METHODS FOR THE SYNTHESIS OF AZOLES CONTAINING INDOLE SUBSTITUENTS (REVIEW)

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A systematic review is given for advances in the synthesis of various azoles (imidazoles, oxazoles, thiazoles, pyrazoles, oxadiazoles, and triazoles) containing indole fragments. A significant number of biologically active compounds have been found among these bisheterocyclic compounds.

An enormous amount of experimental data has now accumulated in the literature on the synthesis and application of heterocyclic compounds containing indole substituents. However, only a few indolylazoles were very briefly considered among other bisheterocyclic compounds in a single review [1].

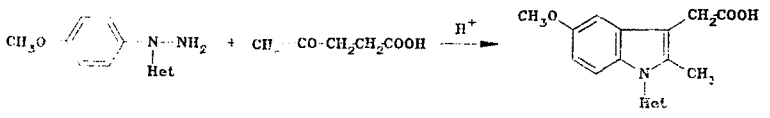
In compiling this review of the literature data, we preferred to organize the subjects not according to the indolylazole types but rather according to the means of their preparation from specific classes of compounds. In our opinion, this approach to the systematization of the vast literature data gives a clearer concept of the synthetic possibilities of the specific methods, which may be useful in selecting approaches for further studies on the preparation of new indolylazoles.

In the present review, we have limited ourselves to noncondensed indolylazoles, in which the residues of the two heterocycles are joined either directly to each other or by carbon chains.

1. PREPARATION OF INDOLYLAZOLES BY THE FISCHER–ARBUZOV REACTION

The Fischer–Arbuzov reaction is the most general and common method for the synthesis of indole derivatives. However, this method has not yet found extensive use for the synthesis of indolylazoles since azole carbonyl derivatives and arylhydrazines containing azole residues have generally been difficult to prepare.

The condensation of $N_{(1)}$-hetaryl-4-methoxyphenylhydrazines with levulinic acid was carried out in order to synthesize structural analogs of the drug indomethacin, [1-(4-chlorobenzoyl)-2-methyl-5-methoxyindolyl-3-acetic acid] [2, 3].



Het = 2-chlorothiazolyl-4-carbonyl, benzthiazolyl-2

The indomethacin analogs I synthesized display analgesic, anti-inflammatory and high fever-reducing activity.

The condensation of $N_{(1)}$-aroyl-$N_{(1)}$-(4-methoxyphenyl)hydrazines with 1,2-diphenyl-4-(3-oxobutyl)-3,5-pyrazolinedione [4] or with (1-(2-oxopropyl)-2-methyl-4-nitroimidazoles [5-7] was used to prepare another type of indomethacin analogs containing heterocyclic fragments at $C_{(3)}$ of the indole ring.

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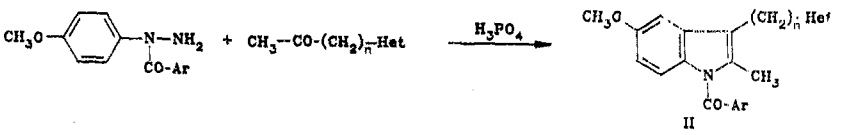
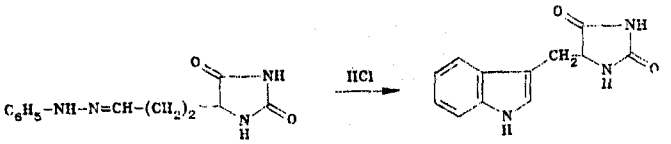


II

n = 1, Het = 1,2-diphenyl-3,5-pyrazolidinedione-4-yl; n = 0, Het = 4-nitro-2-methyl-1-imidazolyl

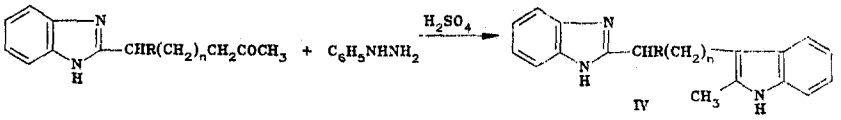
Compounds containing high analgesic activity were found among indolylazoles II.

A patent has been issued for the preparation of 5-(indolyl-3-methyl)hydantoin (III) entailing Fischer–Arbuzov cyclization of the phenylhydrazone of β-(5-hydantoyl)propionaldehyde upon heating in hydrochloric acid [8].



III

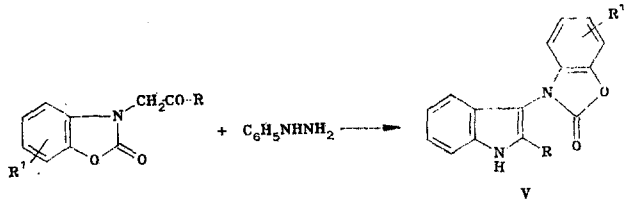
Tatevosyan et al. [9, 10] synthesized indolybenzimidazoles IV, which display strong antiviral activity [11], by heating 2-(3-oxobutyl)- or 2-(4-oxopentyl)benzimidazoles with phenylhydrazine in the presence of sulfuric acid.



IV

R = H, alkyl; n = 0, 1

2-Alkyl-3-(2-benzoxazolon-3-yl)indoles (V) were obtained in 65-70% yield upon heating 3-(2-oxopropyl)- or 3-(2-oxobutyl)-1,3-benzoxazol-2-ones with phenylhydrazine in polyphosphoric acid [12].

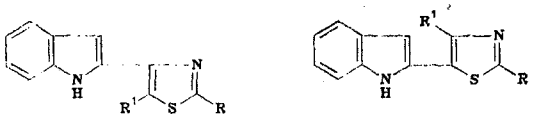


V

R = CH_3, C_2H_5; R^1 = H, 5-CH_3, 5-Cl, 6-SO_2NH_2

2-(1-Methyl-2-R-imidazol-5-yl)indoles (R = H, SC_2H_5) [13] and 2-(3-methylisothiazol-4-yl)indole [14] were prepared by the cyclocondensation of 1-methyl-2-R-5-acetylimidazoles and 3-methyl-4-acetylisothiazole with phenylhydrazines in the presence of zinc chloride. However, the yield of these indolylazoles did not exceed 25-40%.

The phenylhydrazones of 4- or 5-acetylthiazoles were converted by the Fischer–Arbuzov reaction to indolythiazoles VI or VII, respectively [15]. High pesticide activity was noted for these compounds.



VI VII

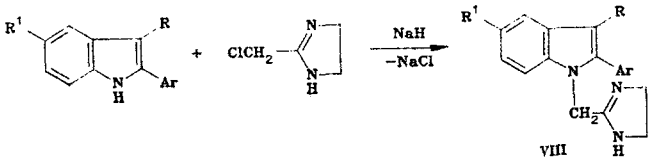
R = H, CH_3, Ph, COOH, $COOC_2H_5$; R^1 = H, CH_3

A patent was issued in 1981 for the synthesis of 2-(5-R-3-R^1-isoxazol-4-yl)indoles (R = H, alkyl; R^1 = H, alkyl, aryl), which were obtained in high yield by the cyclization of 4-acetyl-5-R-3-R^1-isoxazole phenylhydrazone in polyphosphoric acid. These indole derivatives

are key compounds in the preparation of biologically active tryptamine analogs containing isoxazole fragments.

2. PREPARATION OF INDOLYLAZOLES BY THE ALKYLATION OR ACYLATION OF INDOLE AND ITS DERIVATIVES

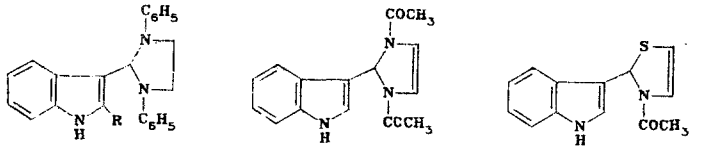
1-(Imidazolinyl-2-methyl)indoles (VIII) are formed upon the alkylation of 2-arylindoles by 2-chloromethylimidazoline in the presence of sodium hydride [17, 18].



VIII

R = H, CH_3, Cl; R^1 = H, CH_3; Ar = Ph, 4-ClC_6H_4, 4-$CH_3OC_6H_4$

Hocker and Merten [19, 20] found that the alkylation of indole and 2-substituted indoles by bis(1,3-diphenyl-2-imidazolidinylidene), which is a cyclic analog of tetraminoethylene, proceeds at $C_{(3)}$ with the formation of 3-(1,3-diphenylimidazolidin-2-yl) indoles (IX).

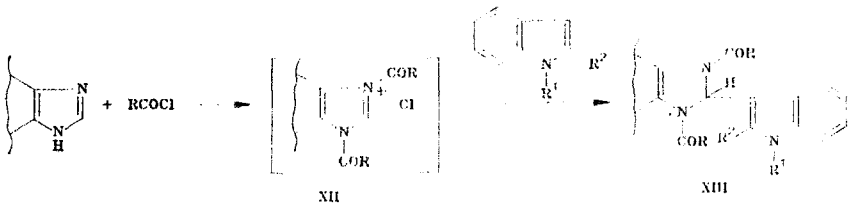


IX X XI

R = H, CH_3, Ph

Bergman [21] in an attempt to acylate indole with N-acetylimidazole in acetic anhydride isolated the indole hetarylation product, 1,3-diacetyl-2-(indol-3-yl)-4-imidazoline (X) instead of the expected N-acetylindole. This author considered that (X) is formed by electrophilic attack at $C_{(3)}$ in indole by the 1,3-diacetylimidazolinium cation generated from N-acetylimidazole. Also, heating indole with thiazole in acetic anhydride gave 1-acetyl-2-(1-acetylindol-3-yl)-4-thiazoline (XI) [21].

D detailed study was carried out on the hetarylation of indoles not substituted at $C_{(3)}$ by N-acylimidazolinium or N-acylbenzimidazolinium salts (XII) *in situ*. Sheinkman et al. [22-24] reported that the reaction of indoles with imidazole or benzimidazole in the presence of the acid chlorides or aliphatic, aromatic, or heterocyclic acids gave 3-(1,3-diacylimidazolin-2-yl)- or 3-(1,3-diacylbenzimidazolin-2-yl)indoles (XIII).



XII XIII

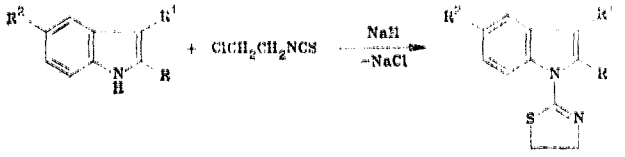
R = CH_3, Ph, thienyl-2; R^1 = H, CH_3; R^2 = H, CH_3

The formation of salts XII as intermediates was confirmed by the preparation of XIII under analogous conditions using N-acylimidazoles instead of imidazole.

The benzoxazole fragment could not be introduced into the indole ring by the reaction of indole with benzoxazole in the presence of acylating reagents in an inert solvent or by using benzoxazole salts, which resulted only in N-acyl-o-aminophenols and tris(indol-3-yl)-methane [25].

The reaction of indole with 4-ethoxymethylene-2-phenyl-5-oxazoline in acid medium gave 4-(indol-3-ylmethyl)-2-phenyl-5-oxazolone, which is an important intermediate in the synthesis of tryptophan [26].

Heating a mixture of indole or its derivatives not substituted at $C_{(1)}$ with 2-chloroethyl isothiocyanate in 1,2-dimethoxyethane in the presence of sodium hydride at reflux gave 1-(Δ^2-thiazolin-2-yl)indoles (XIV), which are intermediates in the preparation of anti-inflammatory agents [27-30].

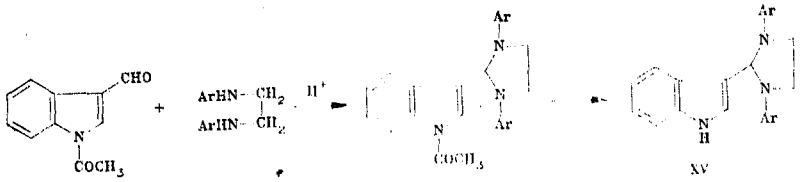


XIV

R = H, thiazolyl-4; R^1 = H, $(CH_3)_2NCH_2$; R^2 = H, CH_3O, NO_2

3. PREPARATION OF INDOLYLAZOLES FROM INDOLE CARBONYL DERIVATIVES

1,3-Disubstituted 2-(indol-3-yl)imidazolidines (XV) were synthesized by the cyclocondensation of 1-acetyl-3-formylindole with N,N'-diarylethylenediamines with subsequent hydrolysis of the N-acetyl derivatives formed [31].



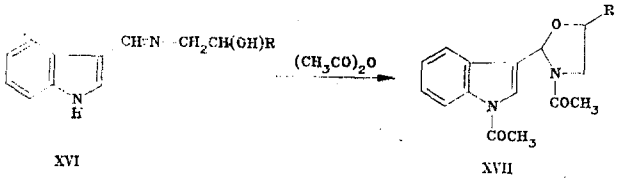
XV

Ar = Ph, $4\text{-}CH_3OC_6H_4$, $4\text{-}BrC_6H_4$, $C_6H_5CH_2$

3-Formylindole does not undergo this reaction, apparently due to insufficient electrophilicity of the carbonyl group carbon atom. The introduction of electron-donor groups in the benzene ring of the amines leads to increased yields of indolylimidazolidines XV. On the other hand, electron-withdrawing substituents hinder the cyclocondensation. For example, indolylimidazolidines could not be prepared from N,N'-di(4-nitrophenyl)- or N,N'-di(4-ethoxycarbonylphenyl)ethylenediamine.

