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Prospects for the chemistry of pyrrole

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ABSTRACT. The principal advances and trends in the development of the chemistry of monopyrrole compounds in the last 15 years are analysed and new approaches to the construction of the pyrrole ring and the introduction of functional groups into the latter as well as the possibilities of pyrroles as building blocks in organic synthesis are discussed.

The bibliography includes 116 references.

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I. Introduction

The modern chemistry of pyrrole is so extensive, is developing so rapidly, and covers so many different aspects that an adequate description of all its prospects and trends is hardly feasible in a single review.

Nature has assigned to pyrrole structures a fundamental role in the molecular logic of the entire living world. The two most important and interrelated biological processes — the photosynthesis of plants and the respiration of animals — are controlled by pyrrole systems — chlorophyll and haemoglobin. The non-fortuitously linked pyrrole rings (tetrapyrroles) have been chosen by evolution to create a microreactor in a molecular cavity with a very high degree of perfection and operating on a principle which we are only now beginning to understand and assimilate in relation to macrocyclic polyethers and their analogues. Special Conferences have been devoted to the properties and structures of tetrapyrroles.[1] In the present review, one can only conclude in the introduction that the chemistry of tetrapyrroles — porphyrins, chlorophylls, and haems — is now at an accelerating stage in its development: methods for their synthesis are being improved,[2–4] their biosynthesis is being investigated,[5–7] preparations for oxygen transport in living organisms are being synthesised from them,[8,9] metal complex catalysis using tetrapyrrole ligands is developing rapidly,[10–12] etc. (The literature on all these problems is extensive and here only some of the latest studies are quoted as an illustration.)

To make the picture complete, it is necessary to note just as briefly that during the last several years the polymerisation of pyrroles, especially electrochemical polymerisation, has received a powerful stimulus.[13–15] It has opened up a pathway to electrically conducting materials[16–22] with extensive prospects for their employment in electrical engineering (light, flexible conductors, powerful accumulators,[16,20] antistatic materials, ribbon heaters, HF screens), in electronics[16–18] (semiconductor devices, solar batteries and photoconductors,[18] photoelectrochromic memory and display devices,[17,19] electrophotographic systems[16]), in lithography,[21] for the photoelectrolysis of water,[22] etc.

The subject of the present review is the principal advances and trends in the development of the modern chemistry of monopyrrole compounds.

II. New methods for the construction of the pyrrole ring

Together with the improvement and modification of the traditional pyrrole syntheses (the Knorr, Paal–Knorr, Hantzsch, Piloti, Chichibabin and Yur'ev synthesis), new effective methods have been discovered for the construction of the pyrrole ring (see the review of Trofimov et al.[23] and the references therein) frequently from more readily available starting materials and perhaps preparatively more attractive. These include the following:

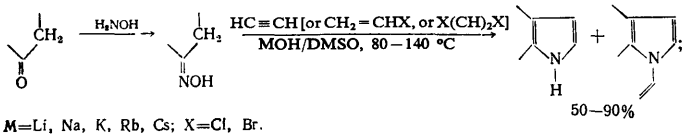
1. The reaction of ketoximes with acetylenes or their cryptoforms — vinyl halides and dihalogenoalkanes (see Refs. 23–25 and the references therein).
2. The condensation of βγ-dihalogenoketones with ammonia and primary amines.[26–34]
3. The decomposition of 1,3-oxazolidines in the presence of bases.[35–39]
4. The condensation of ketimines with 1-cyano-1-(*N*-methylanilino)alk-1-enes.[40,41]
5. The condensation of acetylenes with trimethylsilyl cyanide.[42,43]

1. The reaction of ketoximes with acetylenes (vinyl halides, dihalogenoalkanes)

The method based on the reaction of ketoximes with acetylenes, vinyl halides, or dihalogenoalkanes has developed to the greatest extent. More than 120 papers, more than 30 patents (see Refs. 23–25 and the references therein), a number of monographs[23,25,44] and reviews,[24,45] and a series of dissertations[46–50] have been devoted to this method. This reaction, its modifications, and its products are now being investigated by a series of research groups both in the USSR and abroad. An important place has been assigned to it in the new technical encyclopedia published in the USA (in the article "Acetylenes"[51]).

