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Heterocycles Containing the Indole Residue

G.I.Zhungietu and G.N.Dorofeenko

The review describes the latest advances in the synthesis of heterocyclic compounds containing the indolyl residue, among which many physiologically active substances have been found. It is the first attempt at a general and systematic account of the extensive literature data on this subject.

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I. INTRODUCTION

The pronounced physiological activity of many indole derivatives such as reserpine, serotonin, tryptamine, tryptophan, lysergic acid, etc. has aroused an unflagging interest among chemists and pharmacologists in the chemistry of indole over a period which now runs into several decades. Compounds in which the indole ring is condensed with heterocyclic compounds (numerous derivatives of carbolines, eserine, etc.) are of the greatest interest. However, during recent years there has been a considerable growth of interest in heterocyclic compounds containing the indole residue. Here one should include numerous indolyl derivatives of pyridine, piperidine, pyrrolidine, piperazine, etc. Many physiologically active compounds have been found among them. Such compounds have been isolated also from natural products—for example, the antiobiotics indolemycin and pimprinine.

Extensive data have accumulated in this field, however, they are widely scattered and hitherto have not been described systematically. Therefore we attempted to fill this gap bearing in mind that a review of this kind may prove useful in the choice of a further course of study on the preparation of new pharmacologically active indole derivatives.

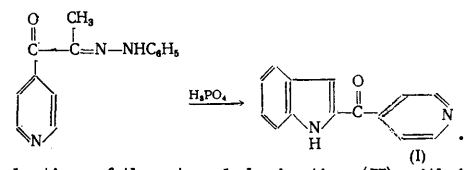
II. PYRIDINE DERIVATIVES OF INDOLE

Among indolyl derivatives of heterocycles, pyridine and piperidine derivatives probably play the most important role. The high interest in these compounds is partly due to the fact that among them many pharmacologically valuable preparations have been found and also because of their suitability as starting materials for studies on the synthesis and preparation of many indole alkaloids.

1. Indolylpyridines

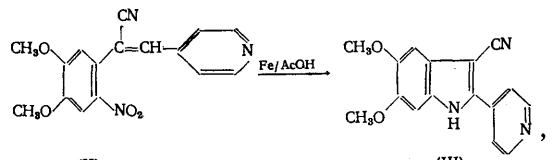
The Fischer indole synthesis is widely used for the preparation of indolylpyridines. For example, the cyclisation of the phenylhydrazones of 2-acetylpyridine in the presence of polyphosphoric acid leads to 2-(2-pyridyl)-indole [1,2]. 2-(3-Pyridyl)indole [1-4], 2-(4-pyridyl)indole [1,3], and 2-(5-ethyl-2-pyridyl)indole [1] were synthesised in the same way. Some of these compounds exhibit a diuretic activity and others may be used to reduce aldosterone concentration or in the treatment of cardiovascular diseases [5]. In addition, certain chemical reactions of the indolylpyridines synthesised have been investigated, such as, for example, their conversion into Mannich bases and cyanoethylation [1].

2-Isonicotinoylindole(I) was also synthesised by the Fischer reaction [6]:



(I)

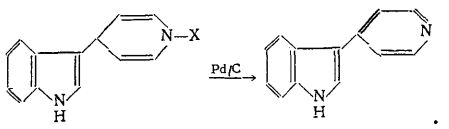
The reduction of the styryl derivative (II) with iron in acetic acid constitutes a very convenient synthesis of 5,6-dimethoxy-2-(4-pyridyl)indole-3-carbonitrile (III),



(II) (III)

and also of its thiophen and furan analogues [7].

3-(4-Pyridyl)indole (IV) is formed as a result of the debenzoylation and simultaneous dehydration of the *N*-benzoyl derivative (V) with atmospheric oxygen [8,9]. It can be obtained in large amounts by refluxing compound (V) in phenyl ether in the presence of palladised charcoal and one equivalent of dibenzylamine [10]:

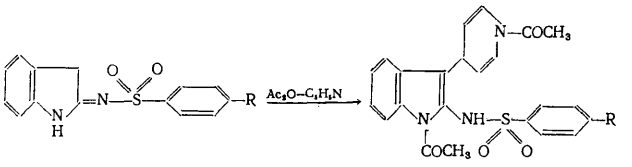


(V, X=C_6H_5CO)
(VI, X=CN)

(IV)

Compound (V) is readily formed from indole, pyridine, and benzoyl chloride [8]. Products with a similar structure are formed by quinoline, isoquinoline, phenanthroline, and scatole [9].

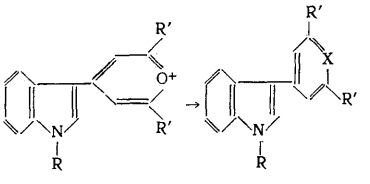
Another example of this kind of reaction is the formation of dihydropyridines of type (VII) from indole and tosyl azide or *N*-acetylsulphanilyl azide [11]:



(VII, R=CH_3, $NHCOCH_3$)

The benzoyl derivative (V) reacts with benzaldehyde to form diphenyltetrahydroindolocarbazole [12], while its analogue (VI) decomposes with formation of indole on treatment with 2% NaOH in aqueous alcohol [13].

The reaction, proposed by Dorofeenko et al. [14], of ammonia with indolylpyrylium salts (VIII), obtained by the interaction of (3-indolyl)-1,5-diketones with triphenylmethyl perchlorate, constitutes a very convenient method for the preparation of 4-(3-indolyl)pyridines (IX) containing various substituents in the pyridine ring. Treatment of compound (VIII) with tri(hydroxymethyl)phosphine in pyridine yields the phosphorus analogues (IX)—derivatives of indolylphosphabenzene (X): [15]

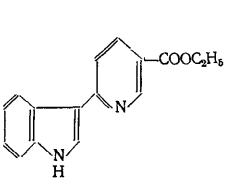


(VIII)

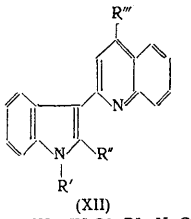
(IX, X=N)
(X, X=P)

This reaction may be of definite interest, since the salts (VIII) are readily formed in high yield also on treatment of *N*-substituted indoles with two moles of a 2,6-diarylpyrylium salt in dimethylformamide (DMF). [16]

Activated pyridine derivatives, such as the *N*-oxides, have been recommended as convenient starting materials for the synthesis of pyridine derivatives of indole. 2-(3-Indolyl)-5-ethoxycarbonylpyridine (XI) is formed from indole and the *N*-oxide of ethyl nicotinate in the presence of benzoyl chloride [17], while quinoline *N*-oxides yield a series of 2-(3-indolyl)quinoline derivatives of type (XII). [17] These reactions have been widely investigated in the interaction between indole, 2-phenylindole, and 1-methyl-2-phenylindole with *N*-acyloxyquinolinium, *N*-acyloxyisoquinolinium, and *N*-acyloxylepidinium derivatives [18]:



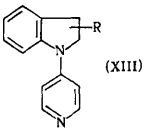
(XI)



(XII)

R′=H, CH_3, CH_3CO; R″=H, C_6H_5; R‴=H,Cl.

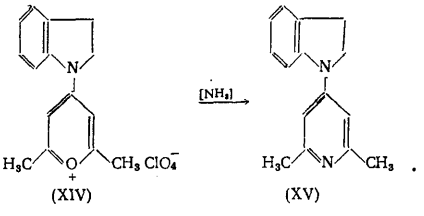
A series of pyridine derivatives of indoline have been described. For example, *N*-(4-pyridyl)indolines of type (XIII) can be readily obtained by fusing together the hydrochlorides of 2,3-dihydroindoles with *N*-(4-pyridyl)-pyridinium chloride [19,20]:



(XIII)

N-(5-Nitro-2-pyridyl)indolines, which have been recommended as polymer stabilisers, can be synthesised by the reaction of 2-chloro-5-nitropyridine with indolines at 80–110°C. [21]

1-(2,6-Dimethyl-4-pyridyl)indoline (XV) is formed in a high yield when 4-(1-indolinyl)-2,6-dimethylpyrylium perchlorate (XIV), obtained from indoline and 4-methoxy-2,6-dimethylpyrylium perchlorate, is treated with ammonium acetate or carbonate [22].



(XIV)

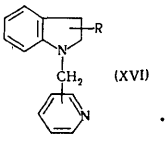
(XV)

The synthesis of indolines containing the isoquinoline residue by the interaction of benzoylisoquinolinium chloride with *N*-substituted indolines was described recently [23]. 1-Acylpyridinium salts are converted by the same reaction into 5-pyridylindolines [24] and 1-acylquinolinium salts give rise to 5-(2-quinolyl)indolines [25].

Many of the pyridine derivatives of indolines suppress the motor capacity of animals stimulated by amphetamine, suppress the orientation reflex, and sharply prolong the duration of Nembutal narcosis in mice, while exhibiting a moderate antiserotonin activity [19].