3-Formylindole reacts readily with 2-mercaptoethylamine, which is a stronger nucleophile, to give 2-(indol-3-yl)thiazolidine in high yield [32].

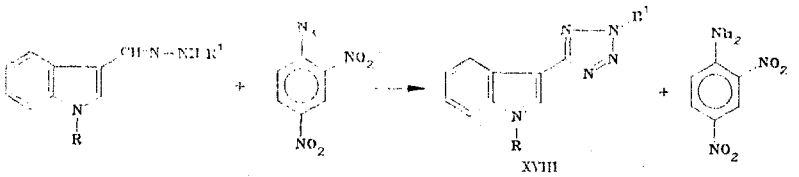
Heating Schiff bases XVI with acetic anhydride gives both acylation and cyclization to form 1-acetyl-2-(1-acetylindol-3-yl)oxazolidines (XVII) [33].



XVI XVII

R = H, CH_3, C_2H_5, Ph, $4\text{-}CH_3C_6H_4$

The reaction of 3-formylindole hydrazones with 2,4-dinitrophenyl azide proceeds anomalously with the formation of 2,5-disubstituted tetrazoles XVIII [34].

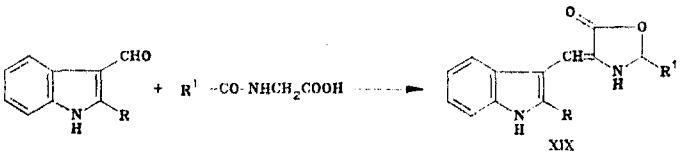


XVIII

R = H, $C_6H_5CH_2$; R^1 = Ph, $4\text{-}BrC_6H_4$, $2,4\text{-}(NO_2)_2C_6H_3$, $CONH_2$

4-(Indol-3-ylmethylene)-5-oxazolones (XIX), which are important intermediates in the synthesis of tryptamine, tryptophan, and other biologically active indoles are readily formed

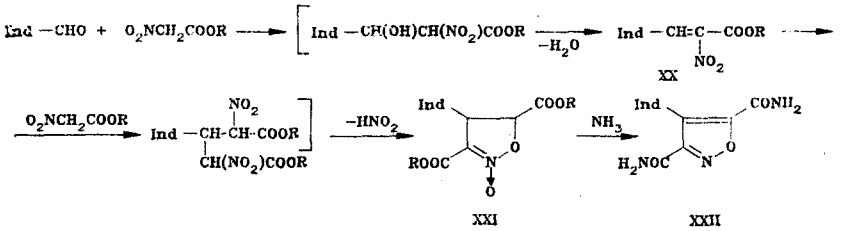
from 3-formylindole and N-acyl derivatives of glycine in the presence of potassium acetate in acetic anhydride [35-38].



XIX

R = H, $COOC_2H_5$; R^1 = CH_3, Ph

The reaction of 3-formylindole with nitroacetate esters in the presence of sodium acetate gives esters of the N-oxides of 4-(indol-3-yl)-3,5-dicarboxyisoxazolines (XXI) [39]. The extremely reactive nitroalkene XX was proposed as an intermediate, which rapidly reacts with the starting nitroesters. The treatment of N-oxides XXI by aqueous ammonia gives the diamide of 4-(indol-3-yl)isoxazole-3,5-dicarboxylic acid (XXII).

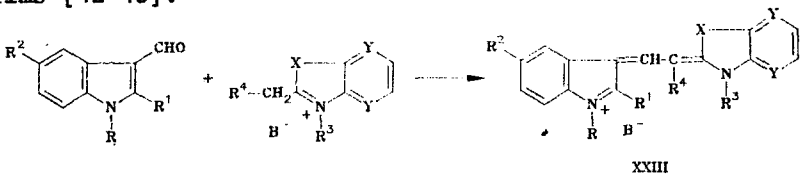


XX XXI XXII

R = CH_3, $C_6H_5CH_2$; here and subsequently, Ind = 3-indolyl

4,5-Diaryl-2-(indol-3-yl)imidazoles were isolated in 60-67% yields as a result of the cyclocondensation of 3-formylindole or its N-methyl derivative with aromatic α-diketones [40, 41].

Indole aldehydes may undergo condensation with some azoles containing active methylene or methyl groups. Thus, cyanine dyes XXIII were synthesized from substituted 3-formylindoles and the corresponding 2-alkylbenzazole salts. These dyes have been proposed for use in photographic films [42-46].

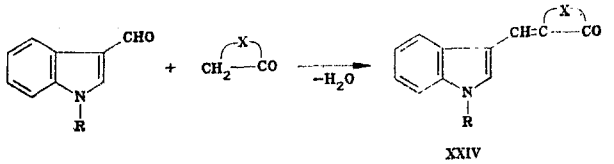


XXIII

R, R^1, R^2, R^3 = H, alkyl, aryl; R^4 = H, CN; X = O, S, Se; Y = CH, N; B^- = I^-, Ts^-, ClO_4^-

Dyes obtained by the condensation of 1-methyl-2-phenyl-3-formylindole with 3-substituted derivatives of 5-pyrazolone and 5-isoxazolone have been used for the same purposes [47, 48].

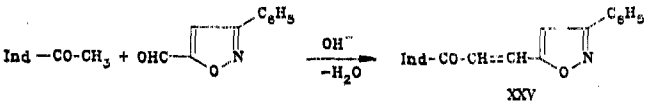
Indolylmethyldenazoles XXIV which display strong anti-inflammatory action are formed by the condensation of 3-formylindoles with derivatives of imidazolidine, isoxazoline, pyrazoline, pyrazoline and thiazolidine containing the —CH_2CO— group in the ring [49-53].



XXIV

X = —NH—CO—NH—, —$C(CH_3)$ = N—O—, —CO—NPh—NR^1—, —CR_3 = N—NR^2—, —NH—CO—S—; R, R^1, R^2 = H, aryl; R^3 = CH_3, NH_2

The Knoevenagel reaction of 3-acetylindole with 5-formyl-3-phenylisoxazoline gave the corresponding α,β-unsaturated ketone XXV [54].



XXV

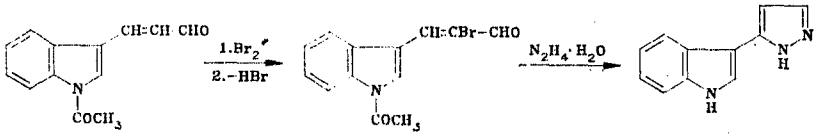
α,β-Unsaturated aldehydes and ketones, α-epoxyketones, β-diketones, and α,β-diketoesters of the indole series are convenient starting compounds for the synthesis of various indolylpyrazoles.

Heating β-(1-acetylindol-3-yl)acrolein (XXVI, R = Ac) with hydrazine hydrate or phenylhydrazine in acetic acid at reflux gave 1-substituted 5-(1-acetylindol-3-yl)pyrazolines (XXVII), which upon treatment with ethanolic alkali are converted to 1-substituted 5-(indol-3-yl)pyrazolines (XXVIII) [55].

The phenylhydrazone of β-(indol-3-yl)acrolein (XXV, R = H) upon heating at reflux in acetic acid is slowly cyclized to 1-phenyl-5-(indol-3-yl)pyrazoline (XXVII, R^1 = Ph). The phenylhydrazone of N-substituted aldehyde XXVI (R = Ac) undergoes more rapid cyclization under the same conditions to give pyrazoline derivative XXVII (R = Ac, R^1 = Ph) and, upon deacylation, pyrazoline XXVIII (R = H, R^1 = Ph).

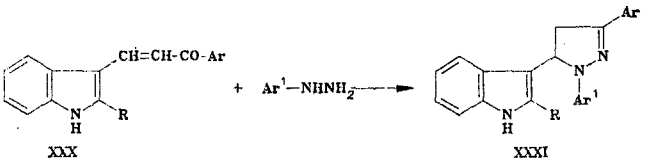
These authors consider that nucleophilic addition at the —CH=CH— double bond is difficult in β-(indol-3-yl)acrolein due to the strong electron-donor effect of the indolyl group. The introduction of an acetyl group at $N_{(1)}$ in the indole system reduces the electron-donor effect of the indole group and increases the reactivity of aldehyde XXVI (R = Ac) relative to nucleophilic reagents.

Suvorov et al. [55] have proposed the following method for the synthesis of 1-phenyl-5-(indol-3-yl)pyrazole (XXIX).



XXVI XXIX

The reaction of 1-(indol-3-yl)-3-aryl-3-propenones (XXX), which are the products of the Knoevenagel reaction of 3-formylindole and methyl aryl ketones, with arylhydrazines lead to the formation of 1,3-disubstituted 5-(indol-3-yl)pyrazolines (XXXI) [56-59].

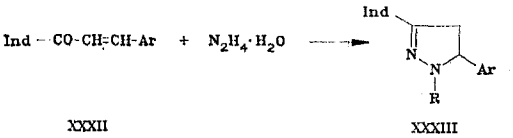


XXX XXXI

R = H, Ar

Indolypyrazolines XXXI have valuable properties and are central nervous system depressants [57], anticonvulsants, monoamine oxidase inhibitors [58], and anti-inflammatory agents [59]. These compounds also have strong luminescence both in the solid state and in solution [56].

Indolylpyrazolines XXXIII which contain indolyl fragments at $C_{(3)}$ of the pyrazoline ring were synthesized by heating 1-(indol-3-yl)-3-aryl-1-propenones (XXXII) with a large excess of hydrazine hydrate [60, 61].

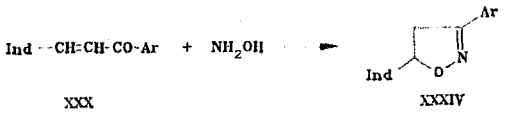


XXXII XXXIII

R = H, Ac

Pyrazolines XXXIII which are not substituted at $N_{(1)}$ of the pyrazoline ring (R = H) are rather unstable compounds which decompose upon purification. However, carrying out the reaction in acetic acid leads to the formation of 1-acetyl derivatives of pyrazolines XXXIII (R = Ac) which are completely stable compounds [61].

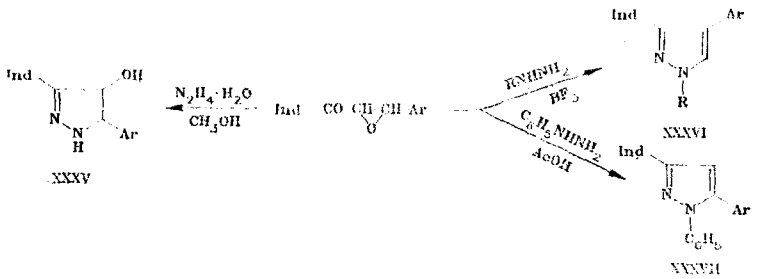
Unsaturated indole ketones may also be used to prepare indolylisoxazolines. For example, the heating of ketones XXX with hydroxylamine gave 3-aryl-5-(indol-3-yl)isoxazolines (XXXIV) [62].



XXX XXXIV

Piozzi and Fuganti [60] studied the reaction of vinyl 3-indolyl ketone with hydroxylamine to give 3-(indol-3-yl)isoxazoline and noted the inability to synthesize analogous isoxazoline derivatives from 1-(indol-3-yl)-3-phenyl-1-propenone (XXXII). lerivatives from 1-(indol-3-yl)-3-phenyl-1-propenone (XXXII).

Considerable interest is found in the reaction of indole α-epoxyketones with hydrazine hydrate, which, depending on the reaction conditions, leads to the formation of either 3-(indol-3-yl)-4-hydroxy-5-arylpyrazolines (XXXV) [54, 63, 64] or 3-(indol-3-yl)-4-arylpyrazoles (XXXVI, R = H) [60]. Pyrazolines XXXV are obtained upon carrying out the cyclocondensation in alcohol using catalytic amounts of acetic acid, while pyrazoles XXXVI are obtained in ether in the presence of $BF_3 \cdot O(C_2H_5)_2$.

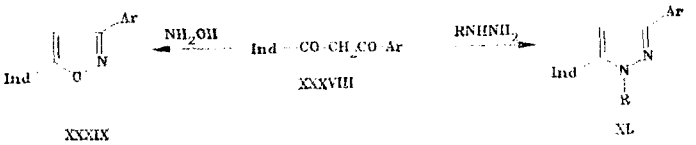


XXXV XXXVI XXXVII

R = H, Ph

Carrying out this reaction in acetic acid gives 1-phenyl-3-(indol-3-yl)-5-arylpyrazoles (XXXVII) [63, 64], while 1-phenyl-3-(indol-3-yl)-4-arylpyrazoles (XXXVI, R = Ph) were obtained in ether in the presence of BF_3 etherate [60].

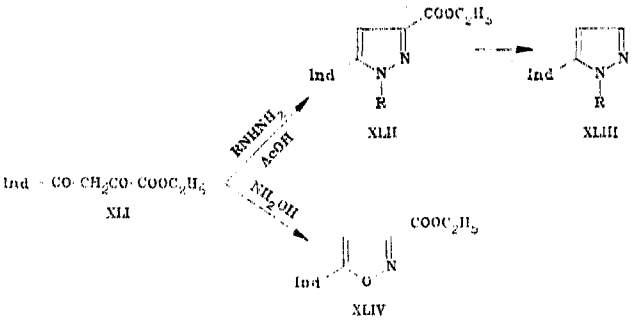
The reaction of β-diketones XXXVIII with hydroxylamine gave 3-aryl-5-(indol-3-yl)isoxazolines (XXXIX) [66], while the action of hydrazine hydrate or phenylhydrazine gave 3-aryl-5-(indol-3-yl)pyrazoles (XL) [64, 67].