Here we shall consider mainly new results which have not been included in the existing monographs and reviews.

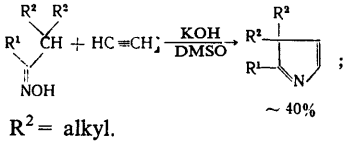
In a general form, the reaction can be represented schematically as follows:



M=Li, Na, K, Rb, Cs; X=Cl, Br.

Pyrroles and *N*-vinylpyrroles (when acetylene is used in excess) are formed from ketoximes with α-methylene or α-methyl groups without substituents sensitive to strong bases. The reaction is catalysed specifically by a superbasic alkali metal hydroxide–dimethyl sulphoxide (DMSO) system, whose activity increases in the sequence LiOH < NaOH < KOH < CsOH, and also in the presence of additives—open-chain additive or macrocyclic polyethers, which weaken ionic association and increase basicity. The KOH–DMSO system, which is readily available, convenient to use, and ensures satisfactory yields of pyrrole, is usually employed in practice. In fact, the chemistry of heterocyclic compounds now has at its disposal a reliable two-stage process involving the conversion of ketones into pyrroles with a wide variety of structures and their *N*-vinyl derivatives.

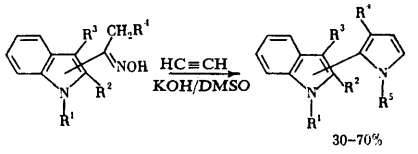
3*H*-Pyrroles, stabilised by two substituents in the 3-position, are formed from the reaction of ketoximes with an aliphatic α-CH group:[25,50,52]



R^1=Ar, R^2= alkyl.

Thus the reaction of ketoximes with acetylene leads to highly reactive but nevertheless difficult to obtain and therefore little investigated pyrrole isomers with an impaired aromatic conjugation. This is one of the promising aspects of the study of the given reaction.

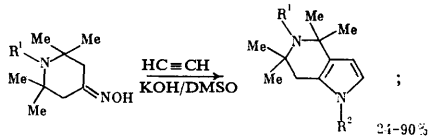
Studies[53,54] where this reaction was successfully extended to the oximes of 2- and 3-acylindoles and where a general approach to the synthesis of pyrrolylindoles—a whole class of previously unknown pyrrole compounds—was developed have made a definite contribution to the development of the process leading to the heterocyclisation of ketoximes by reaction with acetylene:



R^1, R^2, R^3=H, Me; R^4=H, Me, Pr^i, Ph; R^5=H, CH=CH$_2$.

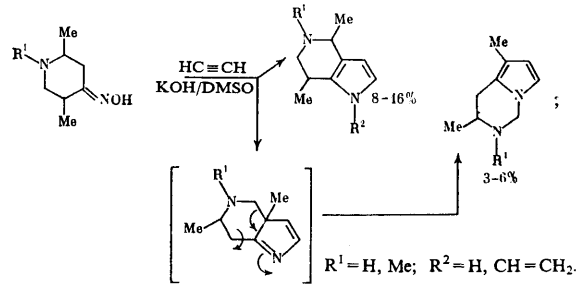
At the same time unambiguous evidence has been obtained for the *O*-vinyloxime heterocyclisation pathway.

