SYNTHESIS OF ALKYLINDOLES (REVIEW)

M. A. Yurovskaya

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Methods for obtaining alkylindoles, excluding the Fischer synthesis and direct alkylation, developed during the last 15 years are correlated.

All of the methods for obtaining alkylindoles can be divided into three major groups: the Fischer synthesis (for example, see [1-3]); alkylation of inodoles (for example, see [1, 2, 4-6]; and methods for the construction of an indole ring that is known to contain alkyl radicals.

The research on the Fischer synthesis in recent years primarily deals with discussions regarding the mechanism of this process [7-9]. A great deal of attention, both in the USSR and abroad, is being paid also to the search for new catalysts [10, 11] and the development of industrial methods for obtaining indoles on the basis of this reaction [12-14].

The Fischer synthesis provides the fundamental possibility for obtaining indoles that contain alkyl substituents in both the pyrrole and benzene rings. Whereas varying the substituents in the 2 and 3 positions is achieved quite simply, viz., by selection of the appropriate ketones, the possibilities of obtaining indoles with any number and position of the alkyl substituents in the benzene ring are limited by the accessibility of the corresponding arylhydrazines, the peculiarities of the cyclization orientation, and diverse rearrangement processes [15, 16].

The alkylation of indoles has become a powerful method for the introduction of alkyl substituents into the 1 and 3 positions of the indole molecule with the development of interphase catalysis [5, 6]; however, it does not make it possible to introduce alkyl radicals into other positions of the molecule.

Of the papers that have been published in recent years, studies devoted to diverse variants of the formation of an indole ring (excluding the Fischer synthesis) that lead to obtaining alkylindoles are of greatest interest. These studies are based on the most modern advances in theoretical organic chemistry, such as cycloaddition reactions, photochemical processes, and metallocomplex catalysis. It is precisely this group of synthetic methods in the chemistry of alkylindoles that constitutes the subject matter of the present review.

The methods for the synthesis of alkylindoles examined in this review can, in turn, be divided into three groups. The first, and most prolific of these groups, is based on the construction of a pyrrole ring from various anilines and related benzene structures. The second method uses, as the starting substances, pyrroles with built-on benzene rings. The third group, which was recently observed, provides for the simultaneous construction of the benzene and pyrrole rings of indole in the reaction of alkyl-3-nitropyridinium salts with ketones in the presence of amines.

1. SYNTHESIS OF ALKYLINDOLES ON THE BASIS OF BENZENE STRUCTURES

All of the methods for the construction of the pyrrole fragment of the indole molecule on the basis of compounds of the benzene series can be conveniently classified with respect to the type of new bond formed. This sort of classification can be represented by the following formal scheme (the corresponding sections of the review are indicated above the arrows):

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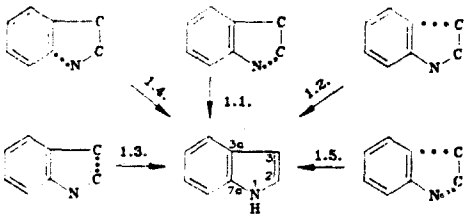
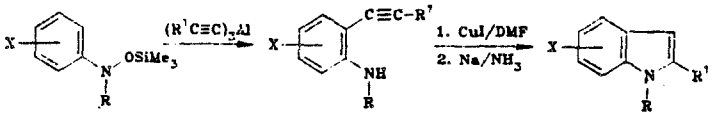


1.1. Formation of an N–C(2) Bond

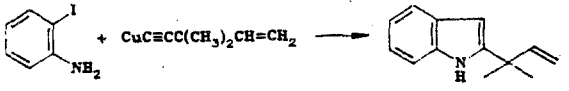
This is the most extensive group of syntheses of the pyrrole fragment of the two-ring indole system and is based on the use of aniline synthones. The presence of alkyl substituents in them suggests the possibility of the synthesis of indoles that are substituted in the benzene ring, whereas the use of the necessary fragments in the construction of the pyrrole part makes it possible to also introduce alkyl substituents into the 1, 2, and 3 positions in the cyclization process. It is evident that in this case ortho substituents with respect to the aniline nitrogen atom should contain a multiple bond or a functional group.

Thus aromatic amines with o-alkynyl substituents serve as promising structural blocks for obtaining indoles [17]. This method takes on special importance in connection with the recently discovered possibility of the nucleophilic introduction of alkynyl substituents into the benzene ring of O-silylated N-substituted phenylhydroxylamines through organoaluminum compounds [17].

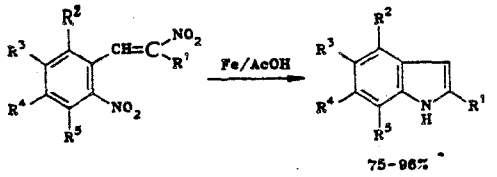


X=F, R=H, R¹=Bu (95%); X=F, R=CH(Me)Ph, R¹=H (96%)

Another possible pathway for the introduction of an alkynyl substituent has been demonstrated definitively in the case of the synthesis of 2-allylindole from o-iodoaniline and the copper salt of the corresponding enyne [18].

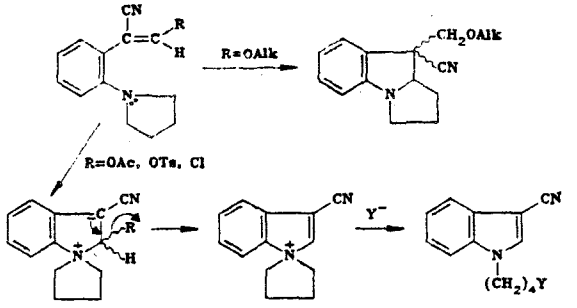


A modified reductive cyclization under the influence of Fe/AcOH in the presence of silica gel has made it possible to use 2,β-dinitrostyrenes as the starting compounds [19]:



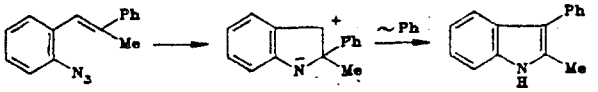
R¹=Me, H; R²=Me, H; R³=OMe, OCH_2Ph; R⁴=H, OMe, OCH_2Ph; R⁵=H, Me, OMe, OCH_2Ph

Another variant of the use of the vinyl group for the construction of the indole ring is the thermal rearrangement of 2-vinyl-1-(1-pyrrolidinyl)benzenes [20], the direction of which depends on the character of the substituent in the vinyl group:

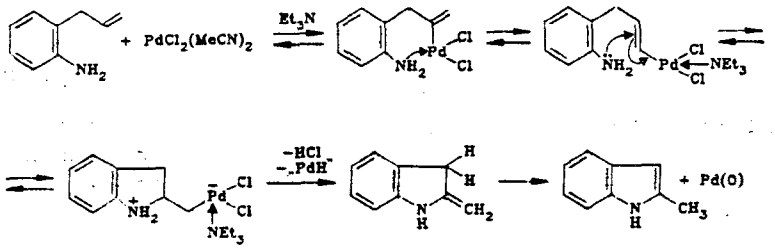


When an alkoxy substituent (R = OAlk) is present, 9-(alkoxymethyl)pyrrolo[1,2-a]indoles are formed, whereas 1-alkylindoles are formed when R = OAc, OTs, or Cl.

o-Vinylarylnitrenes can also be used for the formation of a $C_{(2)}$—N bond [21, 22]. In fact, the formation of 2-methyl-3-phenylindole in low yield has been observed in the thermolysis of o-azido-β-methylstilbene, which was obtained from o-bromobenzyl bromide via the Wittig reaction with acetophenone, and subsequently, via the Grignard reaction with tosyl azide, was converted to the necessary azide [21].