XXXIX XXXVIII XL

R = H, Ph

The ethyl ester of 4-(indol-3-yl)-2,4-butanedionoic acid (XLI) reacts with hydrazine hydrate or phenylhydrazine in acetic acid to form the ethyl esters of 1-R-5-(indol-3-yl)pyrazole-3-carboxylic acids (XLII), which were converted to 1-R-5-(indol-3-yl)pyrazoles (XLIII) upon subsequent hydrolysis to the acid and decarboxylation; these pyrazoles have high anti-inflammatory activity [68, 69].

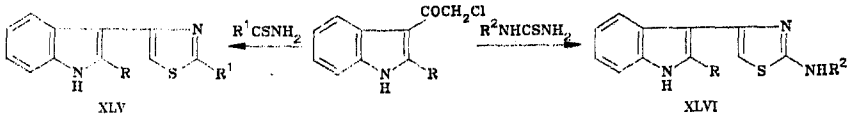


R = H, Ph

Treatment of β-diketoester XLI with hydroxylamine in the presence of pyridine gives a high yield of the ethyl ester of 5-(indol-3-yl)isoxazole-3-carboxylic acid (XLIV) [70]. An interesting transformation occurs in the reaction of ester XLIV with hydrazine hydrate in ethanol at reflux which gives the hydrazide of 5-(indol-3-yl)pyrazole-3-carboxylic acid.

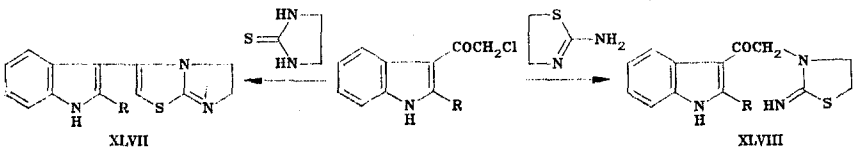
Indole α-haloketones have been used in the synthesis of indolylimidazoles and indolylthiazoles. Thus, heating 3-chloroacetylindole with a large excess of formamide gives 4(5)-(indol-3-yl)imidazole [71], while heating with a stoichiometric amount of formamide and phosphorus pentasulfide gives 4-(indol-3-yl)thiazole [72]. Suvorov et al. [71] noted the inability to extend this method for the preparation of indolylimidazoles from the amides of other acids. For example, the reaction of 3-chloroacetylindole with acetamide proceeds with heavy tar formation and 2-methyl-4-(indol-3-yl)imidazole was isolated from the reaction mixture in only a 4% yield.

The cyclocondensation of 3-chloroacetylindoles with acid thioamides gives 2-substituted 4-(indol-3-yl)thiazoles (XLV) [14, 73], while this reaction with thiourea or N-substituted thioureas gives 2-amino-4-(indol-3-yl)thiazoles (XLVI) or their N-substituted derivatives [14, 72].



R = H, CH_3; R^1 = CH_3, aryl, pyridyl-3; R^2 = H, CH_3, NH_2, C(=NH)NH_2

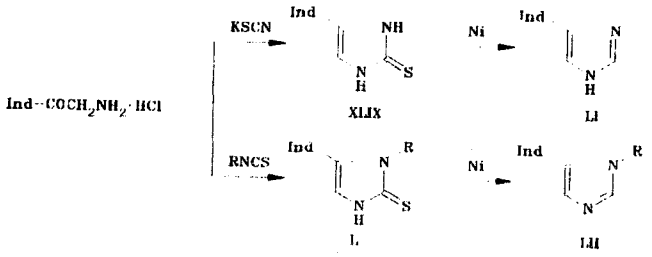
Significant interest is found in the condensation of 3-chloroacetylindoles with the functional derivatives of several azoles in the synthesis of indolylazoles. For example, the reaction of α-chloroketones with 2-imidazolidinethione gives 5,6-dihydro-3-(2-R-indol-3-yl)-thiazolo[3,2-a]imidazoles (XLVII) while this reaction with 2-amino-Δ^2-thiazoline gives 2-imino-3-[1-oxo-1-(2-R-indol-3-yl)ethyl]thiazolidines (XLVIII) [14].



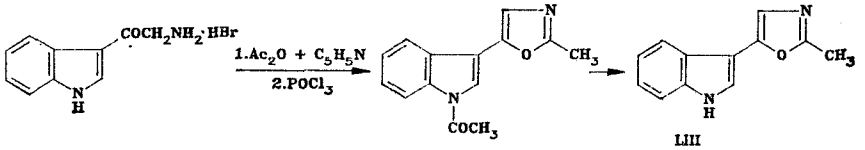
R = H, CH_3

Indolylthiazoles XLV-XLVIII have a broad range of pharmaceutical activity and are central nervous system depressants, analgesics, and antibacterial agents as well as substances used for lowering arterial pressure [14, 72, 73].

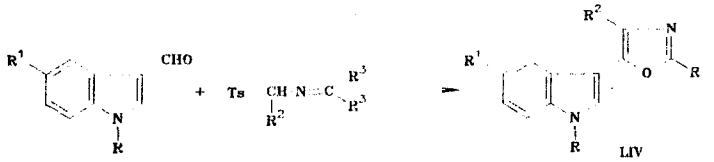
3-Aminoacetylindole hydrochloride was used in the synthesis of indolylimidazoles [71, 74]. The reaction of this hydrochloride with molten potassium thiocyanate gives a 16% yield of 5-(indol-3-yl)-2-imidazolethione (XLIX). Heating this hydrochloride with an equivalent amount of isothiocyanates gives 1-substituted 5-(indol-3-yl)-2-imidazolethiones (L) in 30-50% yield. The desulfurization of 2-imidazolethiones XLIX and L by Raney nickel in ethanol leads to the corresponding indolylimidazoles LI and LII which display tuberculostatic activity [71, 74].



The antibiotic pimprinine was isolated from several natural products and identified in 1960 as 2-methyl-5-(indol-3-yl)oxazole (LIII) [75]. The structure of pimprinine was confirmed by its synthesis from 3-aminoacetylindole hydrobromide [76-78].

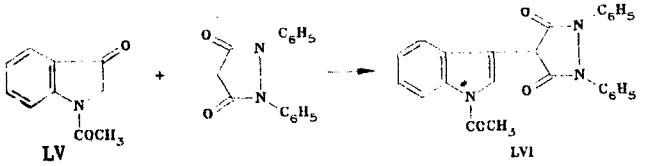


In 1981, Houwing et al. [79, 80] reported the preparation of pimprinine analogs (LIV) by the condensation of substituted 3-formylindoles with α-tosylisocyanide or with dimethoxy-N-tosylmethylimine; these analogs display antihistiminic activity [80].



R = CH_3, $(CH_3)_2NCO$; R^1 = H, CH_3O, NO_2; R^2 = H, CH_3; R^3 = H, CH_3O

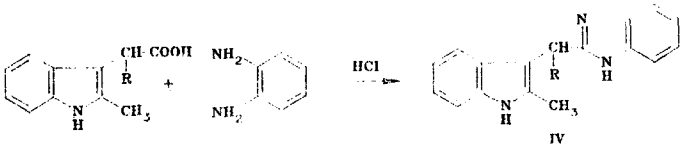
There has been a report of the use of 1-acetylindoxyl (LV) as the starting agent for the preparation of some indolylazoles. For example, the condensation of indoxyl LV with 1,2-diphenyl-3,5-pyrazolidinedione gives a quantitative yield of 1,2-diphenyl-4-(1-acetylindol-3-yl)-3,5-pyrazolidinedione (LVI) [81].



Heating carboethoxyisopropylidene hydrazone with 1-acetylindoxyl in polyphosphoric acid at 90°C gives intramolecular cyclization with the formation of 3-methyl-1-(1-acetylindol-3-yl)-5-pyrazolinone [82].

4. PREPARATION OF INDOLYLAZOLES FROM INDOLE CARBOXYLIC ACIDS AND THEIR FUNCTIONAL DERIVATIVES

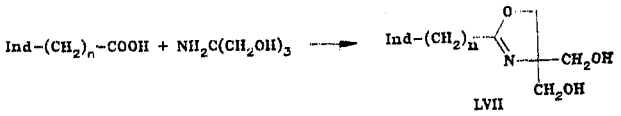
Indole acids themselves have rarely been used for the preparation of indolylazoles until recently. The condensation of derivatives of indol-3-ylacetic acids with o-phenylenediamine leading to the corresponding 2-(indol-3-ylmethyl)benzimidazoles (IV) [9] has been described in [9].



R = H, C_4H_9

The reaction was carried out by heating the corresponding acids with a large excess of o-phenylenediamine in 4 N hydrochloric acid at reflux. However, the yields of indolylbenzimidazoles did not exceed 30%.

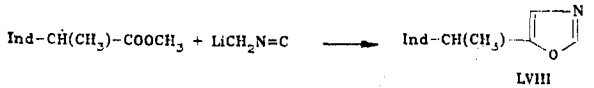
The reaction of ω-(indol-3-yl)alkanoic acids with tris(hydroxymethyl)methylamine gave 4-di(hydroxymethyl)-2-ω-[(indol-3-yl)alkyl]-Δ^2-oxazolines (LVII) [64].



LVII

n = 1-4

5-[α-(Indol-3-yl)ethyl]oxazole (LVIII) is an important intermediate in the synthesis of the alkaloid, ellipticine which stimulates brain activity and was prepared by the reaction of the methyl ester of 2-(indol-3-yl)propionic acid with lithium methyl isocyanide at −50°C [83].



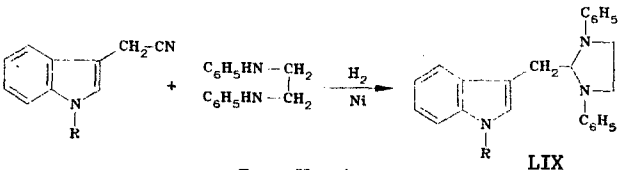
LVIII

Suvorov et al. [84] used the condensation of ethyl (indol-3-ylmethyl)malonate with hydrazobenzene in ethanol in the presence of sodium ethylate to obtain 1,2-diphenyl-4-(indol-3-ylmethyl)pyrazolidine-3,5-dione.

S-[α-Carbomethoxy-β-(indol-3-yl)ethyl]thiuronium hydrobromide obtained from the methyl ester of α-bromo-β-(indol-3-yl)propionic acid and thiourea is cyclized upon heating in water to give 5-(indol-3-ylmethyl)thiazolidine-2,4-dione which has tuberculostatic activity [85].

Of all the functional derivatives of indolecarboxylic acids used as starting materials in the preparation of indolylazoles, the nitriles of indole acids have been studied most extensively.

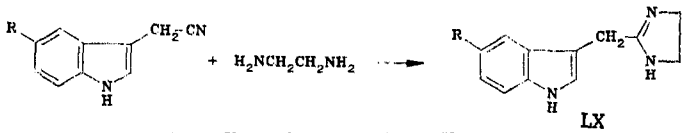
The hydrogenation of 3-indolylacetonitriles or their N-acetyl derivatives over Raney nickel in the presence of N,N'-diphenylethylenediamine leads to 1,3-diphenyl-2-(indol-3-ylmethyl)imidazolidines (LIX) [86, 87].



LIX

R = H, Ac

Great interest has been found in the reaction of 3-indolylacetonitriles with ethylenediamine which gives indolylimidazolines [88-94]. Thus, heating these nitriles with anhydrous ethylenediamine in the presence of sulfur compounds gives 2-(indol-3-ylmethyl)-Δ^2-imidazoles (LX). Hydrogen sulfide, carbon disulfide, phosphorus pentasulfide, aluminum sulfide [88] and p-toluenesulfonic acid have been used as catalysts for this reaction [89, 94].

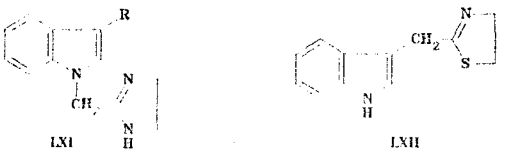


LX

R = H, Cl, Br, F, CH_3O

Indolylimidazolines LX which may be formally considered as tryptamine derivatives have various biological activities and are antidepressants, vasoconstrictors [91], repellants [92], and serotonin antimetabolites [90].

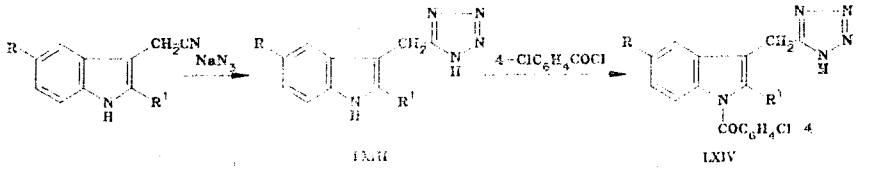
Analogously, 1-cyanomethyl-3-alkylindoles and ethylenediamine give 3-alkyl-1-(imidazolinyl-2-methyl)indoles (LXI), which display strong vasoconstrictor activity [93].



LXI LXII

The cyclocondensation of indol-3-ylacetonitrile with β-mercaptoethylamine gives good yield of 2-(indol-3-ylmethyl)-Δ^2-thiazoline (LXII), which combines significant bacteriostatic activity with low toxicity [95].