Two research teams have recently independently extended this reaction to yet another class of ketoximes—piperidinone oximes, including those with a nitroxy-radical centre.[50,55–59] The latter fact is particularly important, since it indicates the absence of a one-electron stage in the process involving the conversion of ketoximes into pyrroles on treatment with acetylene. Otherwise, the nitroxy-radical, being an effective radical trapping agent, would have prevented the reaction. The outcome of these studies was the development of a general method of synthesis of rare azaindoles—pyrrolo[3,2-*c*]piperidines:



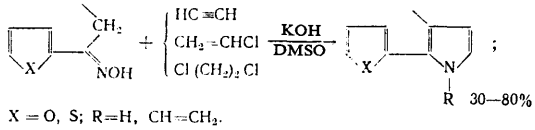
R^1 = H, OH, O$^-$; R^2 = H, CH=CH$_2$.

It is of interest that 1,2,3,4-tetrahydropyrrolo[1,2-*c*]pyrimidines have also been obtained from the oximes of 1,2,5-trimethyl- and 2,5-dimethyl-4-piperidinones apparently as a consequence of the rearrangement and aromatisation of the intermediate 3*H*-pyrroles formed via an alternative reaction involving the CH and not the CH_2 group:



R^1=H, Me; R^2=H, CH=CH$_2$.

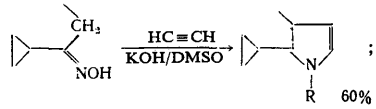
Furyl- and thienyl-pyrroles, which are now readily obtained from the oximes of acylfurans and acylthiophens,[23,25,60–64] have lost their exotic nature:



X = O, S; R=H, CH=CH$_2$.

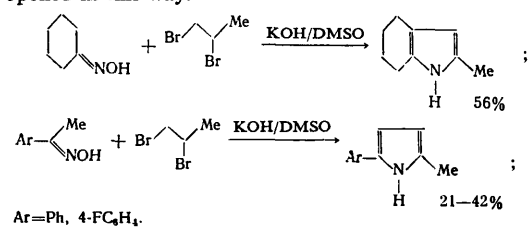
Thus the problem of the synthesis of compounds in which the pyrrole ring is linked to other five-membered aromatic heterocycles has now been obviated. Until recently this problem was solved in more complex ways.[65]

The first representatives of the class of cyclopropylpyrroles have been synthesised from the oximes of cyclopropyl ketones:[66]



R=H, CH=CH$_2$.

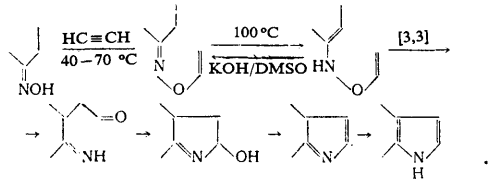
It has been shown recently that, together with dihalogenoethanes, 1,2-dihalogenopropanes can be used successfully in the synthesis of pyrroles from ketoximes.[67] The pathway to 2-R-5-methylpyrroles has been opened in this way:



Ar=Ph, 4-FC$_6$H$_4$.

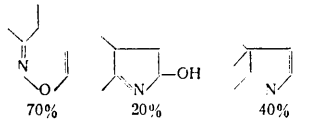
Since 1,2-dihalogenopropanes split off hydrogen chloride under the reaction conditions and are converted into methylacetylene and allene, these results suggest the possibility of pyrrole syntheses based on the industrially available methylacetylene–allene mixture and also on other alkylacetylenes and allenes.

Additional evidence for the intermediate formation of *O*-vinyloximes and for their [3,3]sigmatropic rearrangment has been obtained in a study of the interaction of the oximes of acylindoles and acetylene[49,54] and also of acetophenone oxime and acetylene.[68] It was shown that, even if this is not the only reaction path, it is at any rate the main one:



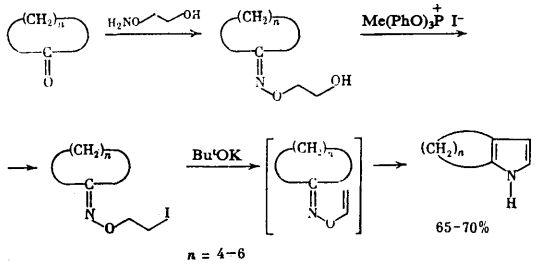
A convenient two-step method has been proposed on the basis of this mechanism[49,54,68] for the selective synthesis of pyrroles free from admixtures of *N*-vinyl derivatives: the *O*-vinyloxime is obtained initially at 40–70 °C from a ketoxime and acetylene and then it is rearranged, without being isolated, into a pyrrole at a temperature of the order of 100 °C.