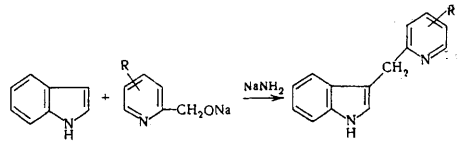
2. Indolylmethylpyridines

Pyridylmethylindolines (XVI) are obtained by the reaction of chloromethylpyridines with indoline [19]:



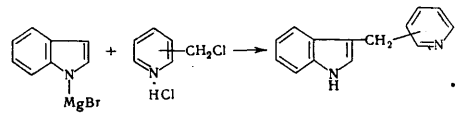
(XVI)

Other methods of synthesis are also known. One of these consists in the interaction of sodium salts of 2-hydroxymethylpyridines with indole [26]:



(R = 3-CH_3, 5-CH_3, 6-CH_3, 5-C_2H_5)

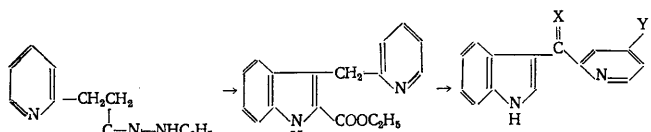
Another involves the interaction of indolylmagnesium bromide with chloromethylpyridine hydrochloride [27]:



Certain 2-scatylpyridines (and their iodides) exhibit anticholinergic and antihistamine activities [28].

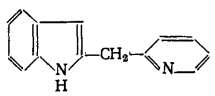
The interaction of indole-3-aldehyde with 2-pyridyllithium leads to the formation of (3-indolyl)(2-pyridyl)methanol (XVII). [29] The same compound is formed when indolylmagnesium halides react with 2-formylpyridine at −25 °C, together with a small amount of di-indolylpyridylmethane [30]. The corresponding carbinols form 4-formylpyridine and 3-formylisoquinoline [30].

2-Scatylpyridine can be readily obtained by the Fischer reaction [31]:



(XVII, X=H,OH, Y= H)
(XVIII, X=H_2, Y=H)
(XX, X=O, Y=H)
(XXI, X=H_2, Y=CH_3)

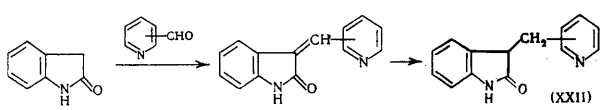
It has also been shown [31] that 2-scatylpyridine (XVIII) rearranges in the presence of $AlCl_3$ to 2-(2-indolylmethyl)pyridine (XIX) and on oxidation with selenium dioxide is converted into 3-indolyl-2-pyridyl ketone (XX).



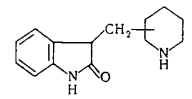
(XIX)

The hydrogenation of 4-methyl-2-scatylpyridine (XXI) methiodide and phenylethiodide, obtained by the Fischer method from the phenylhydrazone of (4-methyl-2-pyridyl)propionaldehyde, leads to tetrahydropyridine, which is cyclised under the influence of phosphoric acid to indolo-[2,3-*f*]morphan. [32] These compounds exhibit analgesic, expectorant, and anti-inflammatory activity.

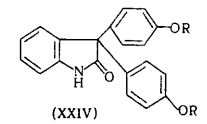
Oxindoles containing pyridylmethyl residues (XXII) are formed when oxindole is condensed with formylpyridines and the products are hydrogenated in ethyl acetate at 20 °C in the presence of palladium on charcoal [33]. Further hydrogenation in ethyl acetate at 75 °C or in acetic acid gives piperidine derivatives (XXIII). The latter exhibit a marked cholinergic effect [33].



(XXII)



(XXIII)



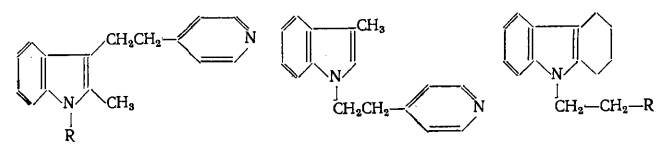
(XXIV)

[R = 3-pyridinoyl or (3-pyridyl)acryloyl]

Pyridine derivatives of oxindole of type (XXIV) were found to have a laxative effect [34].

3. Indolylethylpyridines

The pyridylethylation reaction has led to the wide employment of indole for the synthesis of pyridine derivatives [35]: in an acid medium it leads to 3-pyridylethylindole derivatives and in an alkaline medium it involves the indole nitrogen atom [36]. 4-Vinylpyridine reacts with 2-methylindole in boiling acetic acid to form 2-methyl-3-(4-pyridylethyl)indole (XXV) in 54% yield, while 1-ethylindole gives under the same conditions 1-ethyl-3-pyridylindole [37]. In the presence of sodium ethoxide, scatole reacts with 4-vinylpyridine to form 3-methyl-1-pyridylethylindole (XXVI) in 38% yield [37]. The same product is obtained albeit in an insignificant yield on prolonged refluxing of the reactants in acetic acid [37]. In the indole series, the same type of behaviour may be noted also for the Michael reaction, where, for example, acrylonitrile reacts with 2-phenylindole to form 1-cyanoethyl-2-phenylindole when catalysed by bases and 3-cyanoethyl-2-phenylindole when catalysed by acids [38]:



(XXV, R=H)
[XXIX, R = 2-(4-pyridyl)ethyl]

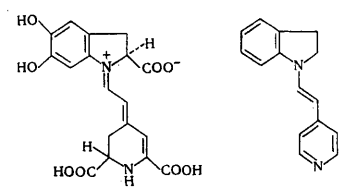
(XXVI)

(XXVII, R = 4-pyridyl)
(XXVIII, R = 2-pyridyl)

It was found that 3-(4-pyridylethyl)indole may increase the stimulation of motor activity by amphetamine [37]. 1-Pyridyl-2,3-tetramethyleneindoles (XXVII) and (XXVIII) and their salts stimulate the activity of the central nervous system [39].

Kost and coworkers [40] suggested that a higher-boiling alcohol be employed for the pyridylethylation reaction and obtained a greater number of pyridylethyl derivatives of indole when the reaction was carried out in hexyl alcohol.

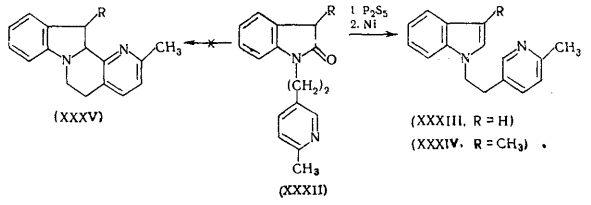
Pyridylethylation of indolines in acetic acid leads to *N*-pyridylethylindolines [19,41]. Analogues of these products have been detected in natural products, for example betanidine (XXX). [42] A simpler analogue (XXXI) was obtained by the condensation of *N*-formylindoline with γ-picoline. [43] Total synthesis of neobetanidine and neobetenamine-derivatives has been achieved [44]:



(XXX)

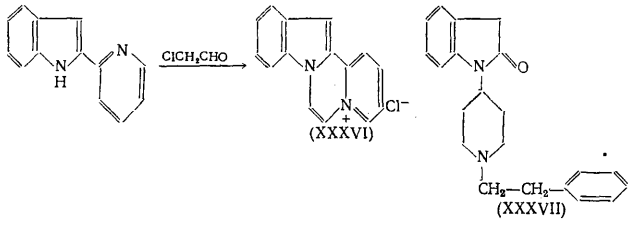
(XXXI)

The 1-(3-pyridyl)ethyl derivative (XXXIII) can be obtained via the corresponding oxindole derivative (XXXII, R = H):[45]



(XXXV) (XXXII) (XXXIII, R = H) (XXXIV, R = CH_3)

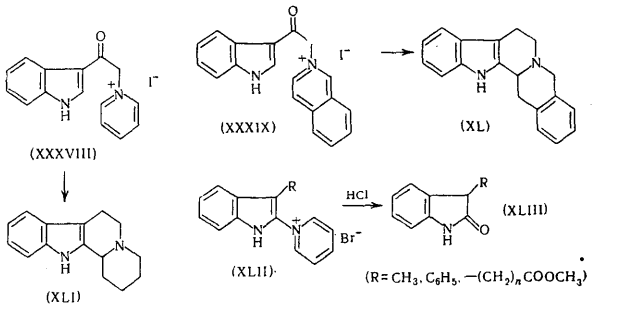
Compound (XXXIV) was synthesised according to the same scheme[46]. Certain reactions of compounds (XXXIII) and (XXXIV) have been investigated: bromination, nitration, the Mannich reaction, and formylation[41]. Compound (XXXII) could not be cyclised to the eburnamenine derivative (XXXV).[47] Its tetracyclic analogue (XXXVI) can be synthesised in a slightly different way[48]:



(XXXVI) (XXXVII)

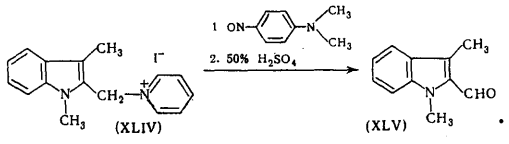
Biological tests showed that many bispyridylethyl derivatives of indole of type (XXIX) and also their piperidine analogues exhibit anticonvulsant activity[49]. The methiodide of compound (XXXII, R = CH_3) has a very pronounced curarelike activity at dilutions of the order of 1 : 10 000, the reactivity being extremely specific, since it disappears in the absence of the methyl group at the 3-carbon atom of the indole ring[45]. Oxindole derivatives of type (XXXVII) and their salts with non-toxic acids were found to have an analgesic activity and absorb ultraviolet light, which makes them valuable for protection from sunlight[50].

