives have been obtained. As with indolines, the introduction of electron-acceptor substituents into the azaindoline molecule hinders dehydrogenation, while electron-donor substituents facilitate it [111]. It is noteworthy that, as a result of the lower electron density of the pyridine ring compared with the benzene ring, azaindolines are dehydrogenated under more severe conditions than indolines. In their capacity for dehydrogenation azaindolines are similar to nitroindolines. *N*-Acylation of indolines also hinders dehydrogenation, since the electron density of the pyrrole ring is thereby reduced. However, it has proved possible to obtain a number of *N*-acylindoles from the corresponding indolines. *N*-Aminoacyl derivatives of indole (CLXXVII) have been synthesised from the *N*-aminoacyl derivatives of indoline (CLIII) by boiling with chloranil in xylene [168]. The last stage in the synthesis of indomethacin (XV) consists in the dehydrogenation with chloranil of 1-(*p*-chlorobenzoyl)-2,3-dehydro-5-methoxy-2-methylindole-3-acetic acid (CLII) [47]. Probably the presence of the methoxy-group in position 5 facilitates the dehydrogenation despite the opposed effect of the *p*-chlorobenzoyl residue. 1-Acetyl-5-bromoindoline-3-acetic and 1-acetyl-5-nitroindoline-3-acetic acids could not be dehydrogenated with chloranil [44].

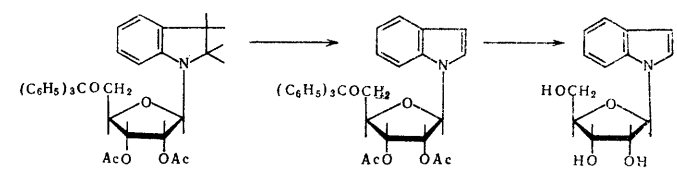
The dehydrogenation of *N*-glycosylindolines has been investigated in detail. The dehydrogenation of 1-(D-β-tetra-*O*-acetylglucopyranosyl)indoline (CLIX, R = $COCH_3$) by boiling with chloranil in xylene gives the corresponding indole in 32% yield (CLXXVIII, R = $COCH_3$) [177,178]. When dichlorodicyanoquinone is used in the synthesis, the yield is quantitative [182]. Dichlorodicyanoquinone has also been used to synthesise 1-(D-β-tetra-*O*-benzylglucopyranosyl)-indole (CLXXVIII, R = $CH_2C_6H_5$) [182].



(CLXXVII) (CLXXVIII) (CLXXIX) (CLXXX)

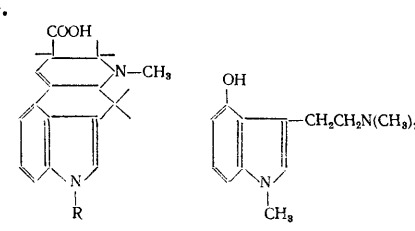
This reagent has also been employed in the synthesis of 1-(D-β-tetra-*O*-acetylgalactopyranosyl)indole (CLXXIX, R = $COCH_3$) [179] and 1-(D-β-tri-*O*-acetylribopyranosyl)indole (CLXXX, X = H, R = $COCH_3$) [180]. In the dehydrogenation of 6-nitro-1-(D-β-tri-*O*-acetylribopyranosyl)indoline (CLXII, R = $COCH_3$) even boiling with chloranil in xylene is insufficient to complete the reaction. The reaction mixture consists of the indoline (CLXII, R = $COCH_3$) and the indole (CLXXX, X = NO_2, R = $COCH_3$), which can be separated after deacetylation. The yield of indole (CLXXX, X = NO_2, R = H) is 19%. [181]

Dichlorodicyanoquinone has been used as the dehydrogenating agent in the conversion of 1-(D-β-5′-*O*-trityl-2′,3′-di-*O*-acetylribofuranosyl)indoline into the corresponding indole derivative which is a key substance in the synthesis of 1-(D-β-ribofuranosyl)indole, an indole analogue of nucleosides [186]:



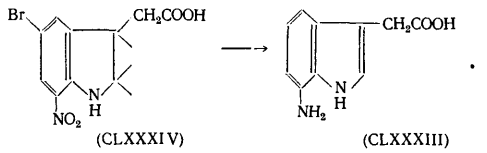
9,10-Phenanthroquinone has also been used as a dehydrogenating agent for indolines [185].

The catalytic dehydrogenation of indoline derivatives has been extensively studied. There is great scope for synthesis using Raney nickel as the catalyst. In the conversion of dehydrolysergic acid (XXXVIII, R = H) into lysergic acid (CLXXXI, R = H) the former was boiled in water with Raney nickel and sodium arsenate [14]. In contrast to this catalyst, which aromatises the pyrrole ring, the use of palladium on charcoal leads to the aromatisation of the naphthalene ring. 4-Hydroxy-3-(β-dimethylaminoethyl)-1-methylindole (CLXXXII) has been obtained by the dehydrogenation of the corresponding indoline over Raney nickel in water [91].



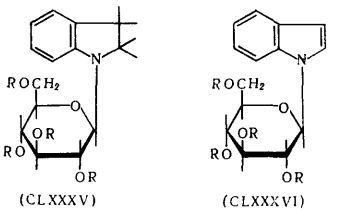
(CLXXXI) (CLXXXII)

In those cases where the indoline molecule contains a group capable of being reduced, Raney nickel causes simultaneous dehydrogenation of the pyrroline ring and reduction of this group. Thus on being boiled with Raney nickel or with the Raney alloy, nitroindolines are converted into aminoindoles. 5- and 6-Aminoindoles, 5-aminoindole-3-acetic acid and 5-aminoidnole-3-propionic acid have been obtained by this method[44,45]. In the presence of a halogen in the indoline molecule, dehydrogenation is accompanied by the elimination of the halogen. By boiling bromonitroindoline with Raney nickel, 7-aminoindole and 7-aminoindole-3-acetic acid (CLXXXIII) have been obtained in one stage from 1-acetyl-5-bromo-7-nitroindoline and 5-bromo-7-nitroindole-3-acetic acid (CLXXXIV) respectively[44,45]:



(CLXXXIV) (CLXXXIII)

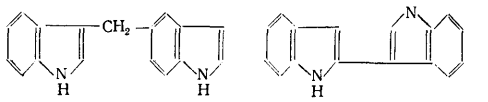
It is interesting that, using Raney nickel, it is difficult to reduce the substituent without the simultaneous dehydrogenation of the pyrroline ring. Thus neither aminoindoline nor nitroindole can be obtained from nitroindoline in the presence of Raney nickel. The nitro-group is reduced even when the reaction is carried out in nitrobenzene or in the presence of added maleic acid. The same phenomenon has been observed in the dehydrogenation of 1-(D-β-tetra-*O*-benzylglucopyranosyl)indoline (CLXXXV, R = $CH_2C_6H_5$)[181]. Dehydrogenation and debenzylation take place simultaneously. The indole (CLXXXVI, R = H) forms in 39% yield. Chromatographic analysis of the reaction mixture showed the absence of the corresponding debenzylated glucosylindoline (CLXXXV, R = H).



(CLXXXV) (CLXXXVI)

Even hydrogenation of compound (CLXXXV, R = $CH_2C_6H_5$) over Raney nickel at 50°C and 50 atm is accompanied by the formation of the indole derivative (CLXXXVI, R = H). In contrast to the *O*-benzyl derivative, the acetylated glucopyranosylindoline (CLXXXV, R = $COCH_3$) and also the unprotected glucopyranosylindoline (CLXXXV, R = H) are not completely dehydrogenated on boiling with Raney nickel. Thus the presence in the molecule of a reducible group greatly facilitates the dehydrogenation. Probably intramolecular transfer of a hydride ion to the reducible group takes place very readily in the complex indole.H^+.AH^- formed in the heterogeneous catalytic dehydrogenation.

Palladium black and palladium on charcoal are also widely used in the dehydrogenation. Hydrogen acceptors—nitrobenzene, cinnamic acid, and maleic anhydride—are frequently added in such reactions. Thus indoline has been converted into indole by heating with palladium black and cinnamic acid[57]. 5- and 6-nitroindoles[16], 6-benzamido-1-methylindole[15], 1-methyl-6-phthalimidoindole[15], and a series of indole-5-sulphonamides (CLXXXVI)[42] have been obtained under the same conditions:

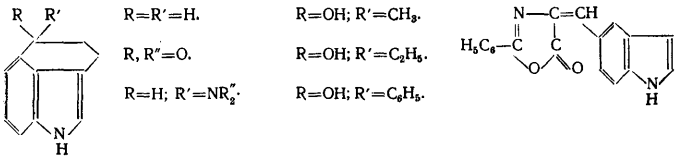


(CLXXXVII) (CLXXXVIII)

The dehydrogenation of indoline derivatives in the presence of catalysts without using hydrogen acceptors has also been described. The following products have been obtained: 5-scatylindole (CLXXXVII)[156] from 5-scatylindoline (CXXXV)[156], 2,3′-di-indolyl (CLXXXVIII) from the indole dimer (LIX)[79], 5-, 6-, and 7-methoxyindoles from the corresponding methoxyindolines[135], and the ketone (CLXXXIX, R, R′ = O) from the ketone (CLXXIV)[184]. 5-Aminoindoline has been converted into 5-aminoindole by heating with palladium on charcoal in the absence of solvent at 190°C.[44] Alkylindolines have also been dehydrogenated by heating with palladium on charcoal up to 200°C.[25] 4-(Indolin-5′-yl)methylene-5-oxo-2-phenyloxazole (CXXXII, R = H), which could not be dehydrogenated with chloranil, gave the corresponding indole derivative (CXC) after boiling for two days with palladium black in xylene[152]. 5,7-Dinitroindoline could not be converted into dinitroindole by boiling with palladium black in mesitylene[125]. The attempt to dehydrogenate 1,1-dimethylindolinium chloride by boiling with palladium black in xylene did not yield the corresponding quaternary indolium salt[18].

The dehydrogenation of indoline on the $Ni/NiCrO_2$ catalyst at 200°C has been described[187]. The pyridine complex of $CuCl_2$ has also been used as the oxidising agent for indolines[91,142]. The yields of indole and 1-methylindole when the corresponding indolines were heated with cupric chloride in pyridine were 55–60%.[142] Similarly a number of 4- and 6-methoxyindolines have been converted into the corresponding indoles[91]. So far, it has not proved possible to use this reagent in the synthesis of indoles containing electron-acceptor groups.

Oxidation with manganese dioxide in benzene[188] or methylene chloride[185] has also been described. The yield of indoline was 56–59%. The following compounds (CLXXXIX) have been obtained by shaking the corresponding indolines with manganese dioxide in methylene chloride[185]:



(CLXXXIX) (CXC)

Indole-3-propionic acid has also been synthesised by the oxidation of indoline-3-propionic acid[185]. 2-Methylindoline, 2,3-dimethylindoline, and 1-acyl derivatives of indoline could not be dehydrogenated by this method[185]. Attempts have been made to oxidise indolines with nickel peroxide[185]. The dehydrogenation of 2- and 3-methylindolines by distillation from silver sulphate has been described[189].

The classical dehydrogenating agent $Hg(OCOCH_3)_2$ is relatively unsuitable for the indoline series, since indole compounds are mercurated by mercury salts, probably with formation of 1,3-dimercuri-derivatives[190]. However, in

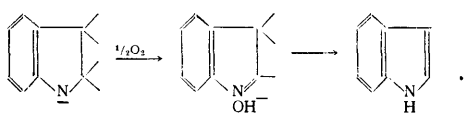
some cases dehydrogenation has been achieved. The dehydrogenation of dihydrolysergic acid derivatives (XXXVIII) with $Hg(OCOCH_3)_2$ has been described[57].

Dinitroindolines can be oxidised to indoles with nitric acid, the oxidation being accompanied by the nitration of the pyrrole ring of indole. 3,5,7-Trinitroindole has been obtained from 5,7-dinitroindoline[125] and 5-nitro and 5,7-dinitroindolecarboxylic acid (XCV) (see p. 756) have been obtained from strychnine.