In a number of instances, the reaction can be arrested at stages involving the formation of 2-hydroxy-2,3-dihydropyrroles and 3*H*-pyrroles:[25,69]



The chemistry of these relatively unstable but undoubtedly very interesting classes of pyrrole compounds developed fairly sluggishly until recently because of the lack of reliable methods of their synthesis. Nowadays, when this limitation has apparently been removed, one may expect an acceleration of the research in this field.

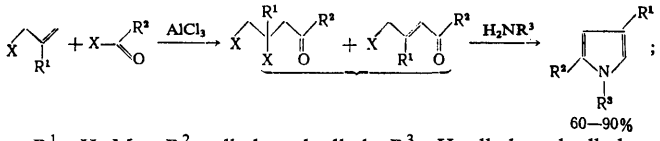
The method of synthesis of pyrroles from ketones via *O*-vinylketoximes has been used recently by English investigators[70] to obtain tetrahydroindole and pyrroles annelated to seven- and eight-membered saturated rings. For this purpose, *O*-(2-hydroxyethyl)ketoximes, prepared from the ketones and *O*-(2-hydroxyethyl)hydroxylamine, were treated with an excess of methyltriphenoxyphosphonium iodide and then the resulting iodide was converted by treatment with potassium t-butoxide into an *O*-vinyloxime, which was rearranged to the pyrrole:



Despite the high yield of pyrroles in the last stage, the advantages of this modification of the ketoxime method[24,25] do not appear unduly convincing in view of the large number of stages and the exotic nature of the reagents.

2. Condensation of βγ-dihalogenoketones with ammonia and primary amines

βγ-Dihalogenoketones or the αβ-ethylene-γ-halogeno-ketones, linked preparatively to them and readily obtainable by acylating allyl and methylallyl halides via the Kondakov reaction, afford 2,4-di- or 1,2,4-tri-substitute pyrroles in 60–90% yield on treatment with ammonia or primary amines:[26–34]

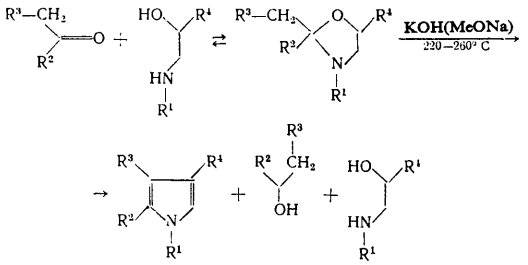


R^1 = H, Me; R^2 = alkyl, cycloalkyl; R^3 = H, alkyl, cycloalkyl, $CH_2=CHCH_2$ Ph.

The attempts to extend this method to other allyl halides were unsuccessful.[29] Nevertheless the synthetic potential of the method is very considerable: by varying the groups in the initial acid chlorides and amines, it is apparently possible to obtain fairly representative series of substituted pyrroles. The most complete publication on this reaction dates back to 1976.[29] Unfortunately this promising method has not been developed further.

3. Alkaline pyrrolysis of *N*-substituted 1,3-oxazolidines

When *N*-substituted 1,3-oxazolidines are fused with potassium hydroxide or alkali metal alkoxides, *N*-substituted pyrroles, secondary alcohols corresponding to the carbonyl component of the molecule, and the corresponding hydroxyalkylamines are formed. It is believed[35–39] that the "disproportionation" of the 1,3-oxazilidines takes place:



R^1 = alkyl, cycloalkyl, Ph, CH_2Ph, $(CH_2)_2OH$, $CH_2CH_2CH(CH_3)OH$;
R^2 = Et, Pr^n;
R^3 = Me, Et, Pr^i;
R^4-H, Me;
$R^2-R^3 = (CH_2)_4$, $(CH_2)_3CH(CH_3)$, $(CH_2)_5$.