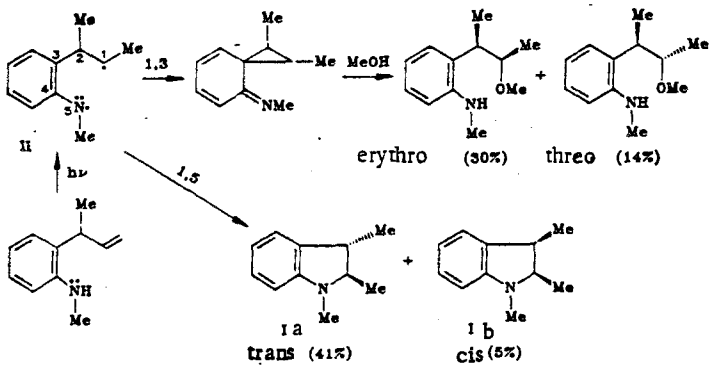


In a whole series of studies o-allylanilines [23-27], which are readily obtained from o-haloanilines by treatment with π-allylnickel halide complexes [27], were used as the starting substances for the synthesis of indoles. o-Allylanilines undergo cyclization to 2-alkylindoles with a stoichiometric amount of palladium chloride. Evidently, the process takes place through a cyclopalladinated intermediate.

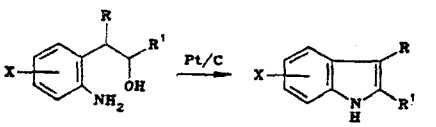


The acid-catalyzed rearrangement of N-allylanilines may serve as another source of o-allylanilines [28]. The cyclization of o-allylanilines can also be accomplished photochemically [26, 28]. Thus trans- and cis-1,2,3-trimethylindolines, along with erythro- and threo-2-(2-methoxy-1-methylpropyl)-N-methylanilines, are formed in the irradiation, with a high-pressure mercury lamp, of N-methyl-2-(1-methylallyl)aniline in methanol.

The formation of both indolines and 2-(2-methoxypropyl)anilines evidently proceeds through the same intermediate diradical II; if a 1,5 interaction leads to the indoline, the 1,3 process gives the corresponding 2-(2-methoxypropyl)anilines through the intermediate spiro compound. The dehydrogenation of indolines Ia,b by palladium on charcoal leads to 1,2,3-trimethylindole. It is interesting to note that, whereas the dehydrogenation of cis-indoline Ib requires 5-15 min, trans-isomer Ia undergoes aromatization in 2 h. The proposed method has also been extended to benzene-ring-substituted o-allylanilines and cyclic allyls.



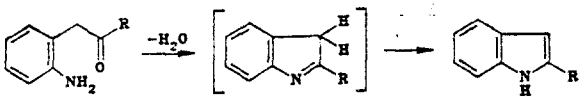
o-(Aminophenyl)alkanols, which undergo cyclization to 2,3-disubstituted indoles in the presence of catalysts of the platinum group on activated charcoal, can serve as examples of the use of anilines that are functionally substituted at the o-alkyl group for the synthesis of indoles [29]:



X=F, H, Alk, OAlk, NH_2; R=H, Me, Et, CH_2OH; R'=H, Ph

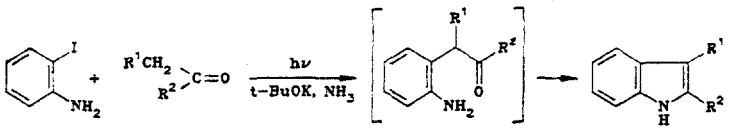
The presence of a carbonyl group in the β position of the alkyl substituent proved to be much more effective. The process involved in the formation of indoles from such

structures is absolutely evident and does not constitute anything unique:



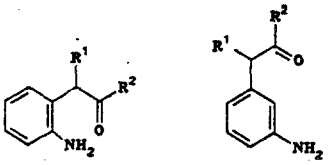
However, a large number of modern original methods for the synthesis of the starting o-aminobenzyl ketones, which are worthy of consideration, have been published recently.

One such method is the reaction of o-haloanilides with the enolates of ketones upon irradiation, in which the formation of indoles proceeds through an o-aminobenzyl ketone intermediate [30-32].

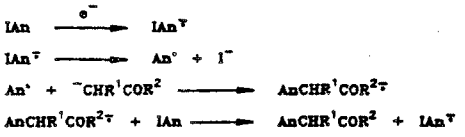


R^1=H; R^2=H, Me, *i*-Pr; $R^1 + R^2 = (CH_2)_4$ 40-100%

The yields of the indoles formed are very high. The method makes it possible to obtain 2-, 2,3- and 3-alkylindoles via the use of methyl alkyl ketones, dialkyl ketones, and aldehydes, respectively [32], as well as indoles that contain substituents (Me, OMe, Ph, COOH) in various positions of the benzene ring [31]. The reaction proceeds via an $S_{RN}1$ mechanism. The following experimental facts serve as a confirmation of this: 1) the reaction does not proceed without irradiation; 2) the process is inhibited by oxygen even during irradiation; 3) the process is regioselective, which is a great advantage of the method. In the case of an alternative dehydrobenzene mechanism there should have been a mixture of ortho- and meta-substituted intermediates and the reaction should not have required photoinitiation.

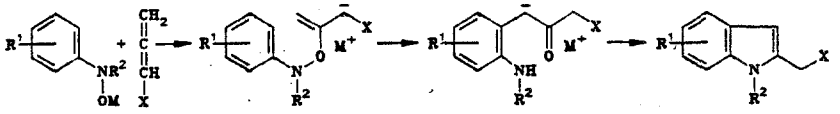


Therefore, the general scheme of the $S_{RN}1$ process proposed by Bunnett [33] is also suitable for o-iodoanilines (IAn):



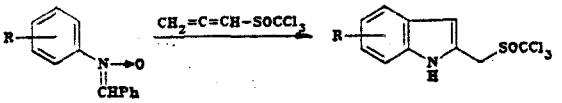
It is evident that, in addition to photochemical initiation, both chemical (catalysis by CuI) [34] and electrochemical initiation of the process are possible.