When 2-methylindoline was heated with concentrated hydrochloric acid at 240°C, 2-methylindole was formed in 28% yield[25]. The mechanism of the process has not been established. Probably atmospheric oxygen is involved. Very interesting data have been obtained on dehydrogenation with atmospheric oxygen in the study of the sodium salts of indolines and azaindolines[22,113]. It has been found that the formation of the *N*-sodio-derivative of indoline in liquid ammonia, toluene, or other solvents is accompanied by the oxidation of this derivative with atmospheric oxygen. Indole, 6-methoxyindole, and 5- and 7-azaindoles and their derivatives have been obtained in high yields from the corresponding indolines[22,113]. *N*-Acyl and *N*-benzyl substituents and halogen atoms are eliminated under the conditions of the reaction. *N*-Metallated secondary amines, for example $(C_2H_5)_2NLi$ or $C_6H_5N(CH_2C_6H_5)Li$, are known to be the most powerful donors of hydride ions and can react as reducing agents for the carbonyl group[191,192]:

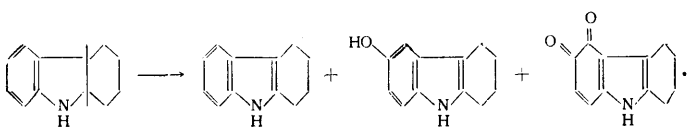
$$(C_6H_5)_2CO + C_2H_5N(Li)CH_2CH_3 \rightleftarrows (C_6H_5)_2CHOLi + C_2H_5N{=}CHCH_3$$
$$(C_6H_5)_2CO + C_6H_5N(Li)CH_2C_6H_5 \rightleftarrows (C_6H_5)_2CHOLi + C_6H_5N{=}CHC_6H_5$$

Evidently, like other *N*-metallated derivatives of secondary amines, the *N*-sodio-derivative of indoline is also a very powerful hydride ion donor, particularly since the removal of a hydride ion leads in this case to indolenine, which is converted into the more stable aromatic indole system:



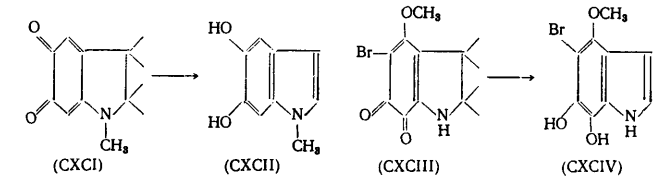
In this case atmospheric oxygen is the hydride ion acceptor[193]. 2,3-Dimethyl-7-ethylindole forms in the reaction of 2,3-dimethylindoline with aluminium anilide and ethylene in aniline at 300°C and 250 atm. It is difficult to say whether dehydrogenation or *C*-alkylation takes place first. Probably the indoline derivative is dehydrogenated as a result of the formation of an $N{-}Al_{1/3}$ derivative which tends to split off a hydride ion like N–Na derivatives[194]. The oxidation of indoline with air in the presence of heavy metal oxides yields indole[195].

When potassium nitrosodisulphonate $(NO)(SO_3K)_2$ is allowed to react with indolines, 5-hydroxyindoles and *o*-quinones of the indole series are formed together with indole derivatives; for example[196]:



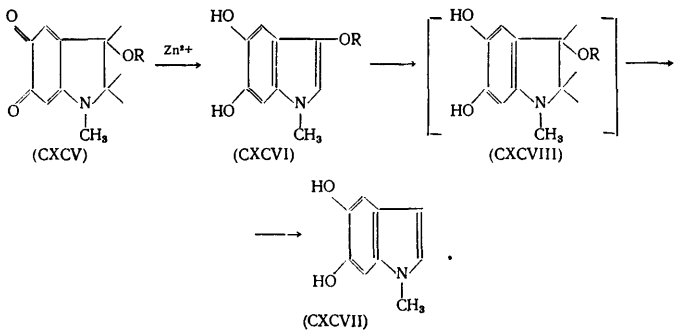
Similar reactions have been achieved with 2-phenylindoline, 2,3-dimethylindoline, and 3-methylindoline[197].

The isomerisation of aminochromes (CXCI) into 5,6-dihydroxyindole derivatives (CXCII) constitutes an unusual reaction involving intramolecular oxidation–reduction[96,198]:



(CXCI) (CXCII) (CXCIII) (CXCIV)

The reaction takes place under the action of Zn^{2+} and Al^{3+} ions. 6,7-Indolinequinones (CXCIII) have been isomerised to 6,7-dihydroxyindoles (CXCIV)[97]. Adrenochrome derivatives (CXCV) give rise to 3,5,6-trihydroxyindoles (CXCVI),[196,199] whose reduction with the Raney nickel alloy yields 5,6-dihydroxyindoles (CXCVII)[96]:

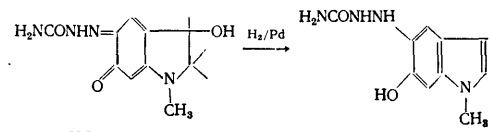


(CXCV) (CXCVI) (CXCVIII)

(CXCVII)

3-Hydroxyindoline derivatives (CXCVIII) probably act as intermediates. The work of Mattlock and Heacock[200] can also be quoted.