Certain indacylpyridium salts (XXXVIII), formed in the interaction between indolylmagnesium halides and iodoacetyl chloride followed by condensation with pyridine[51], should probably be also included in the section on pyridylethylindole compounds. They are obtained in better yields and in only one stage from 3-acetylindole, iodine, and a pyridine (or quinoline and isoquinoline) base via the King reaction[52,53]. These compounds are of interest also as starting materials for the synthesis of many indole alkaloids. In particular, the reduction of the salts (XXXIX) with lithium aluminium hydride and subsequent cyclisation constitute the simplest method for the formation of the yohimbine system (XL).[53] The reduction can also be carried out with sodium borohydride[54]. For example, compound (XLI) was synthesised in this way[55]:



(XXXVIII) (XXXIX) (XL) (XLI) (XLII) (XLIII) (R = CH_3, C_6H_5, $-(CH_2)_nCOOCH_3$)

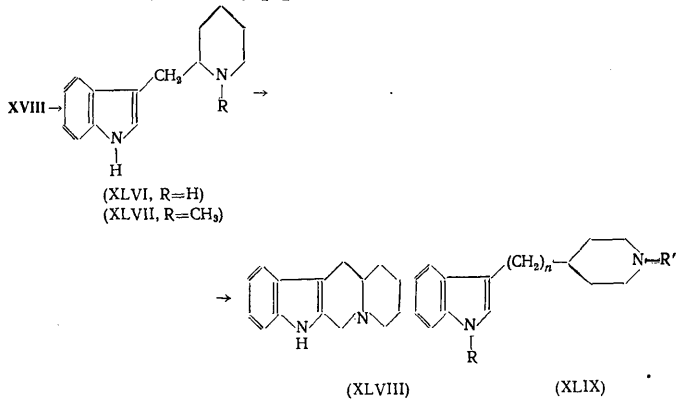
Many *N*-indolylpyridinium salts (XLII) are obtained by the bromination of indoles in the presence of pyridine bases and are then converted into oxindole derivatives (XLIII).[56-58] The salt (XLIV), formed when 1,2,3-trimethylindole is treated with iodine in pyridine, is subsequently converted into 2-formyl-1,3-dimethylindole (XLV):[59]



(XLIV) (XLV)

III. PIPERIDINE DERIVATIVES OF INDOLE

The principal method for the preparation of indolylpiperidines is reduction of the corresponding pyridines. When the pyridine derivative (XVIII) is hydrogenated in the presence of a palladium catalyst in an alcohol–acetic acid mixture, 2-scatylpiperidine (XLVI) is formed:



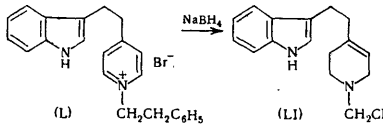
(XLVI, R=H) (XLVII, R=CH_3) (XLVIII) (XLIX)

It is methylated to compound (XLVII) and on treatment with formaldehyde and formic acid is converted into indolohexahydroquinolizine (XLVIII).[29] 1-Methyl-2-scatylpiperidine (XLVII) can also be obtained by the condensation of isatin with α-picoline and the reduction of the resulting dioxindole with sodium in butanol followed by *N*-methylation[60].

The hydrogenation of (3-indolyl)(4-pyridyl)methanol in the presence of Adams catalyst leads to 4-scatylpiperidine (XLIX, n = 1, R,R′ = H), which may be methylated with chloral[61] to the *N*-methyl derivative (XLIX, n = 1, R = H, R′ = CH_3).[30]

Catalytic hydrogenation of pyridylethylindoles in the presence of a platinum catalyst in glacial acetic acid or in aqueous alcoholic HCl leads to the formation of the corresponding piperidines (XLIX, n = 2, R = H or CH_3, R′ = H, CH_3, $C_6H_5CH_2$, etc.). In tests on mice these compounds were found to have an analgesic activity comparable with that of morphine[63]. An approximately similar activity is observed for compounds containing the phenylethyl, benzyl, and phenylacyl residues at the piperidine nitrogen atom; substitution of the indole nitrogen atom has an unfavourable effect on the activity[63].

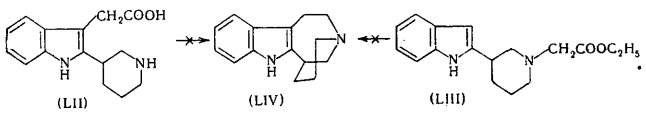
The reduction of salts of type (L) with sodium borohydride gives rise to piperidines (LI):[63]



(L) $CH_2CH_2C_6H_5$ (LI) $CH_2CH_2C_6H_5$

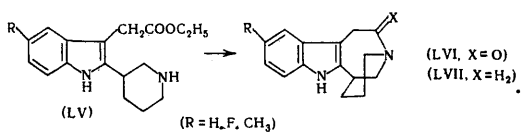
There are many other examples of the reduction of pyridinium salts with sodium borohydride. For example, this reaction has been used to prepare 2-(3-piperidinyl)-indole-3-acetic acid[62] (LII). In general, the reduction of salts of 3-substituted pyridinium with sodium borohydride to 1,3-disubstituted 1,2,5,6-tetrahydropyridines is a well known reaction[64].

Numerous attempts have been made to cyclise the aminoacid (LII) and also the piperidine derivatives (LIII) to the ibogamine structure (LIV), but were unsuccessful:[62]



(LII) (LIV) (LIII)

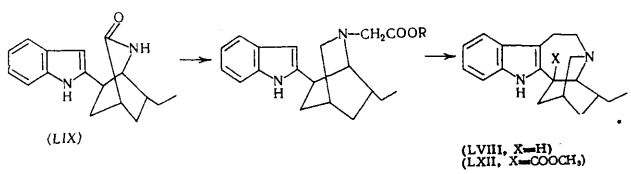
The search for methods of synthesis of systems similar to the ibogamine molecule is important for practical applications, since this alkaloid from *Tabernanthe iboga* (*Apocynaceae*) is well known to have a psychotomimetic activity. An extremely elegant solution has been recently found for the above problem[65]:



(LV) (R = H, F, CH_3) (LVI, X = O) (LVII, X = H_2)

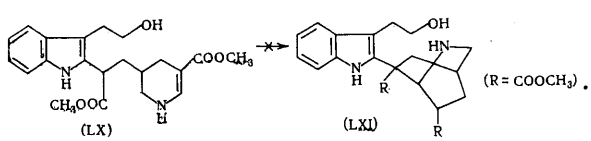
The piperidine derivatives (LV) were converted into ketones (LVI) at a reduced pressure and a temperature of 165–170°C and the ketones themselves were reduced further to compound (LVII) with lithium aluminium hydride in monoglyme.

Epi-ibogamine (LVIII) can be obtained from the piperidinone (LIX):[66]



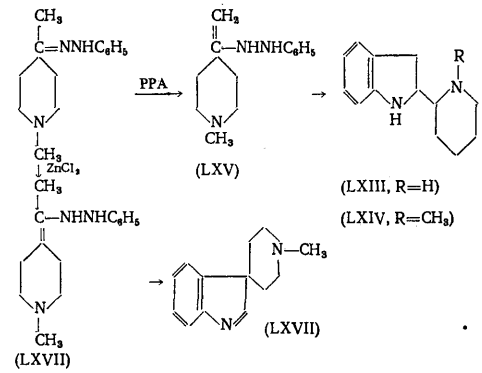
(LIX) (LVIII, X=H) (LXII, X=$COOCH_3$)

Wenkert et al.[67] were unable to cyclise the tetrahydronicotine derivative (LX) to the quinuclidine compound (LXI), which they intended to convert into coronaridine (LXII):



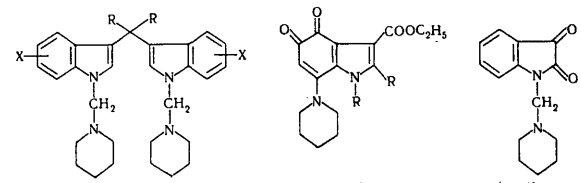
(LX) (LXI) (R = $COOCH_3$)

The piperidine derivative (LXIII) was obtained both on reduction of the corresponding pyridine derivative[62,68] and via the Schmidt reaction from 2-(2-indolyl)cyclopentanone[69]. Its *N*-methyl derivative (LXIV) is formed via the Fischer reaction on treatment of the phenylhydrazone of 4-acetyl-1-methylpiperidine with polyphosphoric acid, probably via the intermediate (LXV). It is interesting that, when zinc chloride is employed in this reaction, the cyclisation is completed by the formation of the 3*H*-indole derivative (LXVII), probably via the intermediate (LXVI):[70]



(LXV) (LXIII, R=H) (LXIV, R=CH_3) (LXVII)

The Mannich reaction has been used to synthesise piperidine derivatives of indole:



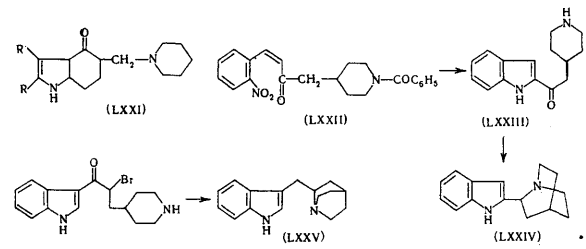
(LXVIII) (LXIX) (LXX)

(X = NO_2, halogen; R, R' = H, CH_3, C_3H_7)

Compounds of type (LXVIII) synthesised in this way and also their morpholine analogues act on the central nervous system[71].