Another method is a reaction similar to the Cope rearrangement of N-phenylhydroxylamine derivatives [36-38]:



R^1=5-Me, R^2=COMe, X=SO_2Ph (95%); R^1=H, R^2=CO_2CH_2Ph, X=SO_2Ph (80%); M=Li, Na, K

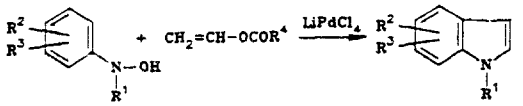
In other words, the reaction of N-phenylhydroxylamine derivatives with electron-deficient allenes is accompanied by a rearrangement that leads to o-aminobenzyl ketones, which undergo cyclization to 1,2-disubstituted indoles. N-Unsubstituted indoles can be obtained by using N-phenylnitrones [36].



R=5-Me (60%); R=7-Me (50%)

The corresponding o-aminobenzyl ketone derivatives were isolated.

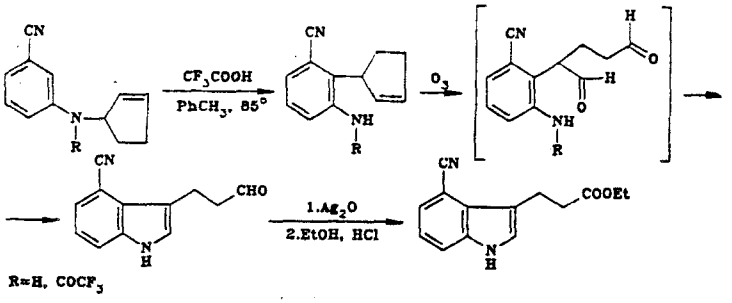
Vinyl carboxylates can also be used for the O-vinylation of N-phenylhydroxylamines [39].



R^1=H, COR; R^2, R^3=H, Hal, Alk, OAlk, CN, NO_2; R^4=Alk, Ph

The reaction is catalyzed by a palladium or mercury catalyst and leads to the production of indoles in yields up to 80%. It is apparent that, as in the preceding process, the reaction proceeds via a mechanism involving a [3,3]-sigmatropic shift (a Cope heterorearrangement).

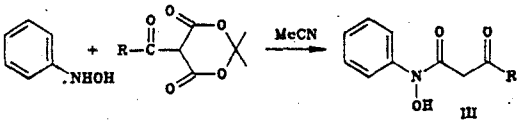
A new route to 4-substituted indoles (possible precursors of ergoalkaloids) includes aza-Claisen rearrangement of m-substituted N-allylanilines with subsequent cleavage by means of ozonolysis of 1,2,3-trisubstituted aniline derivatives [40]:



R=H, $COCF_3$

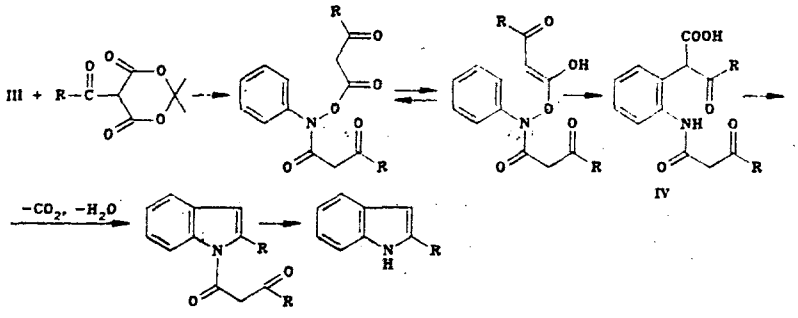
In this case also, after ozonolysis one obtains an o-aminobenzylcarbonyl compound, which subsequently undergoes cyclization to the corresponding indole.

Another rather exotypic method of synthesis of such intermediates consists in the treatment of phenylhydroxylamine with acylated Meldrum acids [41], which are analogs of mixed diketones and display very high acylating activity with respect to nucleophiles, including also phenylhydroxylamine.



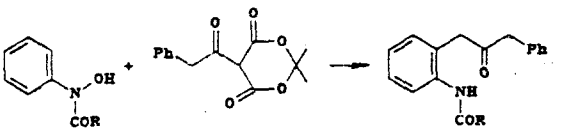
III

The repeated treatment of N-acylphenylhydroxylamines III with Meldrum's acid leads to o-acylation. It is well known [42, 43] that the resulting N,O-diacyl derivatives undergo the Carroll rearrangement to o-(β-carbonylalkyl) derivatives IV, which, after decarboxylation, dehydrative cyclization, and deacylation, form the corresponding indoles.

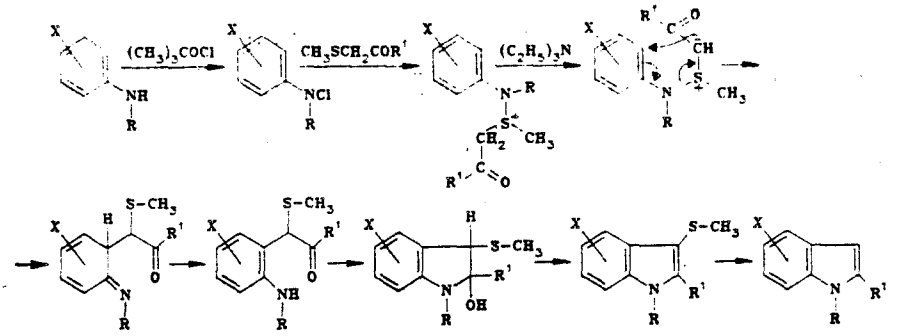


IV

When N-acylphenylhydroxylamines were used as the starting compounds, it was found that it was possible to isolate intermediates of the Carroll rearrangement in yields on the order of 60%.



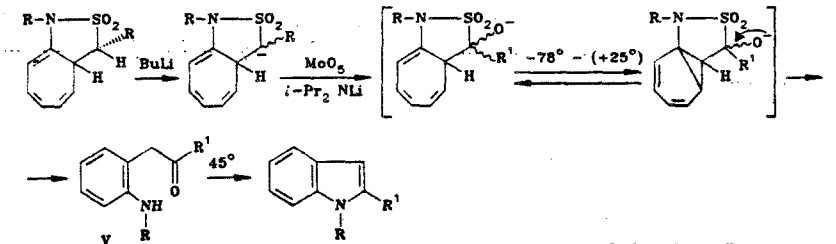
The method of introduction of a β-carbonylalkyl function into the ortho position of anilines relative to the amino group is also a rearrangement process, which accompanies the reaction of N-chloroanilines with a β-carbonyl sulfide [44].



X = OCOMe, Me, H, Cl, CO_2Et, NO_2

This process occurs without isolation of the intermediates and leads, in rather high yields, to methylthioindoles, which are readily converted to the corresponding 1,2-dialkylindoles.