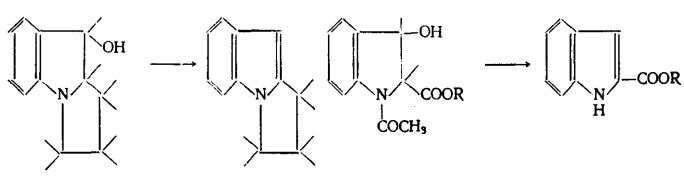
Analogous series of conversions have been described for the semicarbazone of adrenochrome (CIC)[201]:



(CIC)

2. Dehydration of 3-Hydroxyindolines

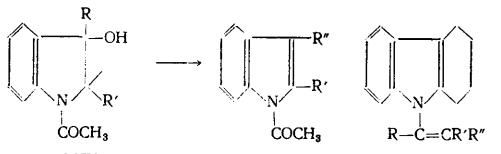
The use of 3-hydroxyindolines for the synthesis of substituted indoles is extremely promising. Unsubstituted 3-hydroxyindoline is relatively stable in the cold to the action of acids and alkalis but on heating to 70°C it is converted into indole[71]. 3-Hydroxy-1-methylindoline is somewhat more stable to heat[71]. 3-Hydroxy-1,2-trimethylindoline (CC) has been converted into the corresponding indole (CCI) by boiling with acetic anhydride[202]:



(CC) (CCI) (CCII) (CCIII)

Derivatives of 1-acetyl-3-hydroxyindoline-2-carboxylic acid (CCII) are converted into derivatives of indole-2-carboxylic acid (CCIII) under the action of mineral acids in

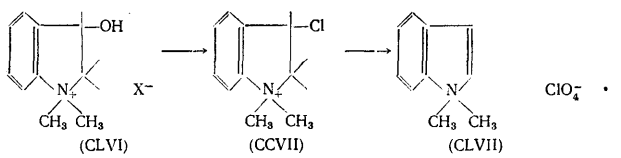
the cold[69] and on heating with alkalis[69]. Under acylation conditions compounds (CCII) give rise to *O*-acyl derivatives. A number of 2,3-disubstituted 1-acetyl-3-hydroxyindolines (CCIV) have been converted into indoles (CCV) by heating with phosphorus pentoxide in benzene[75]:



(CCIV) (CCV) (CCVI)

It has been possible to prepare indole derivatives of the type (CCVI) by heating the corresponding 3-hydroxyindolines (CLVIII) with picric acid in methanol[175].

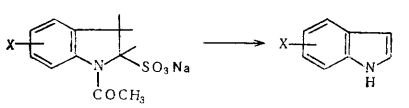
1,1-Dimethylindolium perchlorate (CLVII) has also been synthesised using the corresponding 3-hydroxyindoline derivative (CLVI)[18]:



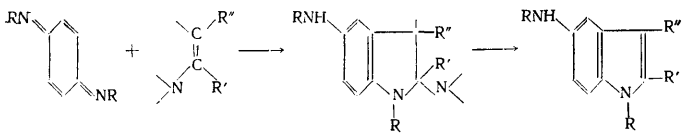
(CLVI) (CCVII) (CLVII)

However, compound (CLVI) could not be dehydrated. The 3-hydroxyindoline (CLVI) was converted into 3-chloro-1,1-dimethylindolinium chloride (CCVII), which was then further converted into the indole derivative (CLVII) by being passed through a column with Amberlite IRA-400. Evidently, the use of 3-hydroxyindolines for the synthesis of substituted indoles requires study of the method of preparation and reactivity of the *trans*- and *cis*-isomers of 2-substituted 3-hydroxyindolines.

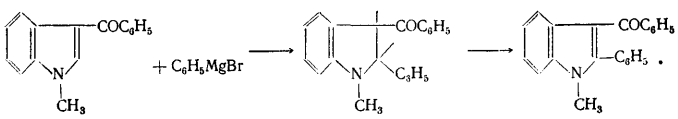
As stated above, derivatives of the sodium salts of indoline-2-sulphonic acid are converted into indoles in an alkaline medium[17]:



The range of substances which can be used for the preparation of compounds of the indole series is not restricted to derivatives of indoline, indoline-2-sulphonic acid, and 3-hydroxyindolines. There are also methods, which have been virtually not investigated, for the synthesis of 2-hydroxy- and 2-amino-indolines and for their conversion into indoles. For example, in the condensation of quinone-imines with enamines, the intermediates are 2-amino-indoline derivatives, which are converted into indoles under very mild conditions[203]:



The conversion of indoles into dihydro-derivatives with the aim of altering the reactivity of substituents in positions 2 and 3 or in order to introduce substituents in position 2 may prove very valuable. Thus 3-benzoyl-1-methyl-2-phenylindoline (CCIX) has been obtained by the reaction of 3-benzoyl-1-methylindole (CCVIII) with phenylmagnesium bromide. Its dehydrogenation over Pd/C gave 3-benzoyl-1-methyl-2-phenylindole (CCX)[204]:



(CCVIII) (CCIX) (CCX)

1. N.N.Suvorov, Zhur.Vses.Khim.Obshch.im.Mendeleeva, 9, 395 (1964).
2. P.Delvigs, W.McIsaac, and R.Taborsky, J.Biol.Chem., 240, 348 (1965).
3. F.W.Straub, "Biochemistry" (Translated into Russian), Budapest, 1963, p.207.
4. J.Bu'Lock, J.Chem.Soc., 52 (1961).
5. G.Kiss and H.Neukom, Helv.Chim.Acta, 49, 989 (1966).
6. M.D.Mashkovskii, "Lekarstvennye Sredstva" (Medicinal Substances), Izd.Meditisina, Moscow, 1967, Part I, p.148.
7. M.D.Mashkovskii, *ibid.*, p.677.
8. T.Shen et al., J.Amer.Chem.Soc., 85, 488 (1963).
9. M.Schach von Wittenau and H.Els, J.Amer.Chem.Soc., 85, 3425 (1963).
10. M.N.Preobrazhenskaya, N.V.Uvarova, E.M.Padeiskaya, G.N.Pershin, and N.N.Suvorov, Dokl.Akad.Nauk SSSR, 172, 870 (1967).
11. J.Webb et al., J.Amer.Chem.Soc., 84, 3185 (1962).
12. Belgian P. 648956 (30th September 1964); Chem.Abs., 63, 18034 (1965).
13. E.Taylor and R.Hendess, J.Amer.Chem.Soc., 87, 1995 (1965).
14. E.Kornfeld, R.Woodward, et al., J.Amer.Chem.Soc., 78, 3087 (1956).
15. A.P.Terent'ev and M.M.Preobrazhenskaya, Dokl.Akad.Nauk SSSR, 118, 302 (1958).
16. T.Kinoshita, H.Inoue, and F.Imoto, J.Chem.Soc.Japan, Pure Chem.Sec., 78, 1372 (1957); Chem.Abs., 54, 491 (1960).
17. J.Thesing, G.Semler, and G.Mohr, Chem.Ber., 95, 2205 (1962).
18. R.Hinmann and J.Lang, J.Org.Chem., 29, 1449 (1964).
19. R.Bent, J.Dessloch, et al., J.Amer.Chem.Soc., 73, 3125 (1951).
20. F.King, J.Barltrop, and R.Walley, J.Chem.Soc., 277 (1945).
21. M.Metayer, Bull.Soc.chim.France, 1093 (1948).
22. L.N.Yakhontov, M.Ya.Uritskaya, and M.V.Rubtsov, Zhur.Obshch.Khim., 34, 1456 (1964).
23. F.Benington, R.Morin, and L.Clark, J.Org.Chem., 24, 217 (1959).
24. H.Adkins and H.Coonradt, J.Amer.Chem.Soc., 63, 1563 (1941).
25. A.Bader, R.Bridgwater, and P.Freeman, J.Amer.Chem.Soc., 83, 3319 (1961).
26. H.Adkins and R.Burks, J.Amer.Chem.Soc., 70, 4174 (1948).
27. A.Smith and J.Utley, Chem.Comm., 427 (1965).
28. M.Robison, F.Butler, and B.Robison, J.Amer.Chem.Soc., 79, 2573 (1957).
29. O.Kruber, Ber., 76, 128 (1943).
30. O.Jackson, Ber., 14, 879 (1881).