In the search for effective anti-inflammatory agents, a series of indomethacine analogs LXIV has been prepared containing a tetrazole residue instead of the carboxyl group. The synthesis of these compounds is carried out by the prolonged heating of 3-indolylacetic acids with sodium azide and aluminum chloride [96] or ammonium chloride [97] in DMF or THF. These tetrazoles (LXIII) were subsequently acylated at the nitrogen atom of the indole fragment in the presence of sodium hydride [97-100].

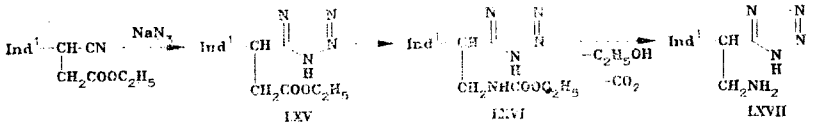


LXIII LXIV

R = H, Cl, Br, CH_3O; R^1 = H, CH_3

Of all the compounds synthesized, greatest activity was found for 5-(1-p-chlorobenzoylindol-3-ylmethyl)tetrazole (LIV, R = R^1 = H) [97]. This compound also has antiserotonin and antihistimine activities [98, 100].

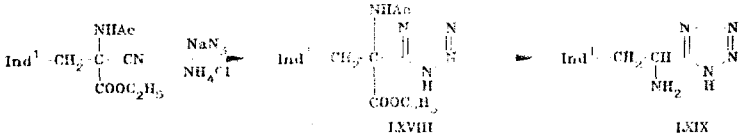
The reaction of ethyl ester of 3-cyano-3-(indol-3-yl)propionic acid with sodium azide and ammonium chloride gives the ester of 3-(tetrazol-5-yl)-3-(indol-3-yl)propionic acid (LXV), which upon hydrazinolysis and subsequent Curtius rearrangement in the presence of ethanol is converted to the corresponding urethane LXVI. Upon alkaline hydrolysis and decarboxylation, LXVI gives β-(tetrazol-5-yl)tryptamine (LXVII) which displays antidepressant and hypotensive activities [101].



LXV LXVI LXVII

Ind^1 = 4-chloroindol-3-yl, 4-chloro-5-methoxyindol-3-yl, 6-chloro-5-methoxyindol-3-yl

N-Acetyl-α-cyano-β-carboethoxy-6-chlorotryptamine reacts with sodium azide in the presence of $AlCl_3$ to give the corresponding tetrazole LXVIII, which upon alkaline hydrolysis is converted to α-(tetrazol-5-yl)-6-chlorotryptamine (LXIX) [102].

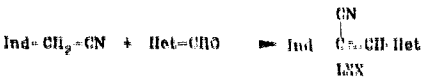


LXVIII LXIX

Ind^1 = 6-chloroindol-3-yl

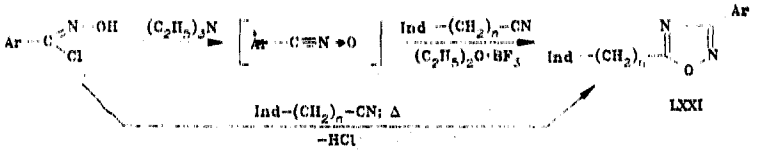
Taborsky [103] obtained an unusual result upon the prolonged heating of indol-3-ylacetonitrile with anhydrous hydrazine (in 2:1 mole ratio), which yielded 4-amino-3,5-bis(indol-3-ylmethyl)-1,2,4-triazole.

Indol-3-ylacetonitrile has been used in the Knoevenagel reaction with several heterocyclic aldehydes to give trisubstituted ethylenes LXX [104].



Het = 1-methylpyrazol-4-yl, 1-benzylimidazolin-2-yl, 4-methylthiazol-2-yl

A convenient method for the preparation of indolyloxadiazoles entails the 1,3-dipolar cycloaddition of indole nitriles with nitrile N-oxides [105]. Thus, 3-cyanoindole, indol-3-ylacetonitrile and β-(indol-3-yl)propionitrile and aromatic nitrile N-oxides, generated *in situ* from the corresponding arylhydroxamic acid chlorides, gave 3-aryl-5-[(indol-3-yl)alkyl]-1,2,4-oxadiazoles (LXXI).



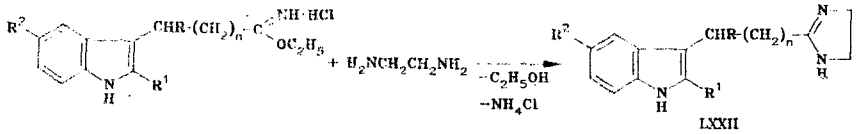
n = 0, 1, 2; Ar = Ph, 4-$O_2NC_6H_4$, 4-ClC_6H_4, 3-$CH_3C_6H_4$

Dyankova et al. [106, 107] have found that the best yield of adducts LXXI is achieved upon carrying out this reaction in the presence of boron trifluoride etherate, which enhances the dipolarophilic activity of the nitrile group due to complexation. Oxadiazoles LXXI were also obtained upon heating of these nitriles and arylhydroxamic acid chlorides in an inert solvent for ≥48 h.

These authors [105-107] have noted that the yields of adducts LXXI synthesized by the thermal condensation of nitriles with arylhydroxamic acid chlorides are significantly higher than in the reaction with nitrile N-oxides.

Carboxylic acid iminoester hydrochlorides may be used as convenient starting materials in the synthesis of various azoles. However, only limited information is available on the use of indole acid iminoester hydrochlorides for these purposes.

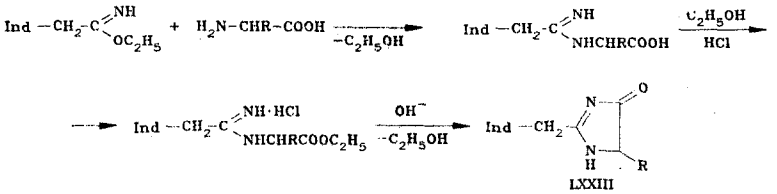
The condensation of indolylalkanoic acid iminoester hydrochlorides with ethylenediamine has been described [108-110]. This reaction proceeds rapidly under mild conditions and gives a high yield of 2-substituted Δ^2-imidazolines (LXXII).



R = H, Ph, 3-$CH_3OC_6H_4$; R^1 = H, CH_3; R^2 = H, Cl, CH_3O; n = 0, 1

2-[β-(Indol-3-yl)phenethyl]-Δ^2-imidazoline hydrochloride (LXXII, R = Ph, R^1 = R^2 = H, n = 1) displays strong sympatholytic activity [108]. We should also note that 2-(indol-3-ylalkyl)-Δ^2-imidazolines (LXXII, n = 1) have recently been found to possess pronounced radioprotective activity [5, 110].

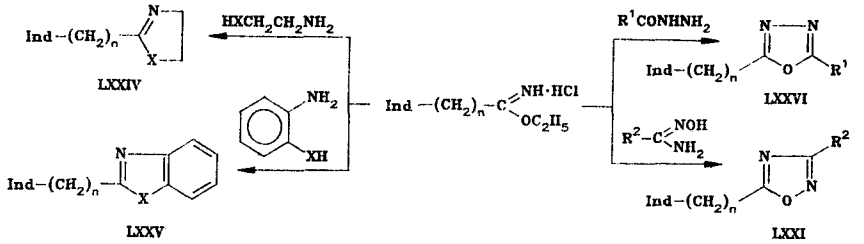
Fel'dman et al. [111] have synthesized 5-imidazolones (LXXIII), which are unstable under ordinary conditions, from the ethyl iminoester of 3-indolylacid and α-amino acids according to the scheme:



R = H, i-C_3H_7, i-C_4H_9, s-C_4H_9, indol-3-ylmethyl

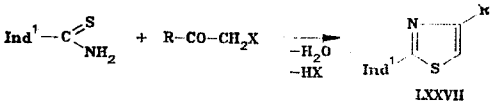
In our previous work [112-116], we have shown that the cyclocondensation of carboxylic acid iminoester hydrochlorides with 1,2-bifunctional compounds yields a large number of var-

ious azoles. Thus, the reactions of 3-indolecarboxylic and 3-indolylacetic acid ethyl hydrochlorides with N-monosubstituted ethylenediamines, monoethanolamine, o-phenylenediamine, o-aminophenol, hydrazides, and acid amidoximes lead to the corresponding 2-substituted Δ^2-imidazolines (LXXIV, X = NR), Δ^2-oxazolines (LXXIV, X = O), benzimidazoles (LXXV, X = NH), benzoxazoles (LXXV, X = O), 2,5-disubstituted 1,3,4-oxadiazoles (LXXVI), and 3,5-disubstituted],2,4-oxadiazoles (LXXI).



n = 0, 1; X = NH, NR, O; R = H, $C_6H_5CH_2$, CH_2CH_2CN, 2-thienylmethyl; R^1 = H, CH_3, Ph, 4-$O_2NC_6H_4$, 4-ClC_6H_4, 5-nitro-2-furyl, indol-3-yl, indol-3-ylmethyl; R^2 = CH_3, CH_2Cl, Ph, 5-nitro-2-furyl

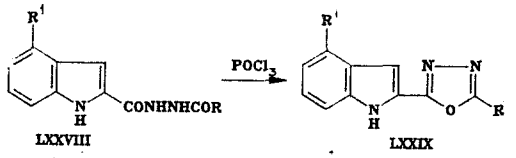
The use of indole acid thioamides for the preparation of indolylazoles has been indicated only in a report of the cyclocondensation of 1-methyl-2-indolcarboxylic and 3-indolecarboxylic acid thioamides with halomethyl ketones to give 2-indolyl-4-substituted thiazoles (LXXVII) [117, 118].



Ind^1 = 1-methylindol-2-yl, indol-3-yl, R = CH_3, CH_2Cl, Ph, 4-$CH_3OC_6H_4$, 2-thienyl, X = Cl, Br

Indole acid hydrazides have found as yet only limited use for the preparation of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, and 1,2,4-triazoles containing indole fragments.

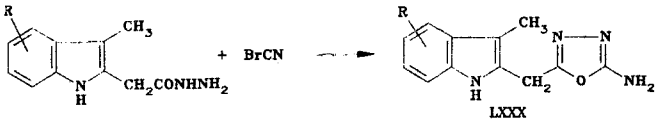
Heating N-acyl derivatives of 2-indolecarboxylic acid hydrazides (LXXVIII) with $POCl_3$ gave 2-substituted 5-(indol-2-yl)-1,3,4-oxadiazoles (LXXIX) [119, 120].



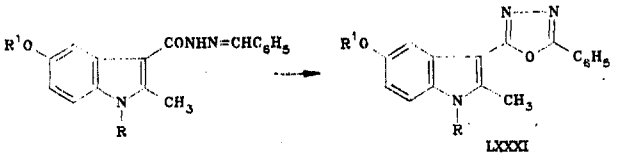
R = H, CH_3, CH_2Cl, $CHCl_2$, Ph; R^1 = H, Cl

5-(Indol-2-yl)-1,3,4-oxadiazole (LXXIX, R = R^1 = H) was also synthesized by the reaction of 2-indolecarboxylic acid hydrozide with ethyl orthoformate [119, 121]. Robba [119] and Ainsworth [121] have noted that heating N-acyl derivatives LXXVII with phosphorus pentasulfide gives low yields of 2,5-disubstituted 1,3,4-thiadiazoles.

Hydrazides of substituted 2-indolylacetic acids upon treatment with cyanogen bromide in an inert solvent give 2-amino-1,3,4-oxadiazoles (LXXX) [122].



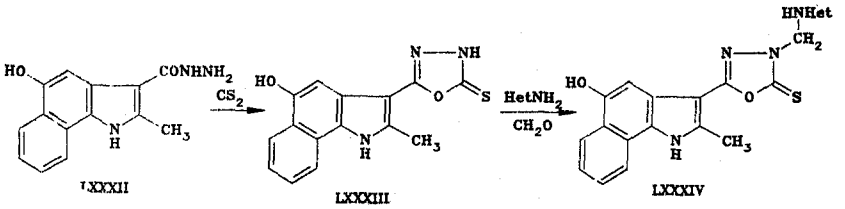
Treatment of benzylidene derivatives of substituted 3-indolecarboxylic acid hydrazides with bromine in the presence of sodium acetate in acetic acid or iron chloride in ethanol gives a 38-40% yield of 2-phenyl-1,3,4-oxadiazoles (LXXXI) containing indole fragments at $C_{(5)}$ [123].



LXXXI

R = H, C_6H_5CO; R^1 = H, CH_3

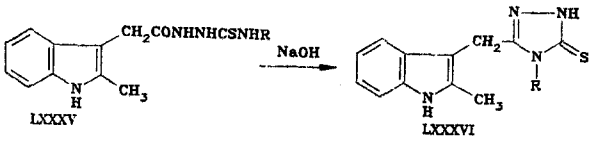
Hiremath et al. [123] also showed that the reaction of 5-hydroxy-2-methylbenz[g]indole-3-carboxylic acid (LXXXII) with carbon disulfide and base in ethanol gives the corresponding 1,3,4-oxazole-5-thione LXXXIII, which upon the action of formaldehyde and 2-aminothiazoles is converted to Mannich bases LXXXIV, which display antimicrobic activity.