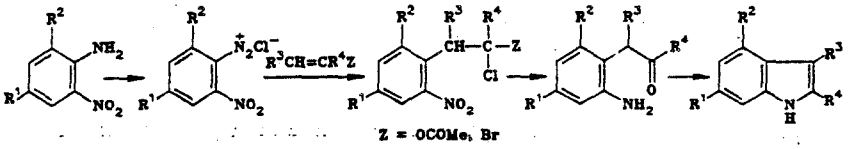
Also, without isolation, in one flask, there has been observed a complex rearrangement process in the oxidation of cycloadducts of azaheptafulvenes with the formation of 1,2-disubstituted indoles, the yields of which reach 50-80% [45].



R=Me, *t*-Bu, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-BrC_6H_4; R¹=H, Me, Et, *i*-Pr

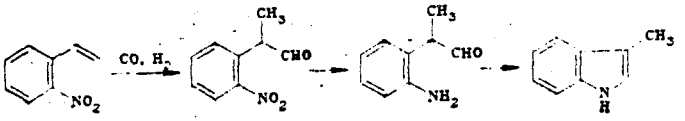
The reaction includes oxidation of the α-sulfonyl anion by the complex of MoO_5 with lithium diisopropylamide, rearrangement, which apparently takes place through a norcaradiene tautomer, and the formation of an indole ring. At low temperatures it was found that it was possible to isolate intermediate V; this made it possible to include this method of synthesis in an examined group of methods based on the condensation of o-(β-carbonylalkyl)-anilines.

Meerwein arylation of vinyl acetate or vinyl bromide with an o-nitrobenzenediazonium salt also leads to an equivalent of an o-nitrobenzylcarbonyl compound, the reduction of which and intramolecular cyclization give substituted indoles [46] in 50-90% yields.



Z = OCOMe, Br

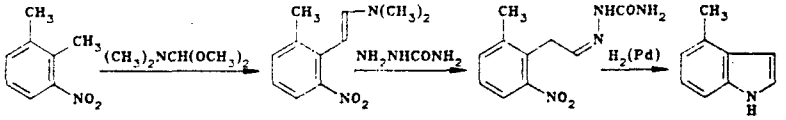
Derivatives of o-aminophenylacetaldehyde also serve as starting compounds for the synthesis of indoles [47, 48]. Thus, under hydroformylation conditions with the aid of a rhodium catalyst, 2-nitrostyrene was converted directly in 70% yield to skatole [47] via a scheme that includes the formation of 2-(o-nitrophenyl)propionaldehyde under conditions of homogeneous catalysis and reduction of the nitro group with heterogeneous catalysis and thermal dehydration:



It is a matter of the greatest importance that the use of a rhodium catalyst selectively leads to branched rather than terminal aldehydes. An interesting finding of the authors is the use of a catalyst formed in situ from rhodium precursors such as Rh/Al_2O_3 and Rh/C.

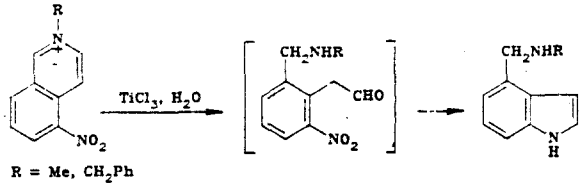
Under the hydroformylation conditions they are the source of rhodium-carbonyl complexes and serve simultaneously for the reduction of the nitro group.

The reaction of o-nitrotoluene with acetals of dimethylforamide (DMF) or aminals leads to enamines of o-nitrophenylacetaldehyde, the reduction of which with simultaneous cyclization leads to indoles [49, 50].

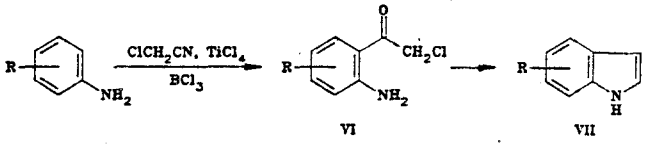


The use of very slightly soluble semicarbazones reduces to a minimum the competitive process of bimolecular condensation in the reduction.

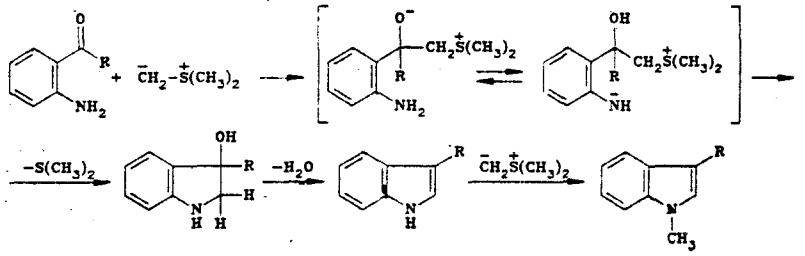
The role of an original source of o-nitrophenylacetaldehyde is played by a 5-nitroisoquinolinium salt, which, by the action of an aqueous solution of $TiCl_3$, gives a 4-methylaminomethylindole, evidently through a step involving the reduction of the nitro group and hydrolytic cleavage of the pyridinium ring [51].



The use of o-acylanilines for the formation of a $C_{(2)}$–N bond requires the presence in the α position of an activating acceptor substituent. Thus a convenient regiospecific method for obtaining o-chloroacylanilines from anilines and chloroacetonitrile with the use of boron trichloride [52]. The accessibility of these o-aminoacetophenone derivatives has made it possible to develop a simple method for the synthesis of indole structures [52, 53]. The reductive cyclization of VI under the influence of metal hydrides ($NaBH_4$, for example) leads to indoles VII.



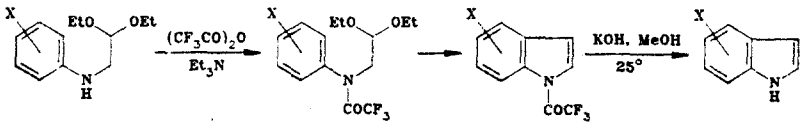
An original method for the conversion of o-acylanilines to 3-substituted indoles consists in the action on them of very effective alkylating agents – sulfur ylids – via the following scheme:



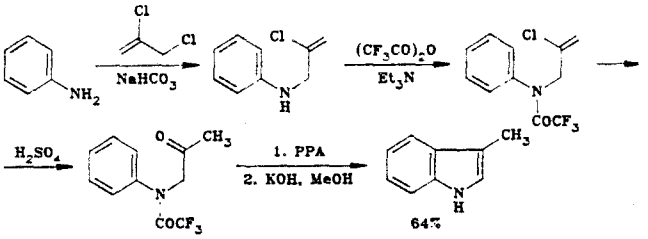
As a rule, the process is accompanied by alkylation by the ylid of the resulting indoles at the nitrogen atom.