31. E. Bamberger and E. Zumbro, Ber., 26, 1285 (1893).
32. M. Wenzig, Annalen, 239, 239 (1887).
33. J. von Braun and G. Kirschbaum, Ber., 45, 1265 (1912).
34. N. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii, Zhur. Obshch. Khim., 34, 1614 (1964).
35. A. Steche, Annalen, 242, 367 (1887).
36. J. Thesing and G. Semler, Annalen, 680, 52 (1964).
37. R. Hinman and E. Whipple, J. Amer. Chem. Soc., 84, 2534 (1962).
38. L. Dolby and G. Gribble, J. Heterocyclic Chem., 3, 124 (1966).
39. F. Anet and J. Muchowski, Chem. and Ind., 81 (1963).
40. P. Julian and H. Printy, J. Amer. Chem. Soc., 71, 3206 (1949).
41. B. P. 726 078 (16th March 1955); Chem. Abs., 51, 1287 (1957).
42. J. von Braun and W. Sobecki, Ber., 44, 2159 (1911).
43. H. Plieninger, H. Bauer, et al., Annalen, 680, 74 (1964).
44. H. Johnson and D. Crosby, J. Org. Chem., 28, 2794 (1963).
45. U. S. P. 3 226 396 (28th December 1965); Chem. Abs., 64, 11 179 (1966).
46. Dutch Appl. 6 405 591 (23rd November 1964); Chem. Abs., 62, 16 198 (1965).
47. Dutch Appl. 6 408 030 (18th January 1965); Chem. Abs., 63, 1770 (1965).
48. H. Plieninger and W. Müller, Chem. Ber., 93, 2029 (1960).
49. F. Kögl and D. Kostermans, Z. physiol. Chem., 235, 201 (1935).
50. B. Blount and R. Robinson, J. Chem. Soc., 3158 (1931).
51. B. P. 948 460 (5th February 1964); Chem. Abs., 60, 14 478 (1964).
52. A. N. Kost, V. N. Eraksina, and E. V. Vinogradova, Zhur. Org. Khim., 1, 129 (1965).
53. J. Fellmann, T. Fujita, and C. Belber, Biochem. Pharmacol., 11, 557 (1962).
54. J. Thesing and F. Schülde, Chem. Ber., 85, 324 (1952).
55. A. Cohen and B. Heath-Brown, J. Chem. Soc., 7179 (1965).
56. H. Hodson and G. Smith, J. Chem. Soc., 1877 (1957).
57. P. Stadler, A. Frey, and F. Troxler, Angew. Chem., 73, 738 (1961).
58. B. Sakurai, Bull. Chem. Soc. Japan, 17, 269 (1942); Chem. Abs., 41, 4486 (1947).
59. S. Sugasawa, J. Satodo, and J. Yanagisawa, Chem. Zentr., II, 1410 (1938).
60. T. Wieland and O. Unger, Chem. Ber., 96, 253 (1963).
61. G. Palazzo and V. Rosnati, Gazzetta, 83, 211 (1953).
62. J. Cook, J. Loudon, and P. McCloskey, J. Chem. Soc., 3904 (1952).
63. J. Cook, J. Loudon, and P. McCloskey, J. Chem. Soc., 1203 (1951).
64. J. Loudon and J. Ogg, J. Chem. Soc., 739 (1955).
65. R. Huisgen, H. König, and A. Lepley, Chem. Ber., 93, 1496 (1960).
66. German P. 515 544; Fortschr. TheerfarbFabr., 17, 638 (1932).
67. German P. 516 676; Fortschr. TheerfarbFabr., 17, 641 (1932).
68. T. Komai, Pharm. Bull. (Japan), 4, 261 (1956).
69. J. Johnson and J. Andreen, J. Amer. Chem. Soc., 72, 2862 (1950).
70. E. Giovannini and T. Lorenz, Helv. Chim. Acta, 40, 1553 (1957).
71. E. Giovannini and T. Lorenz, Helv. Chim. Acta, 41, 113 (1958).
72. E. Giovannini and T. Lorenz, Helv. Chim. Acta, 40, 2287 (1957).
73. A. Hassner and M. Haddadin, J. Org. Chem., 28, 224 (1963).
74. P. Kornmann, Bull. Soc. chim. France, 730 (1958).
75. J. Pretka and H. Lindwall, J. Org. Chem., 19, 1080 (1954).
76. C. Nenitzescu and Dan Raileanu, Chem. Ber., 91, 1141 (1958).
77. B. P. 919 864 (27th February 1963); Chem. Abs., 59, 8710 (1963).
78. A. Katritzky (Editor), "Advances in Heterocyclic Chemistry", New York–London, 1963, Vol. 2, p. 301.
79. T. Young, J. Org. Chem., 27, 507 (1962).
80. R. Acheson, R. Feinberg, and A. Hands, J. Chem. Soc., 526 (1964).
81. T. Leśniak, Roczniki Chem., 37, 499 (1963).
82. G. Bennett and M. Hafez, J. Chem. Soc., 287 (1941).
83. U. S. P. 3 117 131 (7th January 1964); Chem. Abs., 60, 14 479 (1964).
84. U. S. P. 3 102 120 (27th August 1963); Chem. Abs., 60, 2900 (1964).
85. T. Leśniak, Roczniki Chem., 36, 1737 (1962).
86. German P. 606 027 (23rd November 1934); Fortschr. TheerfarbFabr., 21, 360 (1937).
87. S. Sabetay, J. Bleger, and Y. Lestrange, Bull. Soc. chim. France, 49, 3 (1931).
88. R. Huisgen and H. König, Angew. Chem., 69, 268 (1957).
89. R. Huisgen and H. König, Chem. Ber., 92, 203 (1959).
90. B. Hrutford and J. Bunnett, J. Amer. Chem. Soc., 80, 2021 (1958).
91. M. Julia and H. Gaston-Breton, Bull. Soc. chim. France, 1335 (1966).
92. J. von Braun, K. Heider, and E. Müller, Ber., 50, 1643 (1917).
93. J. Hyre and A. Bader, J. Amer. Chem. Soc., 80, 437 (1958).
94. J. Harley-Mason, J. Chem. Soc., 1277 (1950).
95. Finnish P. 33 069 (14th September 1963); Chem. Abs., 61, 8280 (1964).
96. J. Bu'Lock and J. Harley-Mason, J. Chem. Soc., 2248 (1951).
97. S. Senoh and B. Witkop, J. Amer. Chem. Soc., 81, 6231 (1959).
98. R. Heacock, B. Witkop, et al., J. Amer. Chem. Soc., 85, 1825 (1963).
99. R. Heacock and B. Scott, Canad. J. Chem., 38, 508 (1960).
100. U. S. P. 3 098 858 (23rd July 1963): Chem. Abs., 60, 506 (1964).
101. C. Koelsch and C. Stephens, J. Amer. Chem. Soc., 72, 2209 (1950).
102. L. N. Yakhontov and M. V. Rubtsov, Zhur. Obshch. Khim., 30, 3300 (1960).
103. L. N. Yakhontov and M. V. Rubtsov, Zhur. Obshch. Khim., 34, 493 (1964).
104. L. N. Yakhontov and M. V. Rubtsov, Zhur. Obshch. Khim., 34, 1129 (1964).
105. L. N. Yakhontov and M. V. Rubtsov, Zhur. Obshch. Khim., 31, 3281 (1961).
106. L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, Zhur. Obshch. Khim., 34, 1449 (1964).
107. L. N. Jachontov, Pharmazie, 18, 317 (1963).
108. L. N. Yakhontov and M. V. Rubtsov, "Biologicheski Aktivnye Soedineniya" (Biologically Active Compounds), "Sbornik ZhOKh" (Journal of General Chemistry Symposium), Moscow, 1965, p. 90.
109. L. Ya. Yakhontov, Doctoral Thesis, All-Union Ordzhonikidze Institute of Chemistry and Pharmacology, Moscow, 1966.
110. L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, Khim. Geterotsikl. Soed., 59 (1966).
111. L. N. Yakhontov, D. M. Krasnokutskaya, and M. V. Rubtsov, Khim. Geterotsikl. Soed., 66 (1966).
112. L. N. Yakhontov, M. S. Sokolova, and M. V. Rubtsov, Khim. Geterotsikl. Soed., 74 (1966).
113. L. N. Yakhontov, M. Ya. Uritskaya, and M. V. Rubtsov, Khim. Geterotsikl. Soed., 918 (1965).
114. L. N. Yakhontov and M. V. Rubtsov, Zhur. Obshch. Khim., 32, 432 (1962).