Tests of the antimicrobial properties of indolequinones (LXIX) showed that they are not appreciably active[72]. A high antiviral activity was found in piperidine derivatives of isatin of type (LXX)[73] and the Mannich bases (LXXI) obtained from 6,7-dihydroindol-4(5*H*)-ones proved to be effective depressants of the central nervous system[74].

On heating with triethyl phosphite and subsequent debenzoylation, the *o*-nitrostyrene derivative (LXXII) gives 2-(4-piperidinyl)acetylindole (LXXIII), the reduction of which with sodium borohydride and subsequent refluxing in decalin lead to the quinuclidine derivative (LXXIV):[75]



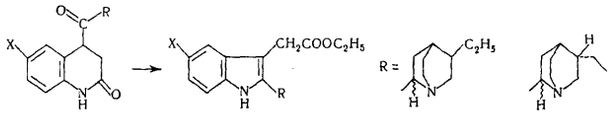
(LXXI) (LXXII) (LXXIII) (LXXV) (LXXIV)

Scatylquinuclidine (LXXV) can be obtained similarly via a stage involving the formation of the 3-indolylpiperidine derivative[76].

A mixture of epimers of quinuclidine derivatives (LXXVII) is formed when 2-oxohexahydrocinchoninones (LXXVI) are heated with hydrogen chloride in alcoholic solution[77,78].

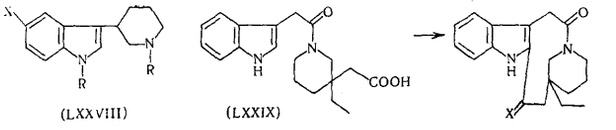
A series of 3-(3-indolyl)piperidines (LXXVIII) were obtained by heating salts of α-indolylglutaric acid with the corresponding amine without a solvent and by the reduction

of the resulting piperidinediones with lithium aluminium hydride[79]. 3-(1-Methyl-3-indolyl)piperidine (LXXVIII, R = CH_3, R′, X = H) and its *N*-methyl derivative (LXXVIII, X = H, R, R′ = CH_3) have a prolonged sedative effect, the second compound also showing some analgesic activity[79].



(LXXVI) (LXXVII) (X = H, CH_3O)

The synthesis of the alkaloid quebrachamine (LXXXI) by the cyclisation of an acylpiperidine (LXXXIX) in polyphosphoric acid and subsequent reduction of the diketone (LXXX) has been described[80]:



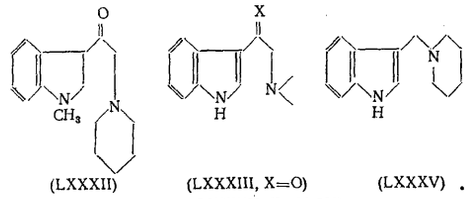
(LXXVIII) (LXXIX)

(LXXX, X = O)
(LXXXI, X = H_2)

1-[γ-(3-indolyl)propyl]piperidine can be conveniently synthesised from indole-3-propionic acid and piperidine[81].

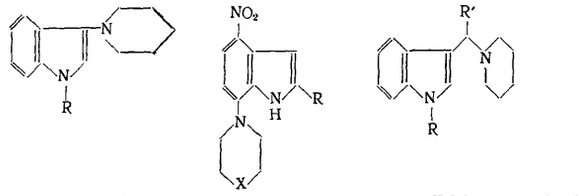
Prolonged refluxing of 3-chloroacetyl-1-methylindole with piperidine in alcohol leads to 1-methyl-3-(*N*-piperidinylacetyl)indole (LXXXII).[82]

When aminoketones of type (LXXXIII) are reduced with lithium aluminium hydride or by hydrogenation over nickel, the aminoalcohols (LXXXIV)[83]—the indole analogues of adrenaline—are formed[83]:



(LXXXII) (LXXXIII, X=O) (LXXXV)
(LXXXIV, X=H,OH)

When the molecules of these alcohols contain a secondary amino-group, they increase arterial blood pressure, but the presence of a tertiary amino-group (piperidine, morpholine, and other residues) leads to a lowering of arterial blood pressure and reduces the tone of the peripheral vessels[83]:



LXXXVI, R=H, CH_3, CH_3CO) (LXXXVII, X=CH_2; R=H,$COOC_2H_5$) (LXXXIX,R=H,R′=CN)
(LXXXVIII, X=NCH_3) (XC, R=CH_3,R′=CN)
(XCI, R=CH_3; R′=CH_2NH_2).

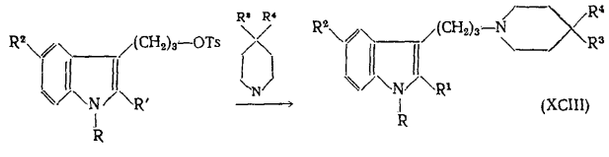
Piperidine can be *N*-alkylated with gramine[84], *N*-acetylindoxyl[85], and 7-chloro-4-nitro-derivatives of indole[86] with formation of the piperidine derivatives (LXXXV), (LXXXVI), and (LXXXVII) respectively.

When the lithio-derivative of piperidine reacts with 5-bromoindole, a mixture of 4-(1-piperidinyl)indole (60%) and 5-(1-piperidinyl)indole (40%) is formed in 59% yield.

The same substances can be isolated also as a result of the interaction of 4- and 5-aminoindoles with 1,5-dibromopentane[87].

The reduction of the nitrile (LXXXIX) and its *N*-methyl derivative (XC), obtained by the Strecker reaction, with lithium aluminium hydride has been investigated[88]. It was found that the reduction is somewhat unusual: the nitrile (LXXXIX) is converted into *N*-scatylpiperidine and compound (XC) gives rise to the tryptamine derivative (XCI).[88]

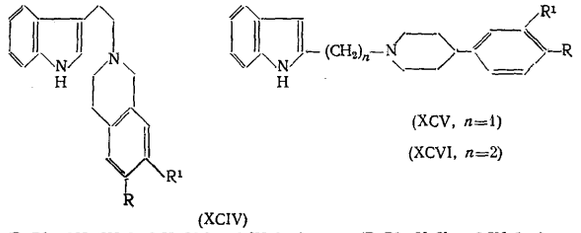
A pronounced sedative, analgesic, spasmolytic, anti-inflammatory, and hypocholesteremic activity was found in a number of piperidine derivatives of type (XCIII) formed when 1-(3-indolyl)-3-propyl *p*-toluene sulphonate (XCII) reacts with 4,4-disubstituted piperidines in alcohol in the presence of potassium carbonate[89-91]:



(XCII) (XCIII)

[R, R^1 = H, alkyl, or aryl; R^2, R^3 = H, alkyl, alkoxy, alkylthio, halogen, CN, etc.; R^4 = aryl, $N(Alk)_2$, or R^3; R^4 = alkylene or a heterocyclic residue].

In order to investigate the dependence of the physiological activity of reserpine on its structure, a series of 2-[β-(3-indolyl)ethyl]-1,2,3,4-tetrahydroquinolines (XCIV) were synthesised[92]:

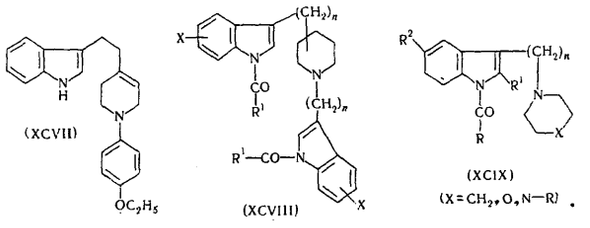


(XCV, *n*=1)
(XCVI, *n*=2)

(XCIV)
(R, R^1=OH, CH_3O, C_6H_5COO,—OCH_2O—) (R, R^1=H,Cl, —OCH_2O—).

The piperidine isomers (XCIII) containing the *N*-piperidinylalkyl group in the 2-position of the indole ring (XCI) are formed when isotryptamine is refluxed with ethyl β-aryl-δ-bromovalerate in xylene in the presence of potassium carbonate with subsequent reduction of the pyridones isolated under these conditions[93]. These compounds and also their salts were found to be effective analgesic and muscular relaxants[93]. The monomethyl derivative (XCV) can be obtained by the reaction of (2-indolyl)methylamine with the anhydrides of 3-aryl-substituted glutaric acids in benzene, the cyclisation of the products to piperidine-2,5-dione in acetic anhydride, and its reduction[93].

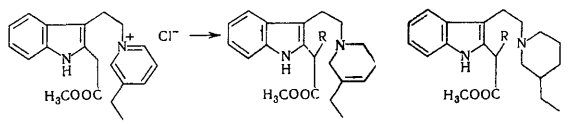
The tetrahydro-derivative (XCVII) was found to have an analgesic activity and also a vasodilating activity[94], while the piperidine derivatives (XCVIII) were found to have a sedative, hypotensive, depressant, anticonvulsive, and analgesic activity[95-97]:



(XCVII) (XCVIII) (XCIX)
(X=CH_2, O, N—R).