1.2. Formation of a $C_{(3)}$–$C_{(3a)}$ Bond

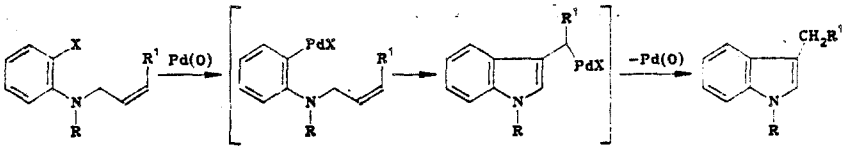
For the formation of the pyrrole ring of indole through the formation of a $C_{(3)}$–$C_{(3a)}$ bond the starting anilines should contain, at the nitrogen atom of the alkyl substituent, a substituent that is capable of attacking the ortho position of the benzene ring. Thus, for example, N-(trifluoroacetyl)-2-anilinoacetals form, in high yields, the corresponding N-(trifluoroacetyl)indoles in trifluoroacetic acid with excess trifluoroacetic anhydride [55].



The method is unsuitable for obtaining 7-alkylindoles, since the donor substituent in the starting anilinoacetal is located in the meta position relative to the site of electrophilic attack. This method can be extended to the preparation of 3-substituted indoles with the use of polyphosphoric acid (PA) as the condensing agent:

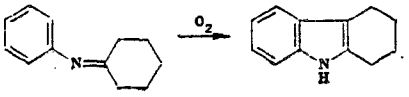


The presence of an allyl substituent attached to the nitrogen atom in the o-haloanilines opens up new possibilities in the synthesis of alkylindoles on the basis of the use of metal-complex catalysis [56-58]. This method consists in the intramolecular arylation of the double bond of the allyl fragment in the presence of complexes of zero-valent nickel [56] and palladium [58].



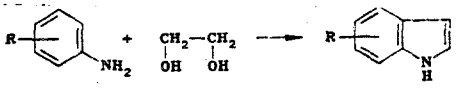
The use of complexes of zero-valent metals makes it possible to avoid deallylation of the starting aniline, and the use of various 3-substituted allyls makes it possible to introduce diverse alkyl radicals into the 3 position of the indole molecule. The yields of alkylindoles range from 20% to 90%.

The catalytic transformations of o-unsubstituted azomethines can also be classified as reactions, the key step in which is the formation of a $C_{(3)}$–$C_{(3a)}$ bond. According to patent data, the oxidative cyclization of N-phenylcyclohexanoneimide at 300-800°C in the presence of oxide catalysts (Al_2O_3, SiO_2, aluminosilicates, etc.) leads to 1,2,3,4-tetrahydrocarbazole [59].



The use of aluminum orthophosphate (the Kirby catalyst) as the catalyst makes it possible to obtain 3-alkylindoles by condensation of aniline with lower aldehydes [60]. It is apparent in this case also that the corresponding azomethine is formed.

A method was recently developed for the synthesis of indoles, including those that contain alkyl substituents in the benzene ring, on the basis of the catalytic condensation of anilines with vicinal diols at 200-500°C [61-66].

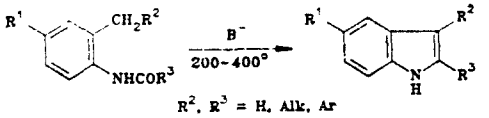


Cadmium, copper, and magnesium salts are used as the catalysts. The yields of indoles range from 80% to 90%. Although data on the mechanism of the process are not available in the literature, one might assume that the thermal dehydration of the glycols leads to the intermediate formation of aldehydes and that the reaction proceeds in a manner similar to that indicated above [60].

1.3. Formation of a $C_{(2)}$–$C_{(3)}$ Bond

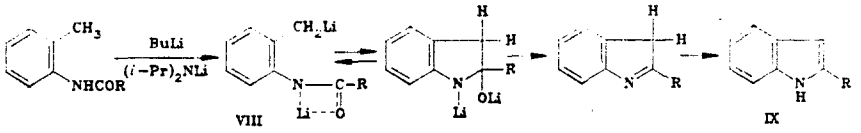
Among the methods for the synthesis of alkylindoles that involve the formation of a $C_{(2)}$–$C_{(3)}$ bond, one of the most prominent positions is occupied by the long-ago discovered

and widely used Madelung synthesis [67], which consists of the intramolecular cyclization of o-alkylanilines under the influence of strong bases at high temperatures:



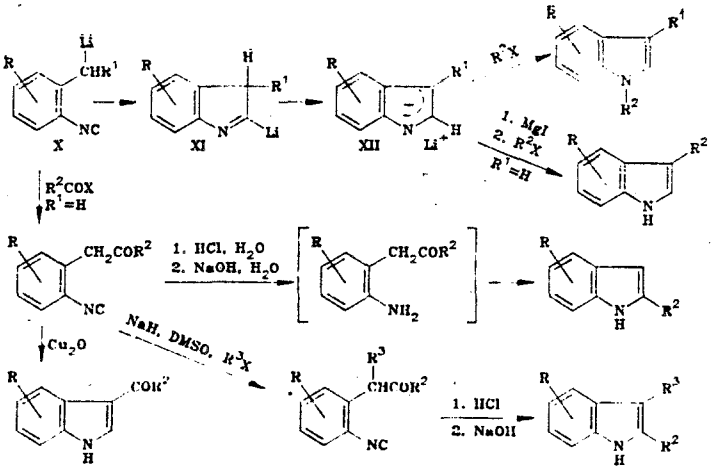
R^2, R^3 = H, Alk, Ar

However, the application of this method is limited by the extremely severe conditions under which it is carried out (for example, see [68]). At present the efforts of researchers have been directed to a modification of the Madelung method that would lead to a substantial increase in the yields of alkylindoles through carrying out the reaction under mild conditions. For the achievement of this end, lithiation of o-alkylanilines has been used successfully [69-71]. It is assumed that organometallic intermediate VIII may be the key compound in the formation of indoles IX. The process takes place through a number of steps:



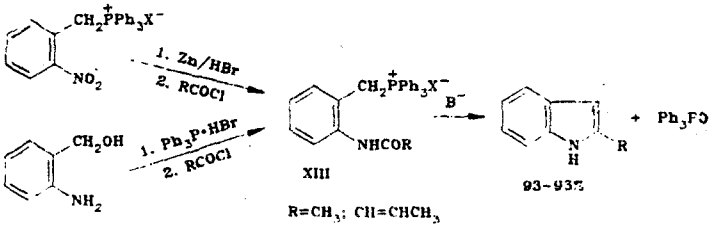
This method presents colossal possibilities for the synthesis of indoles with markedly branched alkyl radicals. Thus, from N-(o-tolyl)amides of pivalic, 1-methylcyclohexanecarboxylic, and adamantanecarboxylic acids, 2-tert-butyl-, 2-(1-methylcyclohexyl)-, and 2-(1-adamanyl)indoles were obtained in 87, 76, and 59% yields, respectively.