115. German P. 1 100 030 (24th August 1961).
116. German P. 1 109 698 (14th May 1959); Chem.Abs., 56, 8727 (1962).
117. A.P.Terent'ev and M.N.Preobrazhenskaya, Zhur.Obshch. Khim., 30, 1218 (1960).
118. F.Benington and R.Morin, J.Org.Chem., 27, 142 (1962).
119. A.P.Terent'ev, M.N.Preobrazhenskaya, A.S.Bobkov, and G.M.Sorokina, Zhur.Obshch.Khim., 29, 2541 (1959).
120. J.von Braun, A.Garbowsky, and M.Rawicz, Ber., 46, 3169 (1913).
121. J.von Braun and H.Ritter, Ber., 55, 3802 (1922).
122. E.Bamberger and H.Sternitzki, Ber., 26, 1291 (1893).
123. A.N.Kost, L.G.Yudin, and V.A.Budylin, Khim.Geterotsikl.Soed., 40 (1966).
124. A.N.Kost, L.G.Yudin, and V.A.Budylin, Zhur.Vses. Khim.Obshch.im.Mendeleeva, 10, 474 (1965).
125. W.Noland and K.Rush, J.Org.Chem., 29, 947 (1964).
126. W.Gall, B.Astill, and V.Boekelheide, J.Org.Chem., 20, 1538 (1955).
127. J.Gurney and S.Plant, J.Chem.Soc., 1314 (1927).
128. J.Massey and M.Tomlinson, J.Chem.Soc., 3324 (1931).
129. A.P.Orekhov, "Khimiya Alkaloidov" (The Chemistry of the Alkaloids), Moscow, 1955, p.612.
130. A.Richardson, J.Org.Chem., 30, 2589 (1965).
131. A.P.Terent'ev and M.N.Preobrazhenskaya, Zhur.Obshch. Khim., 29, 317 (1959).
132. G.Plancher and C.Ravenna, Atti R.Accad.Lincei, Rendiconte, [5], 14, i, 632 (1905); Chem.Zentr., 11, 335 (1905).
133. J.von Braun, Ber., 47, 492 (1914).
134. R.Ikan, E.Hoffmann, E.Bergmann, and A.Galun, Israel J.Chem., 2, 37 (1964).
135. R.Hunt and R.Rickards, J.Chem.Soc., 344 (1966).
136. S.Plant and M.Tomlinson, J.Chem.Soc., 3324 (1931).
137. A.N.Kost, L.G.Yudin, V.A.Budylin, and N.G.Yaryshev, Khim.Geterotsikl.Soed., 632 (1965).
138. M.N.Preobrazhenskaya, M.V.Fedotova, N.P.Sorokina, O.B.Ogareva, N.V.Uvarova, and N.N.Suvorov, Zhur. Obshch.Khim., 34, 1310 (1964).
139. German P. 1 169 450 (6th May 1964); Chem.Abs., 61, 4316 (1964).
140. A.P.Terent'ev and M.N.Preobrazhenskaya, Dokl.Akad. Nauk SSSR, 121, 481 (1958).
141. U.S.P. 3 083 207 (26th March 1963); Chem.Abs., 59, 8706 (1963).
142. A.P.Terent'ev, Ko Pang-lun, and M.N.Preobrazhenskaya, Zhur.Obshch.Khim., 32, 177 (1962).
143. Belgian P. 615 562 (13th April 1962); Chem.Abs., 58, 5817 (1963).
144. B.P. 747 264 (28th March 1956); Chem.Abs., 51, 1286 (1957).
145. U.S.P. 2 809 974 (15th October 1957); Chem.Abs., 52, 9217 (1958).
146. H.Rapoport and J.Tretter, J.Org.Chem., 23, 248 (1958).
147. B.Astill and V.Boekelheide, J.Org.Chem., 23, 316 (1958).
148. J.Shavel, M.Strandtmann, and M.Cohen, J.Amer.Chem. Soc., 84, 881 (1962).
149. A.P.Terent'ev, M.N.Preobrazhenskaya, and G.M.Sorokina, Zhur.Obshch.Khim., 29, 2875 (1959).
150. D.Mitchell and S.Plant, J.Chem.Soc., 1295 (1936).
151. French P. 48 074 (30th January 1936); Chem.Zentr., I, 1668 (1938).
152. H.Behringer and P.Duesberg, Chem.Ber., 96, 377 (1963).
153. A.P.Terent'ev, Ko Pang-lun, and M.N.Preobrazhenskaya, Zhur.Obshch.Khim., 32, 1335 (1962).
154. U.S.P. 2 775 593 (25th December 1956); Chem.Abs., 51, 8804 (1957).
155. German P. 645 880 (11th December 1935); Chem.Zentr., II, 3078 (1937).
156. J.Thesing, S.Klüssendorf, P.Ballach, and H.Mayer, Chem.Ber., 88, 1295 (1955).
157. J.Thesing, H.Mayer, and S.Klüssendorf, Chem.Ber., 87, 901 (1954).
158. A.N.Kost, A.K.Sheinkman, and N.F.Kazarinova, Khim. Geterotsikl.Soed., 722 (1966).
159. A.K.Sheinkman, A.N.Kost, and R.D.Bodnarchuk, Khim. Geterotsikl.Soed., 183 (1967).
160. J.von Braun, K.Heider, and W.Wyczatkowska, Ber., 51, 1215 (1918).
161. A.N.Kost, L.G.Yudin, and A.P.Terent'ev, Zhur.Obshch. Khim., 29, 1949 (1959).
162. H.Fales, L.Giuffrida, and W.Wildman, J.Amer.Chem. Soc., 78, 4145 (1956).
163. A.N.Kost, L.G.Yudin, Yu.A.Berlin, and A.P.Terent'ev, Zhur.Obshch.Khim., 29, 3820 (1959).
164. L.G.Yudin, S.A.Popravko, and A.N.Kost, Zhur.Obshch. Khim., 32, 3586 (1962).
165. A.N.Kost, L.G.Yudin, and S.A.Popravko, Zhur.Obshch. Khim., 32, 1544 (1962).
166. H.Rapoport and J.Tretter, J.Amer.Chem.Soc., 80, 5574 (1958).
167. M.Robison, B.Robison, and F.Butler, J.Amer.Chem.Soc., 81, 743 (1959).
168. A.D.Neklyudov, L.A.Shchukina, and N.N.Suvorov, Zhur. Obshch.Khim., 37, 797 (1967).
169. V.S.Fedorova, Candidate's Thesis, All-Union Ordzhonikidze Institute of Chemistry and Pharmacology, Moscow, 1966.
170. U.S.P. 3 093 632 (1st June 1963); Chem.Abs., 59, 12 771 (1963).
171. U.S.P. 2 909 523 (20th October 1959); Chem.Abs., 54, 7747 (1960).
172. J.Wright, J.Amer.Chem.Soc., 71, 1028 (1949).
173. F.A.Trofimov, A.N.Kost, N.G.Tsyshkova, K.S.Shadurskii, and E.V.Vinogradova, Khimiko-Farmatsevt.Zhur., 22 (1967).
174. E.V.Vinogradova, A.N.Kost, V.N.Mitropol'skaya, and A.P.Terent'ev, Zhur.Obshch.Khim., 33, 1556 (1963).
175. H.Rapoport, R.Windgassen, N.Hughes, and T.Onak, J.Amer.Chem.Soc., 82, 4404 (1960).
176. U.S.P. 2 937 173 (17th May 1960); Chem.Abs., 54, 19 727 (1960).
177. M.N.Preobrazhenskaya and N.N.Suvorov, Zhur.Obshch. Khim., 31, 2839 (1961).
178. M.N.Preobrazhenskaya and N.N.Suvorov, Zhur.Obshch. Khim., 30, 2434 (1960).
179. M.N.Preobrazhenskaya, M.M.Vigdorchik, and N.N.Suvorov, Symposium, "Azot-Soderzhashchie Geterotsikly" (Nitrogen-Containing Heterocycles), Riga, 1967, p.45.
180. M.N.Preobrazhenskaya, M.M.Vigdorchik, and N.N.Suvorov, Symposium, "Biologicheski Aktivnye Soedineniya" (Biologically Active Compounds), Moscow–Leningrad, 1965, p.60.
181. M.N.Preobrazhenskaya, L.A.Savel'eva, and N.N.Suvorov, Khim.Geterotsikl.Soed.(1967), in the press.
182. M.N.Preobrazhenskaya and N.N.Suvorov, Zhur.Obshch. Khim., 35, 893 (1965).
183. W.Carpenter, M.Grant, and H.Snyder, J.Amer.Chem. Soc., 82, 2739 (1960).
184. L.M.Jackman, in "Advances in Organic Chemistry" (Translated into Russian), Inostr.Lit., Moscow, 1964, p.328.
185. A.Jansen, J.Johnson, and J.Surtees, J.Chem.Soc.Suppl.I, 5573 (1964).
186. M.N.Preobrazhenskaya, M.M.Vigdorchik, and N.N.Suvo-