LXXXII LXXXIII LXXXIV

Het = 4-phenylthiazol-2-yl, 4-ethyl-5-methylthiazol-2-yl, benzthiazol-2-yl

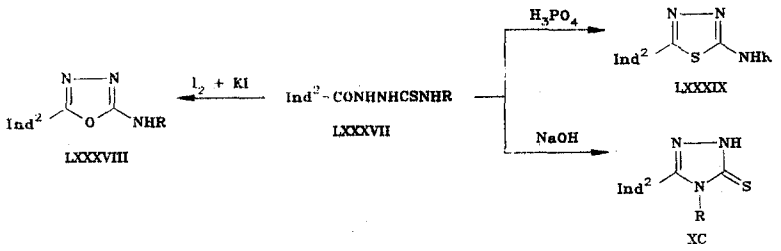
Upon heating at reflux in alkaline solution, 1-(2-methylindol-3-ylacetyl)-4-R-thiosemicarbazides (LXXXV) cyclize to give high yields of 4-R-3-(2-methylindol-3-ylmethyl)-1,2,4-triazoline-5-thiones (LXXXVI) which are cardiac activity stimulators [124].



LXXXV LXXXVI

R = CH_3, CH_2 = CH—CH_2, Ph, 4-ClC_6H_4

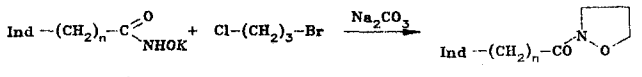
Hiremath et al. [125] in 1981 reported the synthesis of various types of indolylazoles using thiosemicarbazides LXXXVII. The oxidative cyclization of LXXXVII by iodine in an alkaline solution of potassium iodide gives N-substituted 2-amino-1,3,4-oxadiazoles (LXXXVIII). Heating LXXXVII with orthophosphoric acid gives 40-45% yields of N-substituted 2-amino-1,3,4-thiadiazoles (LXXXIX), while heating of this compound with aqueous alkali gives 4-R-1,2,4-triazoline-5-thiones (XC).



LXXXVIII LXXXVII LXXXIX XC

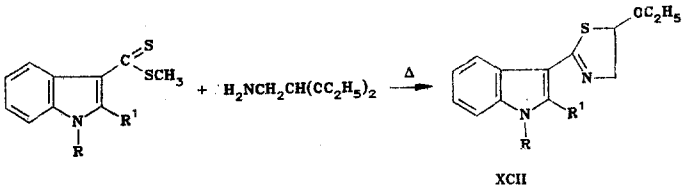
Ind^2 = 5-hydroxy-2-methylbenzo[g]indol-3-yl, R = CH_3, Ph

Indolylisoxazolidines XCI are formed in 50-60% yield upon the treatment of potassium salts of indol-3-ylalkylhydroxamic acids by 1-chloro-3-bromopropane in the presence of base [126].



n=1,3 XCI

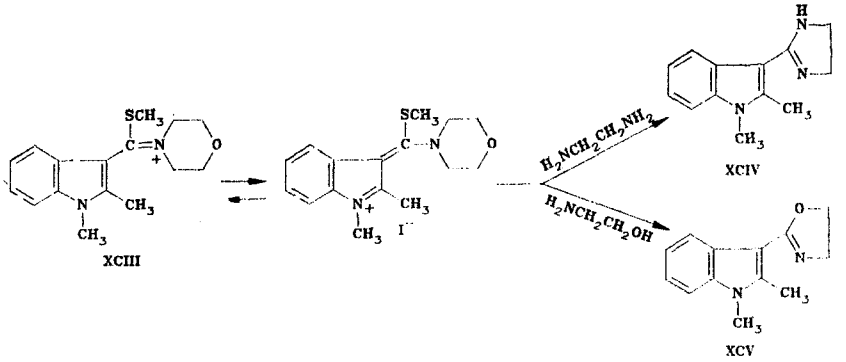
The reaction of methyl thioesters of substituted indole-3-dithiocarboxylic acids with aminoacetaldehyde diethylacetal has been used to prepare 3-(5-ethoxy-Δ^2-thiazolin-2-yl)indoles (XCII) [127].



XCII

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

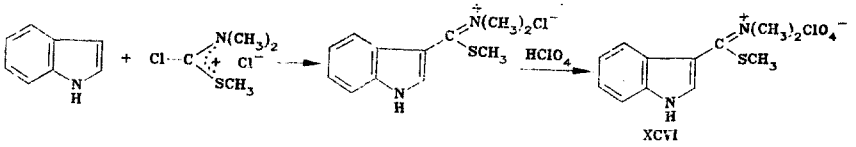
Tominada et al. [128] have described the preparation of indole derivatives of Δ^2-imidazolines XCIV or Δ^2-oxazolines XCV from the iodomethylate of 1,2-dimethyl-3-indolcarboxylic acid thiomorphilide (XCIII) and ethylenediamine or ethanolamine, respectively.



XCIII XCIV XCV

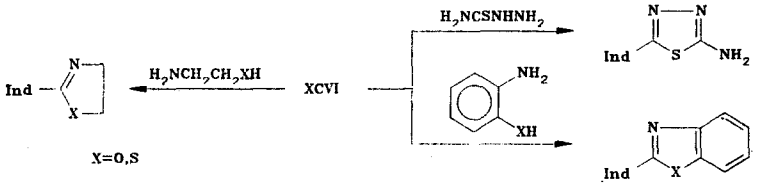
However, the starting sulfur-containing compounds are not readily prepared due to disadvantages of the latter two synthetic methods.

Harris [129] has proposed using indol-3-yltrimethylthioformamidinium perchlorate (XCVI) obtained from indole and chlorotrimethylthioformamidinium chloride as the key compound for the synthesis of indolylazoles.



XCVI

Salt XCVI has high reactivity in reactions with bifunctional nucleophilic reagents and thus various hetarylindoles may be prepared using this compound [130].



X=O,S

However, in using this method, we encounter great difficulties due to the extremely hygroscopicity and instability of the starting chlorotrimethylthioformamidinium chloride and perchlorate, which require special care in their use.

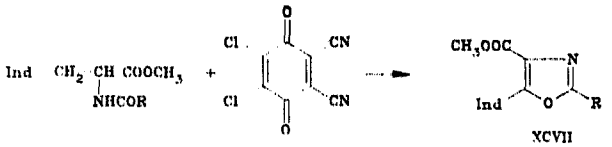
Indole amino acids and hydroxyacids and their derivatives have also been used for the synthesis of several types of indolylazoles.

Thus, tryptophan and ammonium thiocyanate in acetic anhydride gave 1-acetyl-5-(indol-3-ylmethyl)-2-thio-4-imidazolone [131, 132]. The use of phenyl isocyanate instead of ammonium thiocyanate gives 3-phenyl-5-(indol-3-ylmethyl)-2-thio-4-imidazolone [133, 134].

2-Methyl-4-(indol-3-ylmethylen)-5-oxazolone (XIX) was synthesized by the Bergman method involving treatment of N-chloroacetyltryptophan by acetic anhydride in pyridine [37].

Oki and Nagasaka [135, 136] have synthesized 4-(1-acetylindol-3-ylmethyl)-2,5-oxasolidinedione which displays strong anti-inflammatory activity and is a central nervous system stimulant by the action of phosgene on 1-acetyltryptophan.

Considerable interest is found in the method of Oikawa et al. [137, 138] for the preparation of analogs of the pyrimidine antibiotic, 2-methyl-5-(indol-3-yl)oxazole (LIII) which entails the oxidation of the methyl ester of N-acyltryptophan by dichlorodicyanobenzoquinone in anhydrous THF to give a high yield of 2-substituted 4-carbomethoxy-5-(indol-3-yl)oxazoles (XCVII).

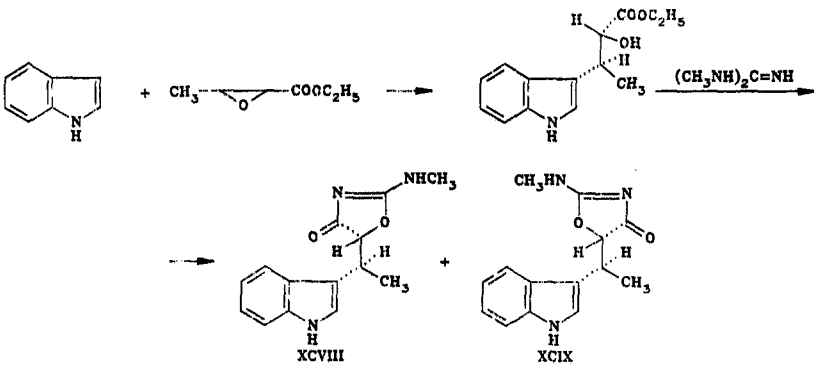


XCVII

R = CH_3, Ph, 4-$CH_3OC_6H_4$

The reaction of tryptophan amide with acetone gave 4-(indol-3-ylmethyl)-5-imino-2,2-dimethyloxazolidine, which is converted upon hydrolysis to the corresponding 5-oxasolidinone, which is an inhibitor of tyrosine and histidine decarboxylases [139].

In 1960, Rao [140] isolated the antibiotic indolemycin from natural substances and identified it as 2-methylamino-5-[α-(indol-3-yl)ethyl]-4-oxazolinone. In 1963, this antibiotic was prepared as a mixture of two isomers XCVIII and XCIX by the scheme of Shach et al. [141].



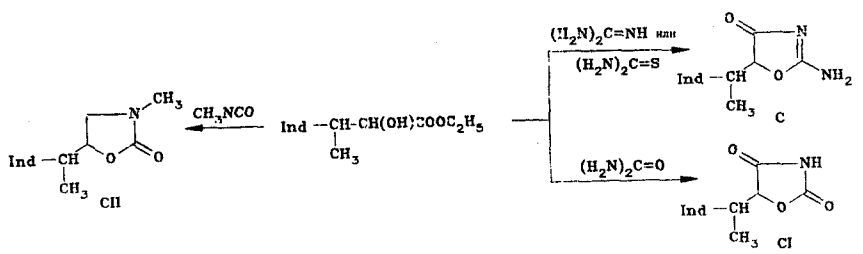
XCVIII XCIX

In addition to indolemycin XCVIII itself, the condensation of the ethyl ester of α-hydroxy-β-(indol-3-yl)butyric acid (α-indolemycinic acid) with N,N'-dimethylguanidine gives some amount of isoindolemycin XCIX as a result of the ready stereoisomerization of indolemycin under alkaline conditions [141].

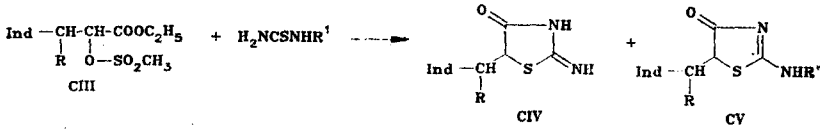
Preobrazhenskaya et al. [142-144] have shown that, in addition to N,N'-dimethylguanidine, N-methylthiourea may be used as the second component of the reaction for the preparation of indolemycin.

The cyclocondensation of the esters of racemic indolemycinic acids with guanidine or urea and several other compounds was studied in order to prepare indolemycin analogs and determine their biological activity [145].

The reaction of indolymycinic acid esters with guanidine or thiourea gives a mixture of racemic 2-amino-5-[α-(indol-3-yl)ethyl]-Δ^2-oxazolin-4-ones (C) [145]. The condensation of these esters with urea leads to a mixture of diastereomeric 5-[α-(indol-3-yl)ethyl]- Δ^2-oxazolidine-2,4-diones (CI), while this reaction with methyl isocyanate leads to diastereomeric 3-methyl-5-[α-(indol-3-yl)ethyl]-Δ^2-oxazolidine-2,4-diones (CII), which are also formed upon the methylation of 2,4-oxazolidinediones CI, which, in turn, may be obtained by the hydrolysis of 2-amino-Δ^2-4-oxazolinones C [145].



The methyl esters of racemic α-hydroxy-β-(indol-3-yl)propionic acids serve as starting materials for the preparation of thiazoline analogs of indolemycin. Upon the action of methanesulfonyl chloride, these esters are converted to O-mesylates CIII. The condensation of CIII with thiourea or its derivatives gives a mixture of 2-imino-3-R-5-(indol-3-ylalkyl)-4-thiazolinone (CIV) and 2-amino-5-(indol-3-ylalkyl)-Δ^2-thiazolin-4-one (CV) [146-148].



CIII CIV CV

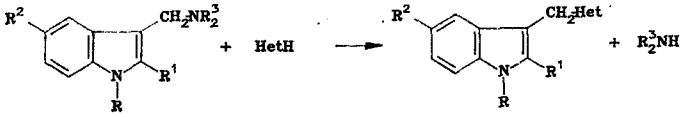
R, R^1 = H, CH_3

Diastereomeric 2-methyl-5-[α-(indol-3-yl)ethyl]-Δ^2-thiazolin-4-ones (CV, R = R^1 = CH_3) and their derivatives obtained upon acylation of the indole ring at the nitrogen atom are effective antiviral compounds [148].

5. SYNTHESIS OF INDOLYLAZOLES FROM INDOLE AMINES

The N-alkylation of azoles of indole Mannich bases, 3-(N,N-dimethylaminomethyl)indole (gramine), 3-(N-piperidinomethyl)indole [149-151] and substituted gramines [152-154] has been used rather commonly for the preparation of indolylazoles.

With the exception of benzimidazole, heterocyclic substrates are alkylated only in aprotic media such as upon heating in xylene at reflux [150, 151].