In addition to o-alkylanilides, o-alkylisonitriles can also be used in the modified Madelung method [72-74]. It is supposed that the initial stage involves the formation of organolithium compound X, which undergoes spontaneous cyclization to intermediate XI. Attempts to pin down this intermediate were unsuccessful, since 2-substitution, rather than N-substitution, proceeds under the influence of electrophiles (for example, alkyl halides) [72].



An elegant and selective method for the preparation of 3-alkylindoles on the basis of o-tolylisonitrile is based on the conversion of lithium derivative XII of indole to the corresponding indolylmagnesium iodide by the action of MgI_2 with subsequent alkylation [73]. The results achieved [72, 73] are in complete agreement with the data from previous studies on the alkylation of lithium and magnesium derivatives of indole [4]. It is apparent from the scheme presented above, that the use of isonitriles also presents the possibility of obtaining both 3-acyl- and 2-alkyl- and 2,3-dialkylindoles [74].

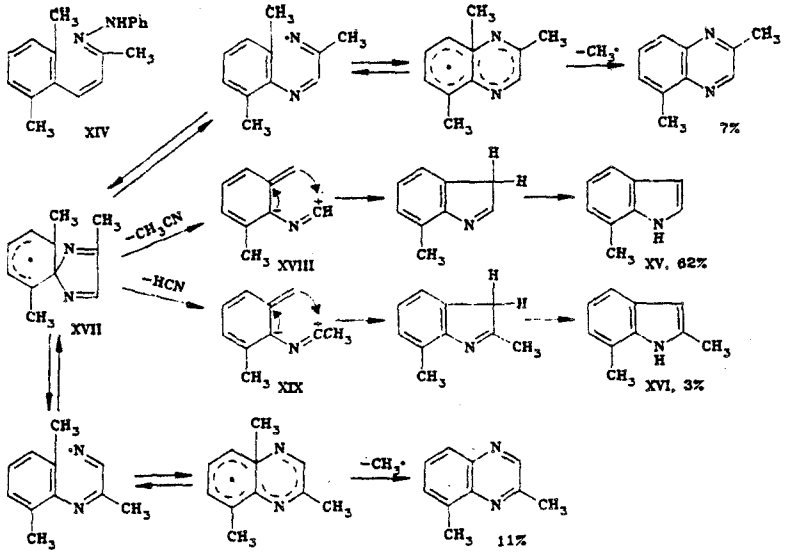
Another convenient modification of the Madelung reaction consists in the intramolecular condensation of amides with alkylidenephosphoranes [75]. Starting o-acylaminobenzylphosphonium salts XIII are obtained either through o-nitrobenzylphosphonium salts by reduction with zinc in hydrobromic acid or by condensation of anthranilic alcohol with triphenylphosphine hydrobromide:



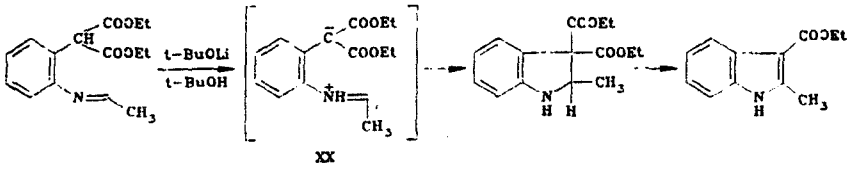
The gas-phase thermolysis of o-substituted azomethines with a complex structure (of the XIV type) makes it possible to obtain 7-methylindoles, in addition to 5-methylquinoxalines [76], also due to the formation of a $C_{(2)}$—$C_{(3)}$ bond.

Both heterocyclic systems are formed by decomposition of spirodienyl radical XVII, the indoles are formed by the loss of a nitrile, and the quinoxalines are formed through the elimination of a methyl radical. Splitting out of a nitrile from radical XVII leads to nitrile ylids XVIII and XIX, which also give an indole skeleton, as the authors surmise, through 1,3-dipolar cycloaddition.

In the opinion of Speckamp [77], when there is a CH-acid grouping in the ortho position relative to the azomethine function one deals with a process involving 1,5-electrocyclic formation of an indole ring with subsequent aromatization of the resulting indoline XX.

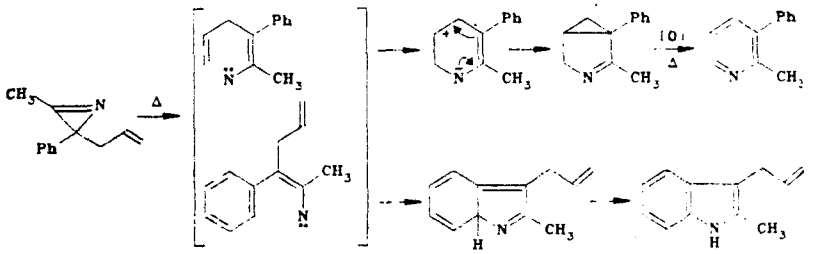


When a CH-acid grouping is present in the ortho position under conditions of basic catalysis, the possibility of proton transfer from the CH-acid group to the imine nitrogen atom with the formation of bipolar intermediate XX plays a decisive role. Since the carbon atom that bears a negative charge is included in a conjugated π system of five atoms with six π electrons, the reaction can be classified as 1,5-electrocyclization [77].



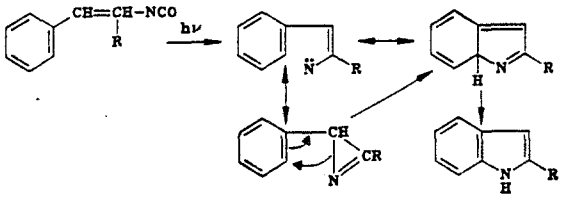
1.4 Formation of a $C_{(7a)}$—N bond

The group of synthetic methods that are united by the formation of a $C_{(7a)}$—N bond is rather meager; this is evidently due to the specific characteristics of the chemical properties of the benzene ring. It is represented primarily by two processes that utilize aryl vinyl nitrenes or take place via a dehydrobenzene mechanism. The formation of the pyrrole ring of indole in the first case proceeds due to attack of the vinyl nitrene at the ortho position of the benzene ring [78-83]. Thus the thermolysis of 3-methyl-2-allyl-2-phenyl-2H-azirine gives a mixture of 3-allyl-2-methylindole (58%) and 1-phenyl-2-methyl-3-azabicyclo[3.1.0]hex-2-ene (31%), which then undergoes transformation to the corresponding pyridine [78].



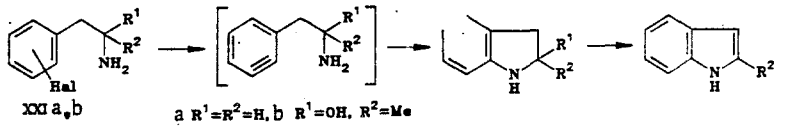
The formation of an indole can be explained by electrocyclic formation of the ring through attack of the vinyl nitrene on the adjacent benzene ring; the best analogy of this process is the formation of a five-membered ring in the cyclization of butadienyl nitrenes [84-86].