rov, Tetrahedron, 23 (1967), in the press.
187. H.Adkins and L.Lundsted, J.Amer.Chem.Soc., 71, 2964 (1949).
188. E.Pratt and T.McGovern, J.Org.Chem., 29, 1540 (1964).
189. M.Kann and J.Tafel, Ber., 27, 826 (1894).
190. G.Kirby and S.Shah, Chem.Comm., 381 (1965); Chem. Abs., 63, 14675 (1965).
191. G.Wittig, H.-J.Schmidt, and H.Renner, Chem.Ber., 95, 2377 (1962).
192. G.Wittig and H.Frommeld, Chem.Ber., 97, 3441 (1964).
193. L.N.Yakhontov, M.Ya.Uritskaya, and M.V.Rubtsov, Zhur. Org.Khim., 1, 2029 (1965).
194. R.Stroh and W.Hahn, Annalen, 623, 176 (1959).
195. T.Leśniak, Roczniki Chem., 37, 347 (1963).
196. H.-J.Teuber and G.Staiger, Chem.Ber., 87, 1251 (1954).
197. H.-J.Teuber and G.Staiger, Chem.Ber., 89, 489 (1956).
198. R.Heacock and G.Mattlock, Canad.J.Chem., 41, 139 (1963).
199. R.Heacock and B.Scott, Experientia, 17, 347 (1961).
200. G.Mattlock and R.Heacock, Canad.J.Chem., 44, 565 (1966).
201. J.Iwao, Pharm.Bull(Japan), 4, 244 (1956); Chem.Abs., 51, 8065 (1957).
202. E.Laschtuvka and R.Huisgen, Chem.Ber., 93, 81 (1960).
203. G.Domschke, G.Heller, and U.Natzeck, Chem.Ber., 99, 939 (1966).
204. J.Szmuszkowicz, J.Org.Chem., 27, 511 (1962).