Anti-inflammatory, antipyretic, analgesic, antidepressant, and psychostimulating activity is shown by indolylpiperidines (XCIX) and also by their pyrrolidine, morpholine, and piperazine analogues[98]. Numerous *N*-[(1-piperidinyl)alkyl]-*N*-[(3,2,1-indolyl)alkyl)amines, which exhibit hypotensive, analgesic, psychomotor, depressant, anti-inflammatory, bacteriostatic, adrenolytic, antihelminthic, and antifungal activity, have been patented[99].

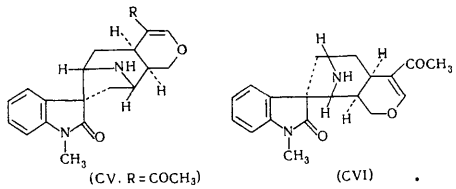
The structure of the alkaloid 16,17-dihydrosecodin-17-ol (CI), isolated from *Rhazya orientalis*, was demonstrated by synthesis from the pyridinium derivative (C):[100]



(C) (CI, R = CH_2OH) (CII, R = CH_2OH)
(CIII, R = CH_3) (CIV, R = CH_3)

Tetrahydrosecodin-17-ol (CII) was isolated from the same plant and dihydrosecodine (CIII) and tetrahydrosecodine (CIV) were identified in *Rhazya stricta*[101].

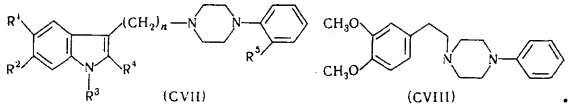
The alkaloids alstonerine (CV) and "alkaloid C" (CVI) were isolated from *Alstonia muelleriana*[102]:



(CV, R = $COCH_3$) (CVI)

IV. PYRAZINE AND PIPERAZINE DERIVATIVES OF INDOLE

A fairly considerable amount of attention is being devoted to piperazine derivatives of indole, mainly after the report in 1962 that the condensation of indolylalkanoic acids with 4-arylpiperazines followed by reduction of the resulting *N*-arylpiperazides yields 4-aryl-1-[(3-indolyl)-alkyl] piperazines (CVII) which are effective depressants of the central nervous system[103]. Among these, the highest activity was shown by compounds in which the methylene bridge consists of 2 or 3 methylene groups. Probably the activity is due to the presence of the indole moiety, because the phenyl analogue of this compound (CVIII) is inactive[103].

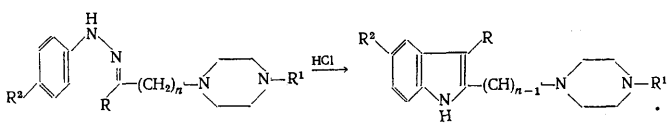


(CVII) (CVIII)

(R^1 R^2 R^3 R^4 = H, CH_3, OCH_3; R^5 = H, CH_3)

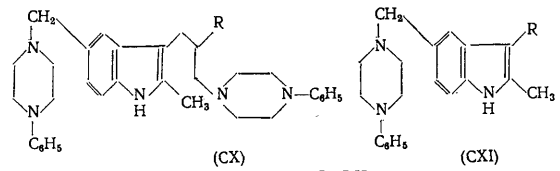
Sedatives, antipyretic agents, and muscle relaxants[104,105] and also compounds with adrenolytic, hypotensive, antipyretic, and sedative activity[106,108] were found among indolylalkylpiperazines.

A series of (2-indolyl)alkylpierazines (CIX) were synthesised by the Fischer reaction[106,107]:



(CIX)

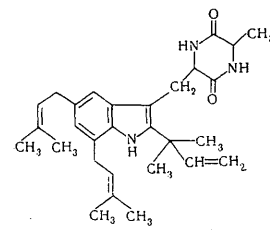
Many compounds of type (CX) and(CXI) containing piperazine residues in the 5-position of the indole molecule were obtained[109,110]:



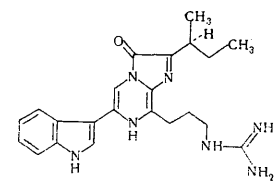
(CX) (CXI)
(R=H, CH_3, C_3H_7, C_4H_9, C_6H_5)

N-Scatylpiperazine is formed from (3-indolyl)methanol and piperazine[111]. Alkylation of piperazine with gramine in an aqueous medium leads to *NN*-discatylpiperazine[84]. The interaction of 6-chloro-4-nitroindole and its 2-ethoxycarbonyl derivative with 4-methylpiperazine is completed by formation of the corresponding 6-(4-methyl-1-piperazinyl)indole (LXXXVIII).[88]

Piperazine derivatives of indole have been found in natural products. Echinuline (CXII)[112,113] can be regarded as a piperazinedione in which the tryptophan residue has the configuration of a D-aminoacid and alanine has the L-configuration[114]:



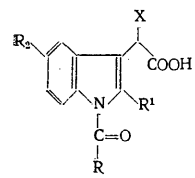
(CXII)



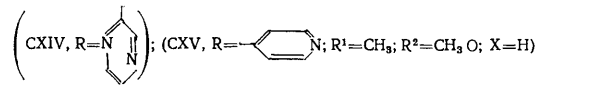
(CXIII)

Another natural pyrazine derivative of indole is luciferin (CXIII),[115-118] a negligible amount of which (5 mg) can produce sufficient light to read a newspaper for 30 min. It was synthesised recently[117].

Many α-halogenomethylindolylacetic acids (CXIV) containing a pyrazinecarboxylic acid residue at the nitrogen atom have been patented[119]. These acids and also their esters, amides, and salts exhibit antipyretic and anti-inflammatory activity and can be used to prevent and suppress the formation of tissue granuloma or to treat arthritis and dermatological affections[119]:



(R^1, R^2=H, Alk, Ar etc, X=CH_2Y, CHY_2, CY_3; Y=F, Cl, Br)



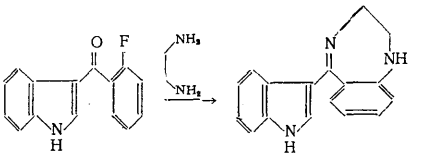
(CXIV, R=N); (CXV, R=N; R^1=CH_3; R^2=CH_3O; X=H)

Many analogues of compound (CXIV) containing aromatic and heterocyclic residues and exhibiting a considerable anti-inflammatory activity are known[120-127]. Among numerous compounds of this type, indomethacin, containing the *p*-chlorobenzoyl residue in the 1-position, may be recommended in practice. The *N*-isonicotinoyl derivative (CXV) is known to show a high anti-inflammatory activity and to be less toxic than indomethacin[129,130].

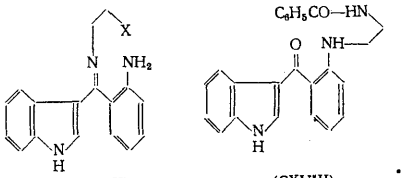
A number of analogues obtained on the basis of indole-3-carboxylic acids also show anti-inflammatory activity[128].

V. INDOLYLAZEPINES AND DIAZEPINES

5-(3-Indolyl)-2,3-dihydro-1*H*-1,4-benzodiazepines of type (CXVI), formed when 3-(*o*-halogenobenzoyl)indoles are treated with ethylenediamine in pyridine or on cyclisation of the imines (CXVII) or imides (CXVIII),[131] show antidepressant activity[132,133]:



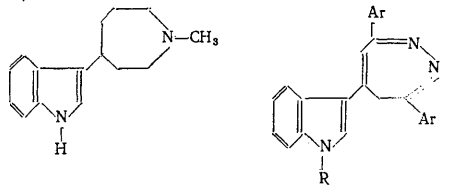
(CXVI)



(CXVII) (CXVIII)

A number of 4-indolylhexahydroazepines of type (CXIX) were found to possess an antiviral and antibacterial activity[134].

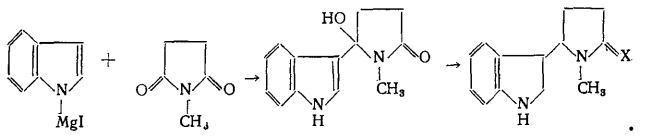
1,2-Diazepine derivatives of indole (CXX) can be simply and conveniently synthesised by the interaction of indolylpyrylium salts (VIII) with hydrazine hydrate[135]:



(CXIX) (CXX, R=CH$_3$, C$_6$H$_5$CH$_2$)

VI. INDOLYLPYRROLIDINES

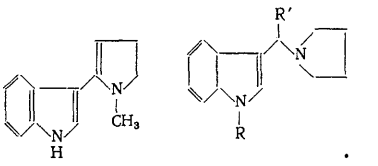
2-(3-Indolyl)-1-methylpyrrolidine-5-one (CXXI), formed by the reaction of indolylmagnesium iodide with *N*-methylpyrrolidine-2,5-dione, proved to be an effective tranquiliser[136]. It has also been reported that compound (CXXII), obtained by its reduction, inhibits the activity of pseudocholinesterase[137]:



(CXXI, X=O)
(CXXII, X=H$_2$)

N-Scatylpyrrolidine can be obtained both by the Mannich reaction[138] and by the alkylation of pyrrolidine with gramine[84].