Another source of an analogous vinyl nitrene is represented by styryl isocyanates, the photolysis of which leads to indoles, though, to be sure, this process is accompanied by considerable polymerization [79].



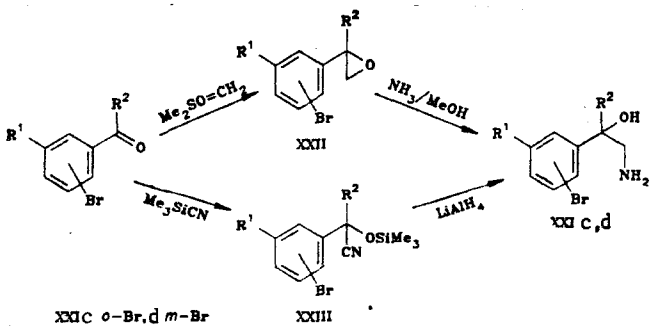
In addition to the possibility of direct attack of the nitrene at the benzene ring, there is also an assumption regarding the intermediate formation of the corresponding 2-phenylazirine, the valence isomerization of which with subsequent proton transfer also leads to the indole.

Another pathway for the formation of a $C_{(7a)}$—N bond, which was proposed by Huisgen [87, 88], suggests the utilization of dehydrobenzene via the scheme



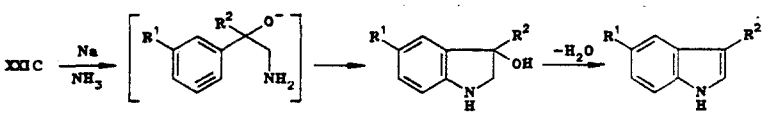
XXI a,b a $R^1=R^2=H$, b $R^1=OH$, $R^2=Me$

However, the oxidation of the intermediate indoline when starting amine XXIa is used proceeds in low yield, and, therefore, amines XXIb, which have a higher oxidation state, were used; the aromatization of the 2-hydroxyindoline in this case proceeds spontaneously [89]. Following the commonly accepted logic, Fleming and Woolies [90] have proposed that, rather than the 1-substituted derivative, one should use 2-amino(o-bromophenyl)ethanols XXIc, which are obtained from o-bromophenyl ketones through epoxides XXII or silyl ethers (XXIII) of cyanohydrins:



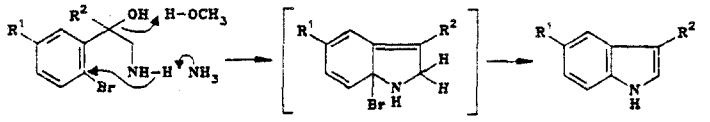
XXIc o-Br, d m-Br XXII XXIII XXI c,d

Amino alcohols XXIc, without isolation, are treated with Na in liquid ammonia; this leads to the formation of 3-substituted indoles in 50-60% yields.



The possibility of the use also of m-bromo derivative XXId, which gives the same dehydrobenzene intermediate, as demonstrated by Fleming and Woolies [90], serves as evidence for the dehydrobenzene pathway in this case.

It is interesting that heating amino alcohols XXIc in the presence of a weaker base (a solution of ammonia in methanol) also leads to indoles, but, undoubtedly, via a different mechanism [91]. It is assumed that the process takes place through nucleophilic attack by the amino group at the benzene ring with the formation of tetrahedral intermediate XXIV with the subsequent elimination of bromine and aromatization:

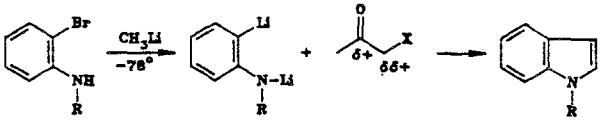


XXIV

It was found that the amino group is capable of nucleophilically attacking the benzene ring at a higher rate than one might have supposed.

1.5 Formation of $C_{(3a)}$–$C_{(3)}$ and $C_{(2)}$–N Bonds

A classic example of the simultaneous formation of $C_{(3a)}$–$C_{(3)}$ and $C_{(2)}$–N bonds is the [3 + 2]-cycloaddition reaction of vicinal biselectrophiles to dimetalloorganic derivatives of o-haloanilines [92, 93]:

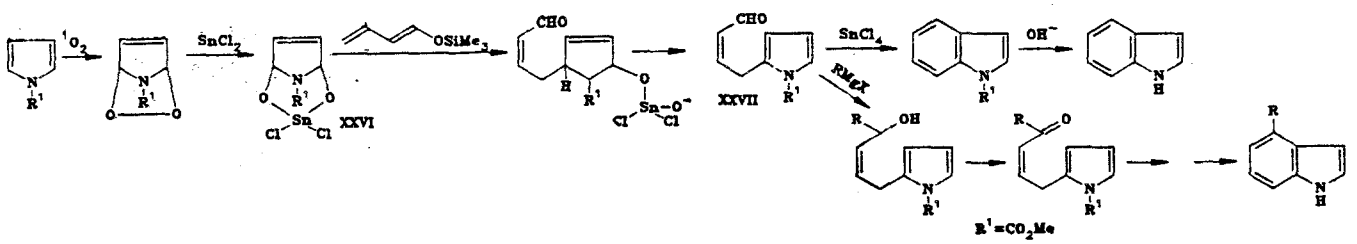


As one might have expected, the use of o-haloanilines is most efficient. The method is suitable for the synthesis of 2-, 3-, 6-, and 2,3-substituted indoles, As a rule, one uses α-halo ketones as the biselectrophiles; the character of the ketone does not affect the regiochemistry of the process, the regulation of which is dictated by the difference in the relative nucleophilicities and electrophilicities of the parts that are joined to one another.

2. SYNTHESIS OF ALKYLINDOLES ON THE BASIS OF COMPOUNDS OF THE PYRROLE SERIES

As we have stated above, an alternative pathway for the construction of the indole ring consists in the building on of a benzene ring to compounds of the pyrrole series. It is only natural, of course, that this pathway for the synthesis of alkylindoles is encountered very rarely in the literature. This is associated both with the difficulties involved in obtaining pyrrole structures and with their significant lability. As a rule, the examples of this approach encountered in the literature do not have general character; however, they are extremely interesting from a theoretical point of view. They are all based on the introduction into the 2 position of the pyrrole ring of substituents that contain an alkyl chain with a functional group that is capable of forming a benzene ring in the case of attack on the 3 position of pyrrole.

For example, the photooxidation of N-methoxycarbonylpyrrole in the presence of $SnCl_2$ and subsequent condensation with appropriate trimethylsilylated ketones create the necessary fragment for the construction of a benzene ring in the synthesis of indoles [94-96]. The unstable cyclic peroxide XXV obtained in the case of photooxidation evidently forms with $SnCl_2$ complex XXVI, the reactive C–O bond of which is cleaved under the influence of nucleophiles to give, after aromatization, a pyrrole with a nucleophile residue in the 2 position.