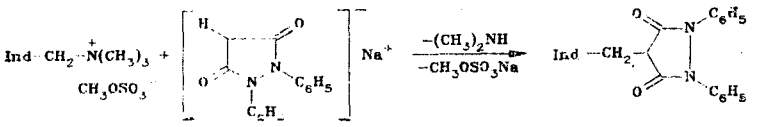
CVI

R, R^1 = H, alkyl, alkenyl, acyl, $C_6H_5CH_2$; R^2 = H, alkyl, alkoxy, HO, CF_3, NH_2; R^3 = CH_3; R_2^3 = $(CH_2)_5$; Het = imidazol-1-yl, pyrazol-1-yl, benzimidazol-1-yl, benztriazol-1-yl

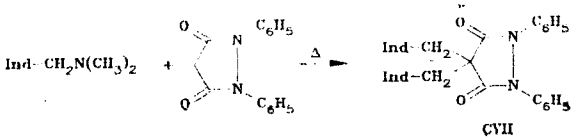
It is noteworthy that in addition to the direct alkylation product in the alkylation of indole by 1-(N-piperidinomethyl)benzimidazole, namely, 1-(indol-3-ylmethyl)benzimidazole (CVI, R = R^1 = R^2 = H), 3-(N-piperidinomethyl)indole is formed as the result of a transamination reaction and benzimidazole is also obtained [149]. On the other hand, the action of indole Mannich bases on azoles does not yield transamination products.

Greatest interest among indolylazoles CVI is found for substituted 1-(indol-3-ylmethyl)-imidazoles which may be used as drugs in cardiac disease, thromboses, and diabetes-related vascular problems [153-156].

As noted above, the condensation of ethyl 3-indolylmethylmalonate with hydrazobenzene leads to 1,2-diphenyl-4-(indol-3-ylmethyl)-3,5-pyrazolidinedione [84]. Subsequently, this compound was obtained in higher yield by treating the sodium salt of 1,2-diphenyl-3,5-pyrazolidinedione by the methylsulfomethylate of gramine in DMF [157].

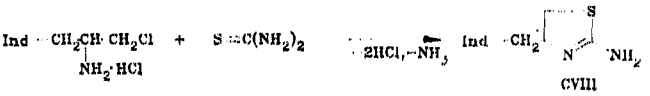


Vampilova [157] also indicated that the reaction of gramine itself with 1,2-diphenyl-3,5-pyrazolidinedione gives exclusively the dialkylation product CVII. The dialkylation reaction is facilitated by an increase in temperature to 160°C and the use of polar aprotic solvents.



CVII

The synthesis of 2-amino-4-(indol-3-ylmethyl)-Δ^2-thiazoline (CVIII) from α-chloromethyltryptamine hydrochloride and thiourea was carried out in a search for radioprotective indole derivatives [158].

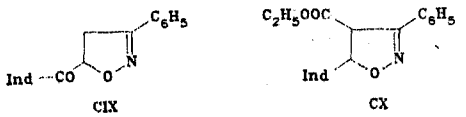


CVIII

6. THE PREPARATION OF INDOLYLAZOLES FROM OTHER INDOLE DERIVATIVES

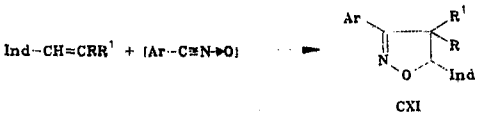
Presently, one of the most general methods for the synthesis of various heterocyclic systems is the 1,3-dipolar cycloaddition reaction. Despite extensive studies in this area, the information of the participation of indole derivatives in these reactions has been limited. The use of indole acid nitriles as dipolarophiles in 1,3-dipolar cycloaddition with nitrile N-oxides has already been discussed above [105-107].

Piozzi and Fuganti [60] have synthesized the corresponding indolylisoxazolines CIX and CX in the reaction of vinyl 3-indolyl ketone or the ethyl ester of β-(indol-3-yl)acrylic acid with benzonitrile N-oxide.



CIX CX

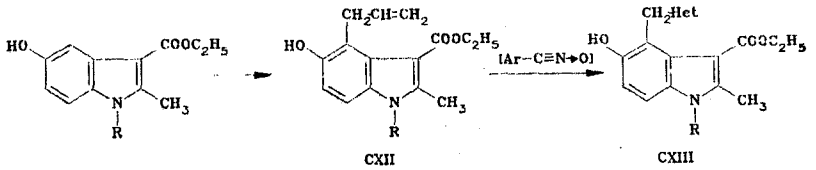
Dyankova [106] has described the cyclocondensation of several substituted indolealkenes with aromatic nitrile N-oxides to give 4-substituted 3-aryl-5-(indol-3-yl)-Δ^2-isoxazolines (CXI) in 17-53% yield.



CXI

R = NO_2, CN, $COCH_3$; R^1 = H, $COOC_2H_5$; Ar = Ph, 4-$O_2NC_6H_4$

A series of indolylisoxazolines with interesting pharmacological properties was obtained upon the introduction of the isoxazoline fragment into known indole drugs, namely, dimecarbine (5-hydroxy-3-ethoxycarbonyl-1,2-dimethylindole) and oxyfemedol (5-hydroxy-3-ethoxycarbonyl-1-phenyl-2-methylindole) [106, 159]. The alkylation of these derivatives at $C_{(4)}$ yielded the corresponding allyl derivatives CXII. These dipolarophiles were used in the 1,3-dipolar cycloaddition with aromatic nitrile N-oxides.

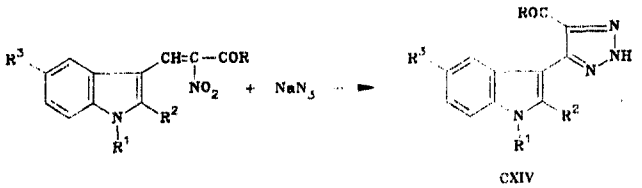


CXII CXIII

R = CH_3, Ph; Ar = Ph, 4-$O_2NC_6H_4$, 4-ClC_6H_4; Het = 3-aryl-Δ^2-isoxazolin-5-yl

The adducts synthesized in this reaction CXIII inhibit cholinesterase activity and act as central nervous system stimulators and hypotensive agents.

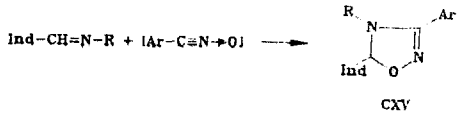
The cyclocondensation of esters of α-nitro-β-(indol-3-yl)acrylic acid or 2-nitro-1-phenyl-3-(indol-3-yl)-2-propen-1-one with sodium azide gives 4-substituted 5-(indol-3-yl)-1,2,3-triazoles (CXIV) [160]. These authors also noted that the presence of electron-withdrawing substituents in the indole ring (5-NO_2 or 1-$COCH_3$) enhances the reaction rate and the presence of a methoxy group reduces the reaction rate.



CXIV

R = CH_3O, C_2H_5O, Ph; R^1 = H, $COCH_3$; R^2 = H, CH_3; R^3 = H, CH_3O, NO_2

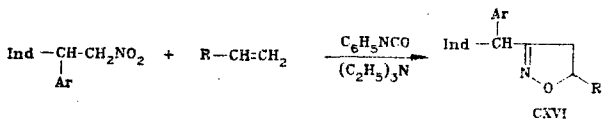
The 1,3-dipolar cycloaddition reaction of indole aldimines with aromatic nitrile N-oxides was used to synthesize 4-alkyl-3-aryl-5-(indol-3-yl)-Δ^2-oxadiazolines (CXV) [106]. These adducts display pronounced anti-inflammatory activity comparable to that of indomethacin.



CXV

R = CH_3, C_2H_5, n-C_3H_7, i = C_3H_7; Ar = Ph, 4-$O_2NC_6H_4$, 4-ClC_6H_4

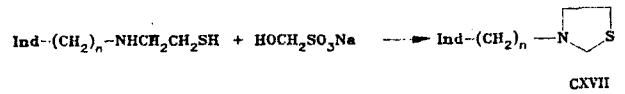
Significant interest is found in the 1,3-dipolar cycloaddition involving indole nitrile N-oxides [106, 161, 162]. These N-oxides are readily formed in the dehydration of the corresponding primary nitro compounds using phenyl isocyanate in the presence of triethylamine. These reactions give good yields of 3,5-disubstituted Δ^2-isoxazolines CXVI, among which compounds have been found with antibacterial and antifungal activity.



CXVI

Ar = Ph, 3,4-$(CH_3O)_2C_6H_3$; R = Ph, 4-$CH_3C_6H_4$, 4-pyridyl, CN, $COOCH_3$

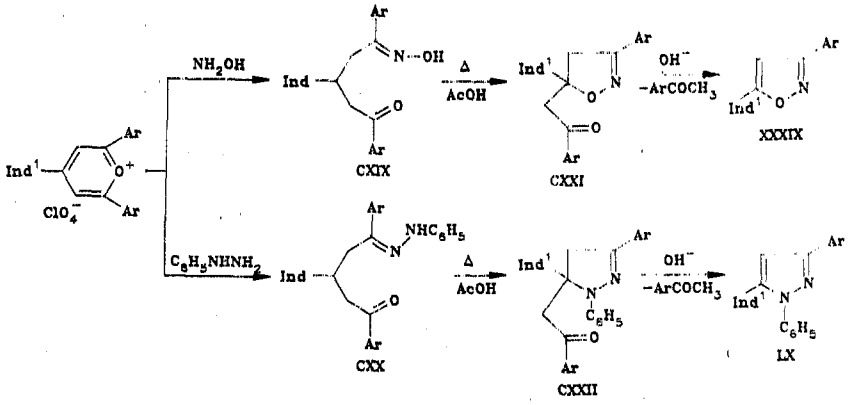
N-(Indol-3-yl)alkylthiazolines (CXVII) displaying antiactinic activity were synthesized by the reaction of 2-[(indol-3-yl)alkylamino]ethanethiols with Rongalite (formaldehyde sodium sulfoxylate) [163].



CXVII

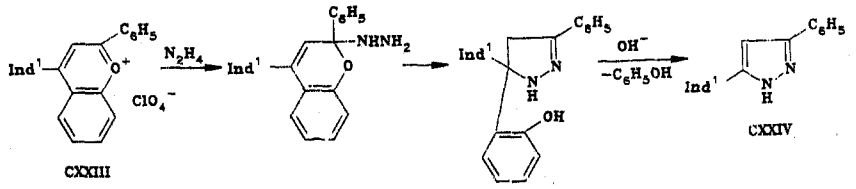
n = 2-5

Zhungietu et al. [164-167] used indolylpyrilium salts for the synthesis of indolazoles. The reaction of 2,6-diaryl-4-(1-R-indol-3-yl)pyrilium perchlorate (CXVIII) with hydroxylamine or phenylhydrazine gave monooxime CXIX or monophenylhydrazone CXX, which upon heating in acetic acid cyclize to give 5-phenacyl-5-(1-R-indol-3-yl)-Δ^2-isoxazolines (CXXI) or 5-phenacyl-5-(1-R-indol-3-yl)-Δ^2-pyrazolines (CXXII). Heating CXXI or CXXII with alkali in water–ethanol at reflux gave 3-aryl-5-(1-R-indol-3-yl)isoxazoles (XXXIX) or 1-phenyl-3-aryl-5-(1-R-indol-3-yl)pyrazoles (LX), respectively [164, 165].



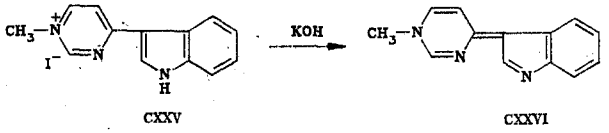
Ind^1 = 1-methylindol-3-yl, 1-benzylindol-3-yl; Ar = Ph, $4\text{-}CH_3C_6H_4$

Heating hydrazine hydrate with 4-(1-methylindol-3-yl)flavinium perchlorate gave 3-phenyl-5-(1-methylindol-3-yl)pyrazole (CXXIV) as the final product [166].



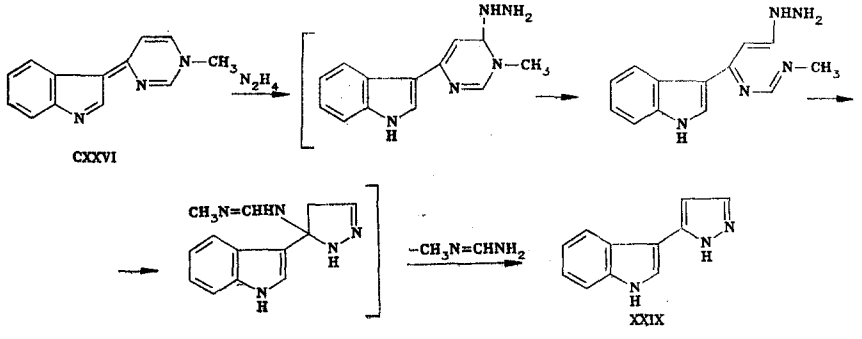
Ind^1 = 1-methylindolyl-3

Stupnikova et al. [168-170] have recently established that treatment of the iodomethylate of 4-(indol-3-yl)pyrimidine (CXXV) under mild conditions with ethanolic KOH gives a quantitative yield of the completely stable anhydrobase, 1-methyl-4-(3-indolinylidene)-1,4-dihydropyrimidine (CXXVI).



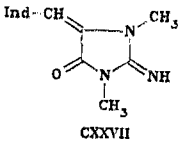
This anhydrobase holds considerable interest as an intermediate in the synthesis of various heterocyclic indole derivatives including indolylazoles [168-171].