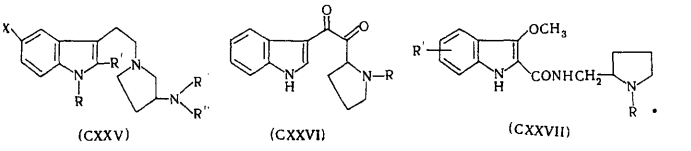
It is interesting to note that 3-(1-alkyl-2-pyrrolinyl)-indoles of type (CXXIII), which have been recommended as intermediates for the synthesis of pyrrolidinylindoles, exhibit anti-inflammatory activity and a capacity to reduce the appetite[139]:



(CXXIII) (CXXIV)

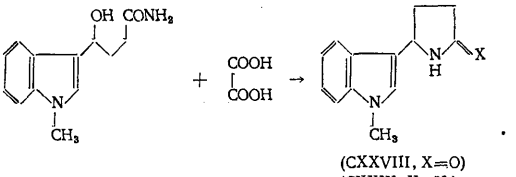
When the nitriles (CXXIV, R = H, R′ = CN) and (CXXIV, R = CH$_3$, R′ = CN) are reduced with lithium aluminium hydride, the latter compound gives rise to α-pyrrolidinyltryptamine (CXXIV, R = CH$_3$, R′ = CH$_2$, NH$_2$), while the former is converted into *N*-scatylpyrrolidine with elimination of the nitrile group[88].

3-Amino-substituted *N*-(β-indolylethyl)pyrrolidines (CXXV) were found to be capable of decreasing appreciably the tremor and muscular rigidity in Parkinson's disease[140] and the pyrrole derivative (CXXVI) was found to exhibit a depressive and an anticonvulsant activity[141]. The pyrrolidine derivatives (CXXVII) have an antipyretic effect, are capable of enhancing the effect of barbiturates, and are morphine antagonists[142]:



(CXXV) (CXXVI) (CXXVII)

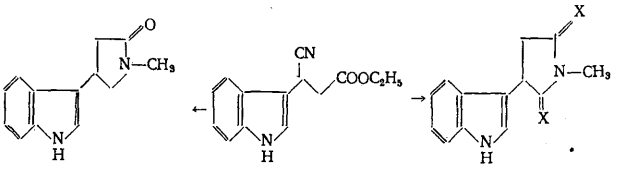
A patent was published recently for the preparation of 5-(3-indolyl)pyrrolidin-2-ones of type (CXXVIII) which exhibit antiviral and sedative activity in tests on birds and animals. Their reduction yielded the corresponding indolylpyrrolidines (CXXIX), which are used in the treatment of neuroses[143]:



(CXXVIII, X=O)
(CXXIX, X=H$_2$)

It has also been suggested that 3-(4-nitrobutyryl)indoles be used for the synthesis of derivatives of 3-(2-pyrrolidinyl)indoles, which show anti-inflammatory and anaphylactic activity and are capable of suppressing the appetite[144]. 2-(3-Indolylpyrrolidine) is obtained by the hydrogenation of 3-(β-cyanopropionyl)indole[145].

3-(3-Indolyl)-1-methylpyrrolidine (CXXX) has been synthesised by the reaction of indolylsuccinic acid[146] with 1,3-dimethylurea at 185–190°C and subsequent reduction of the resulting indolylsuccinimide (CXXXI):[146]

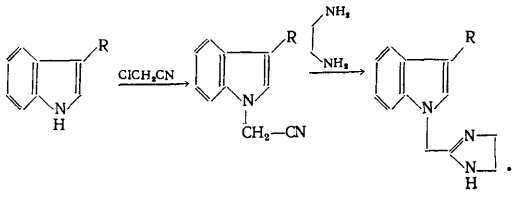


(CXXXIII) (CXXXII) (CXXX, X=H$_2$)
(CXXXI, X=O)

Hydrogenation of the nitrile (CXXXII) in the presence of a nickel catalyst at 80°C (100 atm) leads to 4-(3-indolyl)-pyrrolidin-2-one (CXXXIII) in 50% yield[147].

VII. INDOLYLIMIDAZOLES

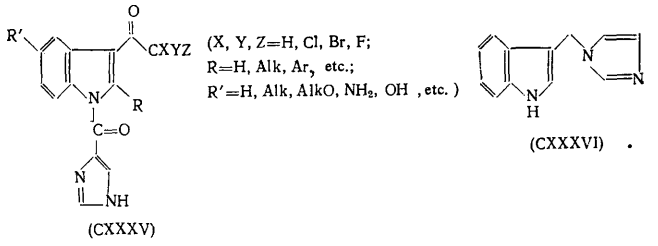
Certain 3-alkyl-1-(2-imidazolinylmethyl)indoles (CXXXIV) show vasoconstrictor activity [148]:



(CXXXIV)

A number of indole derivatives (CXXXV) containing the imidazolecarboxylic acid residue (and also carboxylic acid derivatives of pyrimidine, oxazole, thiazole, isoxazole, isothiazole, pyrazole, etc.), which may be used as intermediates in the synthesis of various derivatives of indolylacetic acids, have been patented [149,150].

1-Scatylimidazole (CXXVI) and its 2-methyl derivative are formed in the alkylation of imidazole with gramine [152]. 1-Scatylindazole, 1-scatylbenzimidazole, and 1-scatylpyrazole were obtained in the same way [153]:

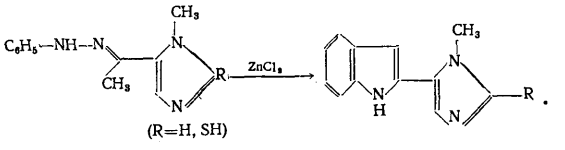


(X, Y, Z=H, Cl, Br, F; R=H, Alk, Ar, etc.; R′=H, Alk, AlkO, NH_2, OH, etc.)

(CXXXV)

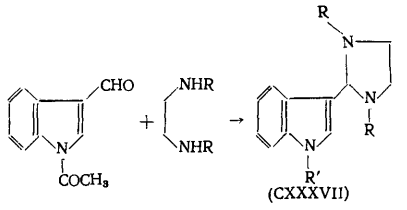
(CXXXVI)

Indole derivatives containing the imidazole residue in the 2-position in indole can be obtained by the Fischer reaction from 5-acetylimidazoles [151]:



(R=H, SH)

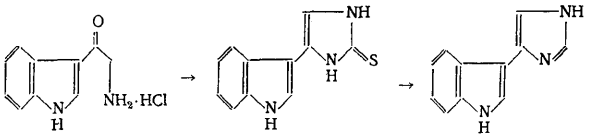
Suvorov and coworkers obtained 1,3-disubstituted 2-(3-indolyl)imidazolines (CXXXVII) from 1-acetylindole-3-aldehyde and *N*-substituted ethylenediamines [154]:



(CXXXVII)

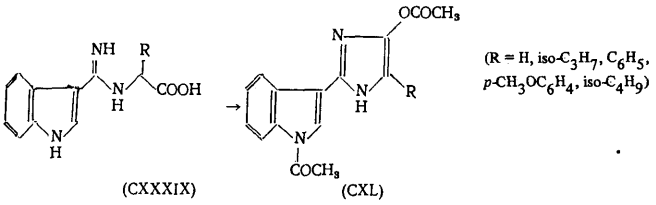
(R=C_6H_5, p-$CH_3OC_6H_4$, $C_6H_5CH_2$, p-BrC_6H_4; R′=H, $COCH_3$)

They also synthesised 4-(3-indolylimidazole (CXXXVIII) by the reaction of 3-chloroacetylindole with formamide or by treating 3-aminoacetylindole with potassium thiocyanate in the melt with subsequent elimination of sulphur from 2-mercapto-4-indolylimidazole formed [155]. The imidazole derivative (CXXXVIII) has a weak bacteriostatic effect in relation to *Mycobacterium tuberculosis* [155]:



(CXXXVIII)

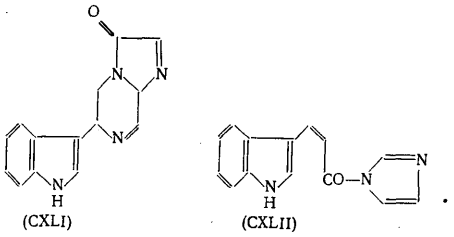
N-Acetyl derivatives of a number of 2-(3-indolylimidazoles (CXL) are formed when indole-3-carbamidicic acids (CXXXIX) are refluxed with acetic anhydride [156]:



(R = H, iso-C_3H_7, C_6H_5, p-$CH_3OC_6H_4$, iso-C_4H_9)

(CXXXIX) (CXL)

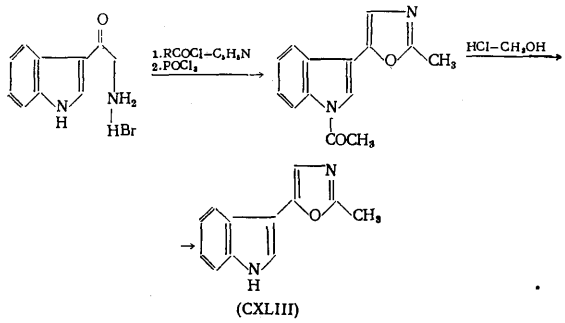
Imidazo[1,2-*a*]pyrazinone (CXLI) was obtained from 2-amino-5-(3-indolyl)pyrazine and methylglyoxal [158]. The synthesis of 1-[β-(3-indolyl)acryloyl]imidazole (CXLII) has also been described [157]:



(CXLI) (CXLII)