The yield of pyrroles is 15–40% relative to the oxazolidine or 30–80% on the basis of the disproportionation mechanism, as stated in the original communications.[35–39] A limitation of the method is the impossibility of obtaining *N*-unsubstituted pyrroles. The conversion of *N*-β-hydroxyethyl derivatives into *NH*-pyrroles[71] (*N*-β-hydroxyethyl → *N*-vinyl → NH) requires at least a further

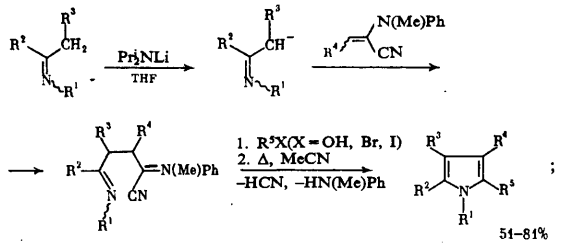
two–three preparative stages. *N*-Benzylpyrroles, which can be reduced to *NH*-pyrroles in one stage,[72] can be obtained by this method in a low yield (20% relative to oxazolidine).

The reaction mechanism has not been discussed.[35–39] It is however clear that this is a complex oxidation-reduction process occurring under the conditions of ultrahigh basicity (ultra-concentrated solutions of strong bases, chelation of alkali metal cations by 2-aminoalkanol molecules), where the dehydrogenating agent is the carbonyl component of the 1,3-oxazolidine. Although it had been established[38] that the addition of a ketone or an aldehyde to the reaction mixture promotes the reaction, subsequently this fact was ignored.[39]

Despite the low yield of products, severe reaction conditions, and the disadvantages and limitations associated with it, this method apparently merits attention and further improvement as a single-reactor synthesis of pyrrole from ketones and amiono-alkanols.

4. Condensation of ketimines with 1-cyano-1-(*N*-methylanilino) alk-1-enes

Yet another reaction permitting the conversion of ketones into pyrroles and based on the condensation of ketimines with 1-cyano-1-(*N*-methylanilino) alk-1-enes in the presence of the Pr^i_2NLi–tetrahydrofuran (THF) superbasic system, has been discovered recently:[40,41]

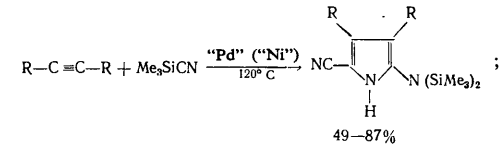


R^1 = Me, Pr^i, cyclo-C_6H_{11}, CH_2Ph;
R^2 = Me, Et, Bu^n;
R^3 = H, Me, Bu^n;
$R^2–R^3 = (CH_2)_3$;
R^4 = H, Et;
R^5 = H, Me, Et, Bu^n.

The key stage of this synthesis is the addition of the ketimine carbanion to the double bond. The carbanion adduct is subsequently protonated or alkylated and is then converted by heating in acetonitrile into the pyrrole with elimination of hydrogen cyanide and *N*-methylaniline, apparently via the [2,3]sigmatropic shift; the yield of the pyrrole is 50–80%. This is a one-pot method and in terms of its possibilities it is in essence similar to the syntheses of pyrroles from ketoximes and acetylene (1-anilino-1-cyanoalk-1-enes behave here as acetylenic synthons). However, in contrast to the ketoxime method, it does not permit the synthesis of *NH*- and *N*-vinyl pyrroles, is applied under dry conditions and in an inert atmosphere (argon), and requires reagents which are more expensive, more difficult to obtain, and less convenient to handle. It is also not clear whether other 1-amino-1-cyanoalk-1-enes can be used just as effectively in this synthesis.