The treatment of CXXVI with hydrazine hydrate in ethanol gave 3(5)-(indol-3-yl)pyrazole (XXIX), whose formation apparently proceeds by the following scheme [170].

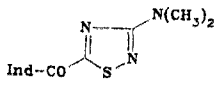


The reaction of CXXVI with hydroxylamine in acetonitrile gives a low yield of 3-(indol-3-yl)isoxazole [171].

In conclusion, we note that two new indolylazoles were recently isolated from natural substances, whose structures were established by chemical and spectral methods. One of these compounds was identified as 2-imino-1,3-dimethyl-5-(indol-3-ylmethylene)-4-pyrazolidinone (CXXVII) [172], while the other was identified as 3-dimethylamino-5-(indol-3-ylcarbonyl)-1, 2,4-thiadiazole (CXXVIII) [173].



CXXVII



CXXVIII

However, information on the synthesis of these compounds has not appeared in the literature.

LITERATURE CITED

1. G. I. Zhungietu and G. N. Dorofeenko, Usp. Khim., 41, 1627 (1972).
2. G. Toth, G. Szabo, G. Eibel, and E. Somfai, West German Patent 2,135,145; Chem. Abstr., 77, 5329 (1972).
3. G. R. Birchall, W. Hepmorth, and S. S. Smith, West German Patent 2,253,927; Chem. Abstr., 79, 31865 (1973).
4. L. Fishnerowa, V. Kakac, and O. Nemecek, Coll. Czech. Chem. Comm., 39, 624 (1974).
5. J. K. Sughen and T. Yoloye, Pharm. Acta Helv., 58, 65 (1978).
6. M. Michalik, V. Sunjic, F. Kajfez, V. Caplar, and T. Kovac, Croat. Chem. Acta, 51, 81 (1978).
7. F. Kajfez and M. Michalik, Swiss Patent No. 605,742; Chem. Abstr., 80, 72049 (1979).
8. Y. Suzuki, S. Komachiya, and S. Sakurai, US Patent No. 3,419,551; Ref. Zh. Khim., 12N659R (1970).
9. E. V. Esayan and G. T. Tatevosyan, Arm. Khim. Zh., 25, 969 (1972).
10. K. S. Karagezyan, R. T. Grigoryan, and G. T. Tatevosyan, USSR Inventor's Certificate No. 455,104; Chem. Abstr., 82, 170945 (1975).
11. Tsung-Ying Shen, V. J. Grenda, and R. F. Czaja, West German Patent No. 2,219,408; Chem. Abstr., 78, 29771 (1973).
12. D. Simov, V. Kalcheva, and C. Roycheva, FECS: First International Conference on the Chemistry and Biotechnology of Biologically Active Natural Products (Sofia), Vol. 3/2 (1981), p. 582; Ref. Zh. Khim., 21Zh291 (1982).
13. A. Jordan and R. Arndt, J. Heterocycl. Chem., 5, 723 (1968).
14. V. P. Arya, J. David, R. S. Grewall, C. L. Kaul, R. H. Modoni, S. Rajappa, and S. J. Shenoy, Indian J. Chem., 15B, 473 (1977).
15. G. Sarodnick and G. Kempter, Z. Chem., 19, 21 (1979).
16. L. J. Brand and J. Nadelson, Europ. Patent No. 32,298; Chem. Abstr., 96, 52291 (1982).
17. W. Schingler and F. Haflinger, US Patent No. 2,751,393; Chem. Abstr., 51, 4440 (1957).
18. H. L. Kung and W. Schingler, Experientia, 15, 66 (1959).
19. J. Hocker and R. Merten, Chem. Ber., 105, 1651 (1972).
20. J. Hocker and R. Merten, West German Patent No. 2,262,187; Chem. Abstr., 81, 105510 (1974).
21. J. Bergman, Tetrahedron Lett., No. 46, 4723 (1972).
22. A. K. Sheinkman, T. V. Stupnikova, N. A. Klyuev, L. Yu. Petrovskaya, and V. G. Zhil'nikov, Khim. Geterotsikl. Soedin., No. 2, 238 (1977).
23. A. K. Sheinkman, T. V. Stupnikova, and L. A. Rybenko, Khim. Geterotsikl. Soedin., No. 4, 561 (1978).
24. A. K. Sheinkman, T. V. Stupnikova, L. M. Kaplan, A. Yu. Chervinskii, and G. I. Makhlai, USSR Inventor's Certificate No. 504,765; Byul. Izobr., No. 53, 55 (1976).
25. A. K. Sheinkman, T. V. Stupnikova, V. I. Zherebchenko, L. A. Rybenko, and N. A. Klyuev, Khim. Geterotsikl. Soedin., No. 7, 904 (1978).
26. K. Takeo, O. Kijoshi, and K. Hakuji, J. Chem. Soc. Japan, Pure Chem. Sec., 79, 91 (1958).
27. V. Narayanan and R. D. Huagwitz, West German Patent No. 2,248,959; Chem. Abstr., 79, 32072 (1973).
28. R. D. Haugwitz, B. V. Maurer, A. J. Martinez, G. Jacobs, and V. Narayanan, Synthesis, No. 5, 336 (1976).
29. V. Narayanan and R. D. Haugwitz, West German Patent No. 2,415,351; Chem. Abstr., 82, 4241 (1975).
30. V. Narayanan and R. D. Haugwitz, US Patent No. 3,853,857; Chem. Abstr., 82, 112060 (1975).
31. Yu. I. Smuskevich, N. N. Mar'yanovskaya, and N. N. Suvorov, Trudy Moskovsk. Khim. Teknol. Inst. im. D. I. Mendeleeva, No. 61, 155 (1969).
32. T. P. Johnston and A. Gallagher, J. Org. Chem., 27, 2452 (1962).
33. G. H. Walker and M. A. Moore, J. Org. Chem., 26, 432 (1961).

34. Nguyen Dinh Trien, Ha Tri Diep, Luong Thu Huong, and Le Thi Thauh Vinh, Tap Chi Hoa Hoc, 18, 22 (1980); Chem. Abstr., 94, 121415 (1981).
35. H. King and E. Stiller, J. Chem. Soc., No. 2, 466 (1937).
36. L. Horner and H. Schwahn, Ann., 591, 99 (1955).
37. K. Shaw, A. McMillan, A. Gundmundson, and M. Armstrong, J. Org. Chem., 23, 1171 (1958).
38. O. Tsude, M. Noguchi, and H. Moriyama, Heterocycles, 16, 209 (1981).
39. L. Kh. Vinograd and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 11, 1505 (1970).
40. A. P. Bhaduri and N. M. Khanna, Indian J. Chem., 4, 419 (1966).
41. B. S. Tanaseichuk and V. N. Belyamov, Uch. Zap. Mordovsk. Univ., No. 81, 95 (1971).
42. L. C. Brooker, R. H. Sprague, C. P. Smyth, and C. L. Lewis, J. Am. Chem. Soc., 62, 1116 (1940).
43. W. S. Gaugh, US Patent No. 3,687,675; Chem. Abstr., 78, 73667 (1973).
44. P. Beretta and L. Val Busa, West German Patent No. 2,429,230; Chem. Abstr., 83, 12227 (1977).
45. J. Mee, French Patent No. 1,599,796; Chem. Abstr., 74, 100,619 (1971).
46. O. Reister and H. Oecheshlaeger, West German Patent No. 2,165,915; Chem. Abstr., 79, 99215 (1973).
47. L. Brooker and F. Webster, US Patent No. 3,539,349; Chem. Abstr., 75, 7444 (1971).
48. Mitsubishi Paper Mills, Ltd., Japanese Patent No. 80-96941; Chem. Abstr., 94, 112466 (1981).
49. F. Eiden and H. Kucklaender, Arch. Pharm. (Weinheim), 304, 523 (1981).
50. F. Eiden and H. Kucklaender, West German Patent No. 1,944,419; Chem. Abstr., 75, 5691 (1971).
51. V. M. Kotlyareskaya and I. M. Gubenko, Methods for the Preparation of Chemical Reagents and Preparations [in Russian], No. 26 (1974), p. 273.
52. C. Wentrup and H. W. Winter, Angew. Chem., 90, 643 (1978).
53. V. S. Velezheva, Yu. V. Erofeev, N. S. Yares'ko, A. G. Balbushevich, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 10, 1343 (1978).
54. F. Piozzi and C. Fuganti, Ann. Chim. (Rome), 56, 1248 (1966).
55. V. P. Gorbunova, K. F. Turchin, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 11, 1508 (1970).
56. S. V. Tsukerman, V. M. Nikitchenko, A. I. Bugai, and V. F. Lavrushin, Khim. Geterotsikl. Soedin., No. 2, 268 (1969).
57. B. R. Pandey, K. Raman, J. P. Barthwall, and S. S. Parmar, Natl. Acad. Sci. Lett. (India), 2, 98 (1979).
58. S. Tripathi, B. R. Pandey, J. P. Barthwall, K. Kishor, and K. P. Bhargawa, Indian J. Physiol. Pharmacol., 24, 155 (1980).
59. K. Raman, B. R. Pandey, J. P. Barthwall, and S. S. Parmar, Eur. J. Med. Chem.-Chim. Ther., 15, 567 (1980).
60. F. Piozzi and C. Fuganti, Ann. Chim. (Rome), 57, 486 (1967).
61. A. Sammour and H. H. Zoorob, Acta Chim. Acad. Sci. Hung., 86, 53 (1975).
62. E. Roeder and J. Pigulla, Arch. Pharm. (Weinheim), 311, 817 (1978).
63. V. E. Zhigachev, Yu. I. Smushkevich, N. A. Mel'nikov, and N. N. Suvorov, Trudy Moskovsk. Khim. Tekhnol. Inst. im. D. I. Mendeleeva, No. 66, 120 (1970).
64. Yu. I. Smushkevich, Chemical Sciences Doctoral Dissertation, Moscow (1982).
65. V. E. Zhigachev, Yu. I. Smushkevich, and N. N. Suvorov, Zh. Vses. Khim. Obshch., 18, 348 (1973).
66. G. Sanna, Gazz. Chim. Ital., 52, 170 (1982).
67. J. Bergman, Acta Chem. Scand., 22, 1063 (1968).
68. V. P. Gorbunova and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 11, 1519 (1973).
69. N. N. Suvorov, V. P. Gorbunova, M. D. Mashkovskii, S. S. Liberman, and S. P. Kushchak, USSR Inventor's Certificate No. 271,523; Byul. Izobr., No. 18, 23 (1970).
70. V. P. Gorbunova and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 7, 936 (1978).
71. N. N. Suvorov, Yu. I. Smushkevich, N. N. Mar'yanovskaya, and A. V. Sulima, Khim.-farm. Zh., 4, 10 (1970).
72. Yu. I. Smushkevich, Ts. M. Babueva, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 1, 91 (1969).
73. G. Y. Sarkis and S. Al-Azawe, J. Chem. Eng. Data, 17, 516 (1972).
74. N. N. Gireva, Chemical Sciences Candidate's Dissertation, Moscow (1969), p. 73.
75. D. S. Bhate, R. K. Hulgalkar, and S. Menon, Experientia, 16, 504 (1960).
76. B. S. Joshi, W. R. Taylor, D. S. Bhate, and S. Karmarkar, Tetrahedron, 19, 1437 (1963).
77. K. Bodendorf and A. Walk, Arch. Pharm. (Weinheim), 294, 484 (1961).