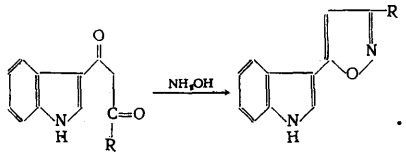
VIII. INDOLYLOXAZOLES AND INDOLYLISOXAZOLES

Compounds of this type have been isolated from natural sources. The antibiotic pimprinin, identified as 5-(3-indolyl)-2-methyloxazole (CXLIII), was obtained from *Streptomyces pimprina* [159]. The structure of pimprinin was subsequently confirmed by synthesis [160]:

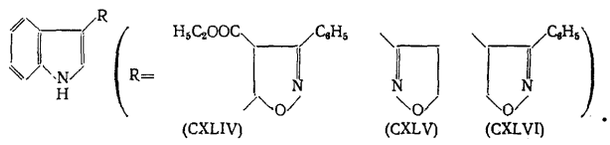


(CXLIII)

Sanna reported previously the synthesis of indolylisoxazoles from β-diketones of the indole series [161]:

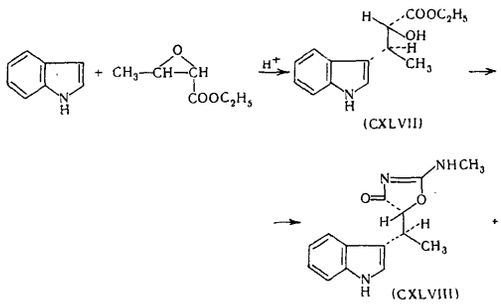


It is also known that the interaction of ethyl indolylacrylate in benzonitrile oxide leads to the formation of the isoxazoline (CXLIV) and that the isoxazoline (CXLV) and compound (CXLVI) may be obtained from 3-indolyl vinyl ketone and hydroxylamine by reaction with benzonitrile oxide [162]. Isoxazole derivatives could not be obtained by the reaction of benzylidene-3-acetylindole with hydroxylamine and benzonitrile oxide [162]:



(CXLIV) (CXLV) (CXLVI)

Strain BA-3972 of *Streptomyces albus* is known to suppress certain strains of staphylococci which are resistant to the usual commercially available antibiotics [163]. The active principle (an antibiotic), which was called indolmycin, was soon isolated [164], its structure (CXLVIII) was established, and it was synthesised according to the following scheme [165]:

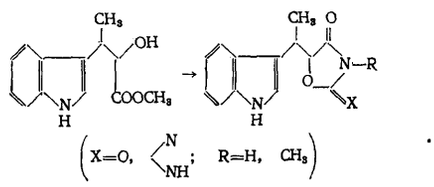


(CXLVII)

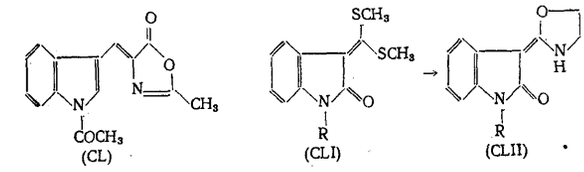
(CXLVIII) (CXLIX).

The ethyl ester of α-indolmycenic acid (CXLVII), which can also be synthesised by the reaction of indolylmagnesium halides with ethyl *trans*-2,3-epoxybutyrate, is condensed with *NN*-dimethylguanidine. Apart from indolmycin itself, this results in the formation also of a certain amount of isoindolmycin (CXLIX) owing to the ready epimerisation of indolmycin under alkaline conditions [165].

In a stereospecific synthesis of indolmycin, Suvorov, Preobrazhenskaya, and coworkers also began with the ethyl esters of indolmycenic acids [166,167], the isomers of which they were able to resolve by crystallisation. In the last stage a mixture of approximately equal amounts of indolmycin and isoindolmycin was obtained with an overall yield of 40%. When *N*-methylthiourea, urea, and methyl isocyanate were introduced into this reaction, structural analogues of indolmycin were obtained [168]:

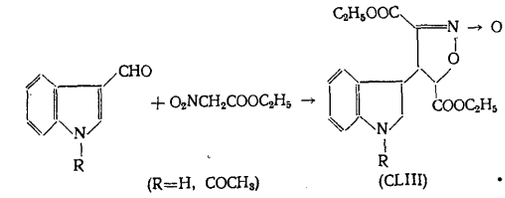


The interaction of indole-3-aldehyde with acetylglycine resulting in the formation of the azlactone (CL) has been described [169]. 3-(2-Oxazolidinylidene)oxindoles (CLII) are readily obtained when 3-bismethylthiomethyleneoxindoles (CLI) are refluxed with ethanolamine in alcohol [170]:



(CL) (CLI) (CLII)

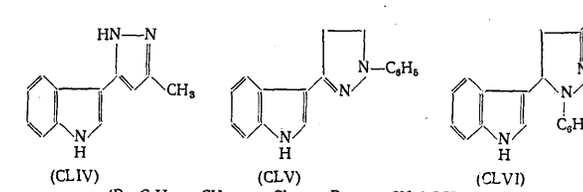
Isoxazoline *N*-oxides (CLIII) were obtained recently by treating indole-3-aldehyde and its *N*-acetyl derivative with nitroacetic ester [171]:



(R=H, $COCH_3$) (CLIII)

IX. INDOLYLPYRAZOLES, INDOLYLPYRAZOLINES, AND INDOLYLQUINOXALINES

The indolylpyrazole derivatives known at present are comparatively few although it would appear that these compounds might include preparations of pharmacological interest, since pyrazoles are in general interesting as biologically active substances [172]. Certain compounds of this type were obtained by the interaction of β-diketones of the indole series with hydrazine derivatives [161]. Thus the reaction of 3-acetoacetylindole with hydrazine hydrate led to the isolation of the pyrazole (CLIV). [173] The pyrazoline (CLV) is formed from 3-indolyl vinyl ketone and phenylhydrazine [162] and a series of Δ^2-pyrazolines (CLVI) were obtained from scatylideneketones and phenylhydrazine [174]:

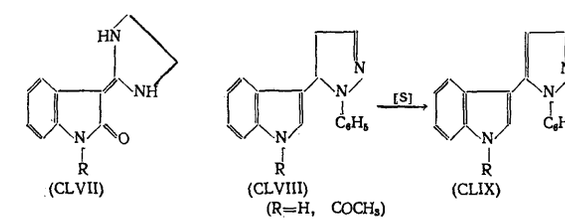


(CLIV) (CLV) (CLVI)

(R=C_6H_5, *p*-CH_3—, *p*-Cl—, *p*-Br—, *p*-$CH_3OC_6H_4$, etc.)

When 3-bismethylthiomethyleneoxindoles (CLI) are refluxed with ethylenediamine, 3-pyrazolidinylideneoxindoles (CLVII) are formed [170].

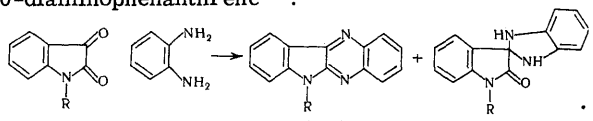
Suvorov and coworkers [175] showed recently that β-indolylacrylic aldehyde and its *N*-acetyl derivative are converted, on prolonged refluxing with phenylhydrazine (or with hydrazine) in acetic acid, into 5-indolylpyrazolines (CLVIII), which can be further dehydrogenated to the corresponding 5-(3-indolyl)pyrazoles (CLIX):



(CLVII) (CLVIII) (CLIX)

(R=H, $COCH_3$)

On reaction with *o*-phenylaminediamine in acetic acid, isatin is converted into 6*H*-indolo[2,3-*b*]quinoxaline (CLX, R = H).[176] When this reaction is carried out in alcohol, the spiro-derivative (CLXI, R = H) is also formed[177,178]. Its analogues have been synthesised also by the interaction of isatin with 4,5-diamino-1,3-dimethyluracil[174], 4,5-diaminopyrimidine[178], 1,2-diaminonaphthalene[177], and 9,10-diaminophenanthrene[178]:

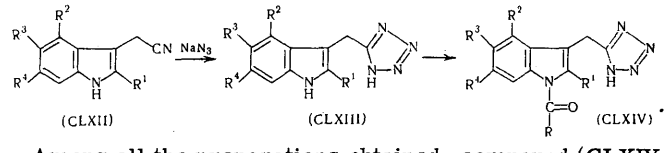


(CLX) (CLXI)

It is interesting that 2,3-diaminonaphthalene forms with isatin only quinoxaline[177], while its reaction with methylisatin gives a spiro-derivative[178] which on recrystallisation from acetic acid isomerises to the corresponding quinoxaline[178].

X. INDOLYLTETRAZOLES

1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid ("indomethacin") is a powerful anti-inflammatory preparation[179]. In order to seek more effective preparations with similar activity, a number of compounds containing the tetrazole residue instead of the carboxy-group were synthesised from the nitriles (CLXII)[180] or from the tetrazoles (CLXIII) by acetylating the latter in DMF in the presence of sodium hydride[180-183]:



(CLXII) (CLXIII) (CLXIV)

Among all the preparations obtained, compound (CLXIV, R = *p*-ClC$_6$H$_4$, R^1, R^2, R^3, R^4 = H) proved to be the most active[180]. However its effectiveness is appreciably lower than that of "indomethacin". In addition, it is noteworthy that this compound has been found to have an antiserotonin and antihistamine activity[184].