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THE ROLE OF THE STATIONARY PHASE IN GAS-LIQUID CHROMATOGRAPHY AND METHODS OF SORBENT SELECTION

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The possibility of controlling the selectivity of the column is one of the principal advantages of chromatography (in the first place gas-liquid chromatography) over other methods for the separation of substances, the nature of the stationary phase constituting the main factor which determines the sequence of the elution of the components from the column and the relative elution times of the peak maxima [1-3]. Furthermore, the effect of the stationary phase extends also to the mode of spreading of the zones.

1. SELECTIVITY OF THE STATIONARY PHASE AND ITS RELATION TO THE DEGREE OF SEPARATION AND THE ERROR OF THE ANALYSIS

An investigator using gas chromatography is able to solve the following groups of problems: (a) qualitative analysis of the mixture; (b) quantitative analysis of the mixture; (c) isolation of a certain amount of pure substances or fractions; (d) determination of certain physicochemical characteristics of the test system.

In qualitative analysis the degree of separation must be sufficient to obtain in the chromatogram separate peak maxima of the individual components and the displacement of these maxima under the influence of the neighbouring components should be fairly small. In quantitative analysis it is important that the analytical error associated with the quality of the separation should be within the permissible limits.

In preparative chromatography the main requirement is to ensure the necessary purity of the fraction for a sufficiently large sample volume, which is also related to the degree of separation. Finally, in the determination of physicochemical characteristics the requirements are determined by the actual problem. Regardless of the aim of the chromatographic analysis, it is desirable that the separation should be attained in a short time.

The ratio of the distance between the ordinates of the maxima to the sum of the peak widths may serve as a measure of the separation of two components. Thus the degree of separation K is defined by the formula [1]:

$$K = \frac{\Delta l}{\mu_{0.5(1)} + \mu_{0.5(2)}},$$

where Δl is the distance between the ordinates of the maxima and $\mu_{0.5(1)}$ and $\mu_{0.5(2)}$ are the peak half-widths [1,4].
K can be found from the expression

$$K = \frac{V_{R_2} - V_{R_1}}{\omega_{0.5(1)} + \omega_{0.5(2)}} = 0.212 K_c \sqrt{n}, \quad (2)$$

where V_{R_1} and V_{R_2} are the retention volumes of the components, $\omega_{0.5(1)}$ and $\omega_{0.5(2)}$ the zone widths expressed in volume units, $K_c = 2(V_{R_2} - V_{R_1})/(V_{R_2} + V_{R_1})$ is the selectivity coefficient of the column, and $n = 5.55(V_R/\omega_{0.5})^2$ the number of theoretical plates characterising the efficiency of the column. The coefficient K_c depends not only on the nature of the stationary phase but also on the fraction of the column volume occupied by this phase. This follows from the equation

$$\frac{1}{K_c} = \frac{1}{k_c} + \frac{V_0}{V_{R_2} - V_{R_1}},$$

where $k_c = 2(V'_{R_2} - V'_{R_1})/(V'_{R_2} + V'_{R_1})$ is the selectivity coefficient of the stationary phase, V'_{R_1} and V'_{R_2} are the reduced retention volumes of the components, and V_0 is the gas volume (the retention volume of the non-sorbed substance).