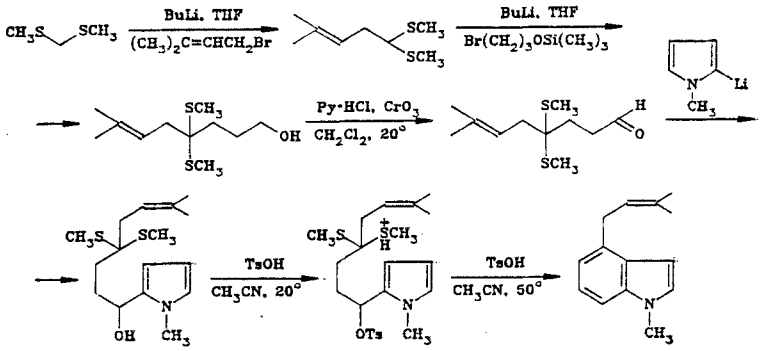


XXVI XXVII

R^1=CO_2Me

The acid-catalyzed cyclization of the substituted pyrroles XXVI under the influence of perchloric acid in ethyl acetate, boron trifluoride etherate, or stannic chloride in methylene chloride under very mild conditions (0-20°C) leads to an N-methoxycarbonylindole in 48, 59, and 69% yields, respectively. The starting unsaturated ketones that are necessary for obtaining 4-alkylindoles are formed readily from pyrroles XXVII via the Grignard reaction with subsequent oxidation of the resulting carbinols by pyridine chlorochromate.

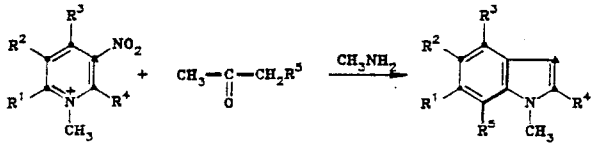
A particularly specific and unusual method based on the use of thionium compounds was used to build a benzene ring onto the pyrrole ring [97]. The high polarity and low order of the π bond in the thionium grouping suggest that it should be more active with respect to weak nucleophiles such as the aromatic ring than a simple carbonyl group. This is precisely the peculiarity of this grouping and has been used for the last step in the formation of a six-membered ring in the synthesis of 4-alkyl-2,3-unsubstituted indoles via the following scheme:



It must be noted that the use of a thionium ion as a cyclization initiator can be realized only for π-surplus aromatic systems (the pyrrole system in this case) and only for the formation of a six-membered ring. In contrast to the Fischer synthesis, an advantage of this method is the strict regiocontrol of the formation of 4-substituted indoles, and the very mild conditions under which the reaction is carried out make it applicable for the preparation of 2,3-unsubstituted indoles that are labile in acidic media. In particular, the method has been used for the synthesis of 1-methyl-4-(3-methyl-2-butenyl)indole – the starting compound for the synthesis of the corresponding tryptamine, which is the biological precursor of ergoalkaloids.

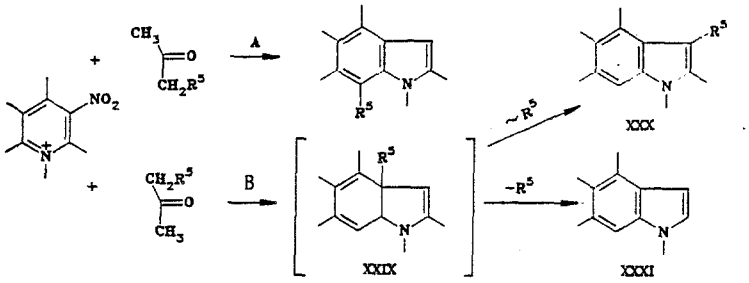
3. SYNTHESIS OF ALKYLINDOLES ON THE BASIS OF 3-NITROPYRIDINIUM SALTS WITH THE SIMULTANEOUS FORMATION OF BENZENE AND PYRROLE RINGS

A fundamentally new method for the formation of an indole ring, viz., the reaction of alkyl-3-nitropyridinium salts with ketones in the presence of amines, has been recently observed [98]. Formal structural rules for the construction of an indole molecule from fragments of the starting molecules ("a molecular design" process) have been proposed on the basis of a specially developed spectral method for the establishment of the structures of the resulting polyalkylindoles [99, 100].



A distinctive feature of this unusual reaction is the simultaneous formation of both rings of the two-ring indole system, which takes place via the formal incorporation of the three-carbon fragment of the ketone between the fragments of the pyridine ring, which are formed through cleavage at the $C_{(3)}$–$C_{(4)}$ and $C_{(6)}$–N bonds. The detection, by means of chromatographic mass spectrometry, of various indolization pathways by means of the utilization of methyl alkyl ketones serves as a confirmation of the proposed "molecular design" [101]. It is evident that two variants of the regioorientation of the ketone upon reaction with the pyridinium salt are possible in this case. One of them (pathway A) leads to indoles with

the "normal" XXVIII structure. The other (pathway B) gives intermediate XXIX, the aromatization of which may occur through migration of an R^5 radical from the 3a position to the 3 position (indole XXX) or through its elimination (indole XXXI):



It has been shown that the use in the reaction of preprepared ketimines (instead of a mixture of the ketone with the amine) in polar aprotic solvents significantly accelerates the process involved in the formation of the indoles and, in a number of cases, raises the yields and simplifies the isolation procedure [102]. This new method allows one to obtain previously inaccessible polyalkylindoles with prescribed alkyl substituents in practically all positions of the indole ring, with indole yields approaching 87% [102].

The literature data examined in this review constitute evidence that organic chemists have an unflagging devotion to and interest in the search for new efficient methods for the synthesis of indoles based on the most recent advances in chemical science.

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MACROHETEROCYCLES.

31.* BINUCLEAR CROWN ETHERS BASED ON 1,1,2,2-TETRAHYDROXYMETHANYLETHANE

N. G. Luk'yanenko and O. T. Mel'nik

UDC 547.898.07

Methods for the synthesis and production of a number of new binuclear crown ethers based on 1,1,2,2-tetrahydroxymethylethane and its derivatives were developed.

The selectivity of the complexing of crown ethers with metal cations frequently increases substantially as a result of the formation of complexes of the "sandwich type" with a 2:1 crown ether–cation composition [2]. From this point of view a great deal of attention has been directed to binuclear crown ethers, which are structurally prepared for the formation of such complexes and in many cases display greater cationic selectivity as compared with their monocyclic analogs [3-5].

*See [1] for Communication 30.

A. V. Bogatskii Physicochemical Institute, Academy of Sciences of the Ukrainian SSR, Odessa 270080. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1173-1178, September, 1987. Original article submitted March 31, 1986.

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