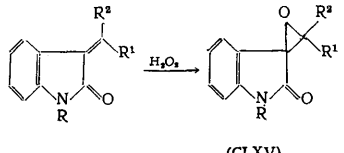
The tetrazole analogue of indole-3-acetic acid stimulates weakly the elongation of *Avena* cells[185].

XI. OTHER INDOLYL DERIVATIVES OF HETEROCYCLES

1. Derivatives of Oxygen-containing Heterocycles

A number of oxirans obtained from oxindole are of definite interest. When products of the condensation of oxindole with ketones are treated with 30% hydrogen peroxide in the presence of alkali in methanol, high yields of 3,1′-epoxides of 2-oxoindoline (CLXV) are obtained[186,187]. Among these compounds, preparations with sedative, diuretic, and anticonvulsant activity were discovered.

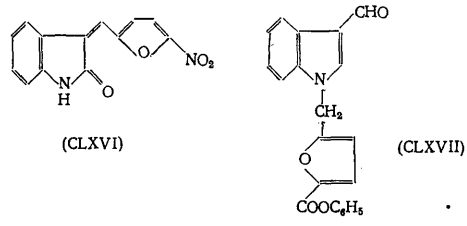
The 3,1′-epoxide of 3-cyclopentyl-2-oxoindoline exhibits a contraceptive effect[186]:



(CLXV)

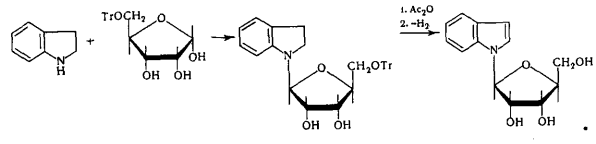
[R = H or CH$_3$; R^1, R^2 = (CH$_2$)$_n$, lower alkyls, aryls, arylalkyls, or pyridyl]

Among other oxygen-containing heterocycles with an indolyl residue, mention should be made of 3-(5-nitrofurfurylidene)oxindole (CLXVI), which shows antibacterial activity[188]. A compound containing a furan ring at the nitrogen atom of the indole molecule (CLXVII) has also been described[189]:



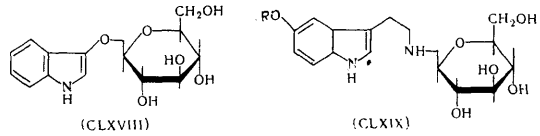
(CLXVI) (CLXVII)

N-Glycosylindoles may be obtained from indoline according to the following scheme[190]:



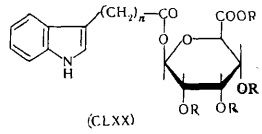
A number of indolyl-β-D-glycopyranosides (CLXVIII) have found application as agents for the histochemical location of individual β-glycosidases in mammalian tissues[191,192].

The synthesis of the *N*-glucosides of serotonin, 5-methoxytryptamine, and melatonin (CLIX) by brief refluxing of the corresponding indole derivatives with D-glucose in methanol has been described[193]:



(CLXVIII) (CLXIX)

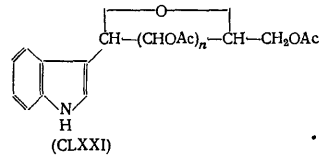
(R = H, CH$_3$, C$_6$H$_5$CH$_2$)



(CLXX)

The glucuronides of 3-indolyl derivatives of aliphatic acids (CLXX) exhibit high anti-inflammatory activity and low toxicity[194].

The interaction of indolylmagnesium bromide with certain acetohalogenoses yielded tetra-acetyl-β-indolylglucose, tetra-acetyl-β-indolylgalactose, and tri-acetyl-β-indolylxylose—the indole series of *C*-glycosides of type (CLXXI), which had not been described hitherto[195]:

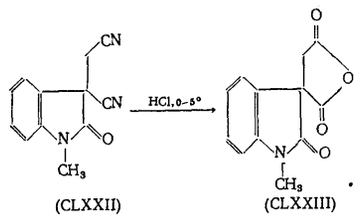


(CLXXI)

The application of mass spectrometry in the investigation of acetylated derivatives of glucopyranosylamine containing the indole residue was described in a review published recently[196].

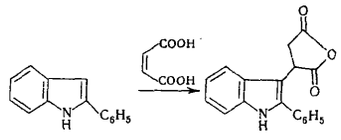
Certain additional information concerning the preparation of a series of carbohydrate derivatives of indoles may be found in a recent review[197].

Spiro[oxindole-3,3′-succinic]anhydride (CLXXIII) is formed in 79.5% yield on acid hydrolysis of the oxindole derivative (CLXXII) in a dioxan–methanol mixture [198]:



(CLXXII) (CLXXIII)

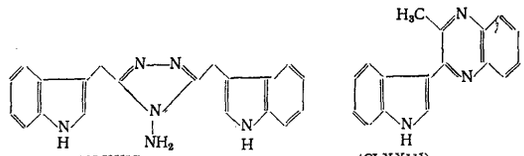
The interaction between 2-phenylindole and maleic acid with brief heating to 140°C leads to the formation of 3-(2-phenyl-3-indolyl)succinic anhydride (CLXXIV): [199]



(CLXXIV)

2. Derivatives of Nitrogen- and Sulphur-containing Heterocycles

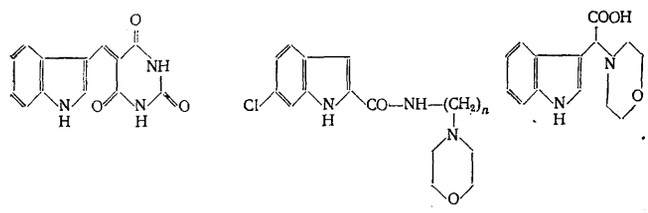
Prolonged refluxing (18 h) of indole-3-acetonitrile with anhydrous hydrazine leads to the formation of 4-amino-3,5-discatyl-*sym*-triazole (CLXXV). [200] As was to be expected, the product of the reaction of 1-(3-indolyl)propane-1,2-dione and *o*-phenylenediamine in alcohol is 2-(3-indolyl)-3-methylquinoxaline (CLXXVI): [201]



(CLXXV) (CLXXVI)

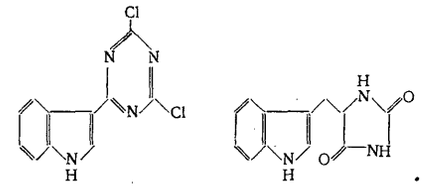
5-Scatylidenebarbituric acid (CLXXVII) is obtained in 84% yield by the condensation of indole-3-aldehyde with barbituric acid [202]. The attempts to reduce the product of this reaction to the 5-scatyl derivatives with triethylammonium formate were unsuccessful [203].

Morpholinylamides of type (CLXXVIII) were found to have antidepressant activity [204]. The morpholine derivative (CLXXIX) is formed by the Mannich reaction from indole, glyoxylic acid, and morpholine [205]:



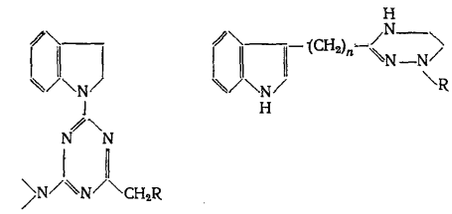
(CLXXVII) (CLXXVIII) (CLXXIX)

When indole reacts with cyanuryl chloride, the product is the derivative (CLXXX) [206] and cyclisation of the phenylhydrazone of β-(5-hydantoyl)propionaldehyde by an alcoholic solution of hydrogen chloride leads to 5-scatylhydantoin (CLXXXI): [207]



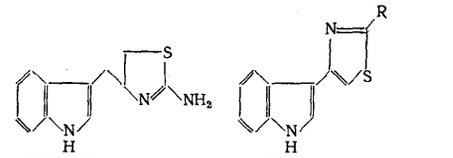
(CLXXX) (CLXXXI)

A number of 2-amino-4-(1-indolinyl)-*S*-triazines (CLXXXII) were found to have anti-inflammatory and analgesic activity [208], while indolylalkyltriazine derivatives (CLXXXIII) and their salts exhibit an antidepressant effect [209]:



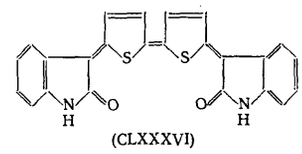
(CLXXXII, R=H, CH_3) (CLXXXIII, n=1, 2, 3; R=H, alkyl.)

In connection with their search for agents affording protection against radiation, Japanese chemists recently described the synthesis of 2-amino-4-scatylthiazoline (CLXXXIV) from α-chloromethyltryptamine and thiourea [210]. It is also known that the interaction of 3-chloroacetylindole with thioformamide, thiourea, and ammonium dithiocarbamate leads to the corresponding derivatives of 4-(3-indolyl)thiazole (CLXXXV): [211]



(CLXXXIV) (CLXXXV, R=H, NH_2, SH)

The indophenine pigment formed on interaction between isatin and thiophen may be included among compounds of this type; the structure (CLXXXVI) was recently finally demonstrated for this derivative [212]:



(CLXXXVI)

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Institute of Chemistry,
Academy of Sciences of
the Moldavian SSR

Institute of Physical and
Organic Chemistry at
Rostov-on-Don State
University