78. T. J. Turchi and M. J. S. Dewar, Chem. Rev., 75, 389 (1975).
79. H. Houwing and A. M. van Luesen, J. Heterocycl. Chem., 18, 1127 (1981).
80. H. Houwing, J. Wildeman, and A. M. van Leusen, J. Heterocycl. Chem., 18, 1133 (1981).
81. V. V. Vampilova, N. N. Suvorov, and V. S. Velezheva, Trudy Moskovsk. Khim. Tekhnol. Inst. im. D. I. Mendeleeva, No. 80, 150 (1974).
82. A. N. Grinev and O. Yu. Ryabova, Khim. Geterotsikl. Soedin., No. 2, 201 (1982).
83. A. P. Kozikowski and N. M. Hasan, J. Org. Chem., 42, 2039 (1977).
84. N. N. Suvorov, V. S. Velezheva, V. V. Vampilova, and E. I. Gordeev, Khim. Geterotsikl. Soedin., No. 4, 515 (1974).
85. N. N. Suvorov and B. I. Buyanov, Khim. Geterotsikl. Soedin., No. 3, 377 (1970).
86. H. Plieninger and G. West, Chem. Ber., 88, 1956 (1955).
87. H. Plieninger and G. West, Chem. Ber., 89, 2783 (1956).
88. H. Isler, US Patent No. 2,505,247; Chem. Abstr., 44, 6888 (1950).
89. D. V. Wysong and H. C. White, US Patent No. 3,586,695; Chem. Abstr., 75, 76789 (1971).
90. C. W. Schneider, S. K. Ewans, M. B. Chenoweth, and F. L. Bewan, Proc. Soc. Exp. Biol. Med., 140, 1221 (1972).
91. J. Eble, US Patent No. 3,377,247; Chem. Abstr., 69, 5206 (1968).
92. F. J. Rosenberg and J. G. Miller, US Patent No. 3,689,655; Chem. Abstr., 78, 12704 (1973).
93. S. Archer, US Patent No. 3,404,156; Ref. Zh. Khim., 5N499 (1970).
94. V. I. Kelarev and G. A. Shvekhgeimer, Izv. Muzov. Khim. Khim. Tekhnol., 24, 1354 (1981).
95. R. Kuhn and F. Drawent, West German Patent No. 937,231; Chem. Abstr., 53, 409 (1959).
96. J. M. McManus and R. M. Herbst, J. Org. Chem., 24, 1464 (1959).
97. P. F. Juby and T. W. Hudyma, J. Med. Chem., 12, 396 (1969).
98. Bristol-Myers Co., Dutch Patent No. 6,609,235; Chem. Abstr., 67, 82215 (1967).
99. W. G. Finnegan, R. A. Henry, and R. Letquist, J. Am. Chem. Soc., 80, 3908 (1958).
100. H. J. Bisher, D. F. Bruley, and M. H. Knisely, Adv. Exp. Med. Biol., 37B, 657 (1973).
101. M. E. Safdy, E. Kurchacova, R. N. Schut, H. Vidrio, and E. Hong, J. Med. Chem., 25, 723 (1982).
102. E. Kornfeld, South African Patent No. 6,904,486; Chem. Abstr., 75, 76800 (1971).
103. R. S. Taborsky, J. Med. Chem., 10, 880 (1967).
104. T. M. Efremova, K. N. Kuchkova, A. A. Semenov, Khim. Geterotsikl. Soedin., No. 10, 1382 (1974).
105. G. A. Shvekhgeimer, V. I. Shvedov, L. A. Kyankova, D. I. Stefanova, and M. P. Nikolova, Bulgarian Inventor's Certificate No. 31,238.
106. L. A. Kyankova, Chemical Sciences Candidate's Disseration, Moscow (1979).
107. G. Shvekhgeimer, V. Shvedov, L. Dyankova, D. Stefanova, and M. Nikolova, Tr. Nauchn.-Issled. Khim.-farm. Inst. (Sofia), 11, 70 (1981).
108. G. Ehrhart and H. Leditschke, US Patent No. 2,752,358; Chem. Abstr., 51, 2873 (1957).
109. H. Piotrowska, B. Serafin, and K. Wejroch-Matacz, Pol. J. Pharmacol. Pharm., 27, 297 (1975).
110. S. Bithy-Szlahto, S. Kweiek, H. Piotrowska, B. Serafin, and K. Wejroch-Matacz, Acta Pol. Pharm., 34, 527 (1977).
111. I. Kh. Fel'dman, N. A. Kogan, and É. S. Voikhanskaya, Khim.-farm. Zh., No. 9, 21 (1967).
112. V. I. Kelarev and G. A. Shvekhgeimer, Khim. Geterotsikl. Soedin., No. 5, 645 (1980).
113. V. I. Kelarev and G. A. Shvekhgeimer, Zh. Vses. Khim. Obshch., 26, 457 (1981).
114. V. I. Kelarev and G. A. Shvekhgeimer, Khim. Geterotsikl. Soedin., No. 3, 343 (1982).
115. V. I. Kelarev and G. A. Shvekhgeimer, Izv. Vuzov. Khim. Khim. Tekhnol., 25, 1458 (1982).
116. G. A. Shvekhgeimer, V. I. Kelarev, and L. A. Dyankova, Khim. Geterotsikl. Soedin., No. 12, 1609 (1984).
117. N. A. Kogan, Khim. Geterotsikl. Soedin., No. 10, 1327 (1977).
118. V. I. Kelarev and G. A. Shvekhgeimer, Khim. Geterotsikl. Soedin., No. 6, 761 (1984).
119. M. Robba and D. Maume, Tetrahedron Lett., No. 23, 2333 (1972).
120. M. Robba, D. Maume, and J. C. Lancelot, Bull. Chim. Soc. France, Nos. 3-4, Part 2, 333 (1977).
121. C. Ainsworth, J. Am. Chem. Soc., 77, 1148 (1955).
122. H. M. Stroh and H. Beitz, Ann., 700, 78 (1966).
123. S. P. Hiremath, N. N. Goudar, and M. G. Purohit, Indian J. Chem., 19B, 1031 (1980).
124. V. K. Rastogi, V. K. Agarwall, J. N. Sinha, A. Chandhari, and S. Rarmar, Canad. J. Pharm. Sci., 9, 107 (1974).
125. S. P. Hiremath, N. N. Goudar, and M. G. Purohit, Indian J. Chem., 20B, 388 (1981).
126. Yu. I. Smushkevich, V. Kayumov, and N. N. Suvorov, Trudy Moskovsk. Khim. Tekhnol. Inst. im. D. I. Mendeleeva, No. 74, 65 (1973).

127. G. Kobayashi, J. Matsuda, R. Natsuki, and Y. Tominada, J. Pharm. Soc. Japan, 90, 1251 (1970).
128. Y. Tominada, J. Matsuda, and G. Kobayashi, J. Pharm. Soc., Japan, 95, 1073 (1975).
129. R. L. M. Harris, Tetrahedron Lett., 5217 (1970).
130. R. L. M. Harris, Austral. J. Chem., 27, 2635 (1974).
131. J. K. Kuck, J. J. Herba, W. E. Kowac, and J. V. Karabinos, J. Am. Chem. Soc., 73, 5470 (1951).
132. J. M. Swan, Austral. J. Chem., A5, 711 (1952).
133. L. K. Ramachahdran, A. Epp, and W. McConnel, Anal. Chem., 27, 1734 (1955).
134. J. Sjöquist, Acta Chem. Scand., 7, 447 (1953).
135. S. Oki and T. Nagasaka, Chem. Pharm. Bull., 19, 1734 (1971).
136. S. Oki and T. Nagasaka, Japanese Patent No. 73-14668; Chem. Abstr., 78, 124573 (1973).
137. Y. Oikawa and O. Yonemitsu, J. Org. Chem., 42, 1213 (1977).
138. T. Yoshioka, K. Nohri, Y. Oikawa, and O. Yonemitsu, J. Chem. Res. Synops., No. 7, 194 (1981).
139. E. E. Smisman, R. L. Inloes, S. El-Antably, and P. Shaffer, J. Med. Chem., 19, 161 (1976).
140. K. V. Rao, Antibiotic Chemotherapy, 10, 3121 (1960).
141. V. Shach, M. Wittenan, and H. Els, J. Am. Chem. Soc., 85, 3425 (1963).
142. M. N. Preobrazhenskaya, L. M. Orlova, and N. N. Suvorov, Zh. Obshch. Khim., 33, 1378 (1963).
143. M. N. Preobrazhenskaya, L. M. Orlova, L. A. Savel'eva, A. V. Kisin, N. N. Yaretskii, N. S. Vul'fson, and N. N. Suvorov, Dokl. Akad. Nauk SSSR, 166, 611 (1966).
144. M. N. Preobrazhenskaya, N. V. Uvarova, E. N. Padieskaya, G. N. Pershin, and N. N. Suvorov, Dokl. Akad. Nauk SSSR, 172, 870 (1967).
145. M. N. Preobrazhenskaya, E. G. Balashova, K. F. Turchin, E. N. Padeiskaya, N. V. Uvarova, G. N. Pershin, and N. N. Suvorov, Tetrahedron, 24, 1631 (1968).
146. M. R. Harden and N. D. Wright, West German Patent No. 2,611,089; Chem. Abstr., 86, 43694 (1977).
147. M. R. Harden and N. D. Wright, J. Chem. Soc. Perkin Trans. 1, No. 9, 1012 (1977).
148. M. R. Harden, S. Bailey, M. R. Boyd, I. B. Wilkinson, and N. D. Wright, J. Med. Chem., 22, 191 (1979).
149. T. Ocuda, J. Chem. Pharm. Soc. Japan, 80, 208 (1960).
150. F. Andreani, R. Andrisano, and C. Della Casa, J. Chem. Soc., No. 8, 1157 (1970).
151. G. Decordts and M. C. Wakselman, Comptes Rendus Acad. Sci. Paris, C, 266, 1168 (1968).
152. P. Gross and R. Dickinson, European Patent No. 3901; Chem. Abstr., 92, 94394 (1980).
153. Pfizer Corp., Dutch Patent No. 80-0351; Chem. Abstr., 94, 156925 (1981).
154. P. Gross and R. Dickinson, British Patent No. 2,045,244; Ref. Zh. Khim., 6094P (1981).
155. S. Heptinstall, I. Bevan, S. R. Cockbill, S. Hauley, and M. Parry, Throm. Res., 20, 219 (1980).
156. P. Gross, R. P. Dickinson, M. I. Parry, and M. I. Raundall, Agents Actions, 11, 274 (1981).
157. V. V. Vampilova, Chemical Sciences Candidate's Dissertation, Moscow (1976).
158. T. Hino, K. Hoji, and S. Acaboshi, Chem. Pharm. Bull., 18, 384 (1970).
159. G. A. Shvekhgeimer, V. I. Shvedov, L. A. Kyankova, and V. I. Apostolova, Bulgarian Inventor's Certificate No. 42858.
160. V. S. Velezheva, Yu. V. Erofeev, and N. N. Suvorov, Zh. Org., Khim., 16, 2157 (1980).
161. G. A. Shvekhgeimer, V. I. Shvedov, and L. A. Dyankova, Tr. Nauchn.-Issled. Khim.-farm. Inst. (Sofia), 12, 57 (1982).
162. G. A. Shvekhgeimer, V. I. Shvedov, L. A. Dyankova, and V. I. Apostolova, Bulgarian Inventor's Certificate No. 42857.
163. N. N. Suvorov, L. Kh. Vinograd, L. N. Lavrishcheva, V. M. Bondarenko, M. V. Vasin, and N. V. Gorelova, Trudy Mokovsk Khim. Tekhnol. Inst. im. D. I. Mendeleeva, No. 94, 9 (1977).
164. G. N. Zhungietu, I. V. Shantsevoi, and V. I. Sukhanyui, Zh. Vses. Khim. Obshch., No. 2, 232 (1971).
165. G. N. Zhungietu and I. V. Shantsevoi, Abstracts of the Third All-Union Colloquium on the Chemistry and Pharmacology of Indole Compounds [in Russian], Izd. Stinitsa, Kishinev (1971), p. 32.
166. G. N. Zhungietu, I. V. Shantsevoi, and D. D. Buburuz, Khim. Geterotsikl. Soedin., No. 2, 281 (1971).
167. B. I. Sukhanyuk, Chemical Sciences Candidate's Dissertation, Kishinev (1977).

168. T. V. Stupnikova and Kh. Ya. Lopatinskaya, Khim. Geterotsikl. Soedin., No. 11, 1566 (1980).
169. T. V. Stupnikova, T. V. Nuzhnaya, G. A. Zaritovskaya, and S. N. Baranov, Dokl. Akad. Nauk UkrSSR, Ser. B., No. 8, 51 (1980).
170. T. V. Stupnikova, T. V. Nuzhnaya, N. A. Klyuev, and L. Yu. Chervinskii, Khim. Geterotsikl. Soedin., No. 2, 212 (1982).
171. T. V. Stupnikova, T. V. Nuzhnaya, N. A. Klyuev, S. N. Baranov, and S. M. Klyuev, Dokl. Akad. Nauk UkrSSR, Ser. B., No. 6, 53 (1982).
172. R. Kazlanskas, P. Murphy, R. J. Quinn, and R. J. Wells, Tetrahedron Lett., No. 1, 61 (1977).
173. S. Heitz, M. Durgeat, M. Guyot, C. Brassy, and B. Backef, Tetrahedron Lett., No. 15, 1457 (1980).

QUANTUM-CHEMICAL TREATMENT OF RECYCLIZATION REACTIONS. 9.* PHOTOISOMERIZATION OF FIVE-MEMBERED HETEROCYCLES

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The photoisomerization of a number of five-membered heterocycles has been considered in the framework of the coupled variant of perturbation theory for a one-electron transition density matrix in the π-electronic approximation of the MO—LCAO—SCF method.

A method for describing photochemical reactions of the X type in Dougherty's terminology [3], one of whose main steps is photoelectrocyclic contraction or ring formation, we developed in [2]. In such reactions the energy of the light is utilized only for bringing the reactant into an excited state and is not converted into the thermal energy needed for overcoming the activation barrier, spent on light-induced electron transfer, etc. In this case, the reactivity is determined mainly by the changes in the electronic structure of the molecule upon excitation and is, therefore, more easily subjected to quantum-chemical treatment.

Without dwelling in detail on the problem of using the index approach for the description of the reactivity of molecules in electronically excited states (see, for example, [4, 5]), as well as on the alternative method of correlation diagrams (see [3, 6-8], etc.) in the case of electrocyclic reactions, we note only that expressions for the reactivity indices of such reactions, which were obtained on the basis of the coupled variant of perturbation theory for a transition density matrix in the PPP method [9], were presented in [2]. Here the perturbation may be characterized as intramolecular coupling (see [3]), and the perturbation matrix is represented by the following matrix elements:

$$(H_{ik})_{rs} = (\delta_{ir}\delta_{ks} + \delta_{is}\delta_{kr})\Delta\beta_{ik}. \quad (1)$$

Then from the expression for the change in the π-electronic energy of the ground state in first-order perturbation theory with respect to $\Delta\beta_{ik}$

$$\delta E_{ik}^{\pi} = 2P_{ik}\Delta\beta_{ik} \quad (2)$$

it follows that in the ground state the bond orders between the not directly bonded atoms P_{ik} can serve as the reactivity indices in intramolecular recyclization and cyclization reactions.

*For report 8 see [1].

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