5. Condensation of acetylenes with trimethylsilyl cyanide

Two groups of Japanese investigators[42,43] have recently discovered independently that the reaction of substituted acetylenes, catalysed by palladium or nickel compounds, with an excess of trimethylsilyl cyanide quite unexpectedly leads to 2-cyano-5-[*NN*-bis(trimethylsilyl)amino] pyrroles;



R = H, alkyl, aryl, 2-C_4H_3S, C≡CSiMe$_3$;
"Pd" = Pd(0), Pd/C, $PdCl_2$, $PdBr_2$, $Pd(OAc)_2$, $Pd(CN)_2$, $Pd(PhCN)_2$, $PdCl_2/C_5H_5N$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$;
"Ni" = Ni(0), $NiCl_2/Bu^i_2AlH$, $NiCl_2/Et_3Al$.

There is such a profound redistribution of the atoms of trimethylsilyl cyanide during the reaction that so far it is difficult to put forward any reasonable mechanism for this process, particularly since in the case of disubstituted acetylenes it is necessary to assume the transfer of hydrogen from the methyl group to the nitrogen atom, since there are no other hydrogen donors in the system.

The single-stage nature and regioselectivity of the reaction, the availability of the initial compounds, and the high yields of pyrroles with reactive functional groups, which are difficult to introduce into the pyrrole ring by the usual methods, are all factors leading to good prospects for the new method.

6. General comments

In conclusion of this Section of the review, we may note that the majority of new methods for the construction of the pyrrole ring are based on ketones and acetylenes or their synthons and ultrastrong bases are used in many methods. These are the trends in modern pyrrole synthesis.

Unfortunately none of the methods examined permits the synthesis of pyrroles having both α-positions free (including, paradoxically, pyrrole itself), although such pyrroles are necessary, for example, for the construction of porphyrin structures. The search for reactions which might fill this gap remains urgently necessary.

III. Trends in the study of the reactivity of pyrrole compounds

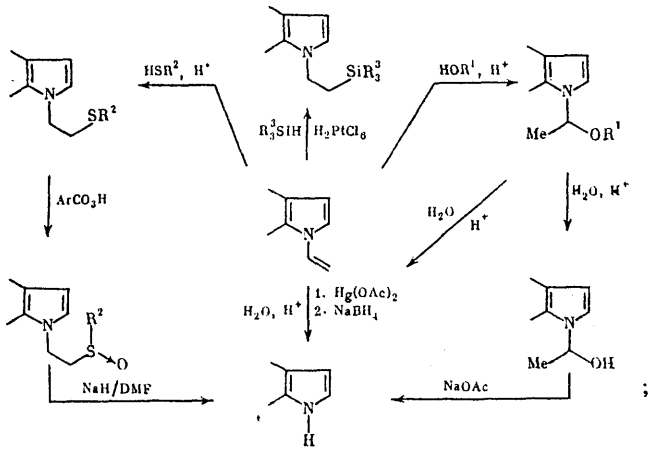
The following new trends have come to the fore in the field of the reactivity of pyrrole compounds: (a) systematic study of *N*-vinylpyrroles which have become available; (b) development of new methods for the introduction of functional groups into the pyrrole ring; (c) the growth of interest in 2*H*- and 3*H*-pyrroles as azadienes.

1. The reactions of *N*-vinylpyrroles

After it became possible to obtain *N*-vinylpyrroles in high yields in a single stage from ketoximes and acetylene (see Section I), they became the most readily available class of pyrrole compounds and, being completely uninvestigated, naturally attracted the attention of not only specialists in synthetic and polymer chemistry and biologists[25] but also of spectroscopists[25,44,46,73] and theoreticians.[75] The question arose how the reactivity and spectroscopic parameters of the pyrrole ring and of the double bonds are affected by the competition between the π-systems for conjugation with the unshared electron pair of the nitrogen atom. New prospects arose

for the synthesis of *N*-substituted pyrroles which are difficult to obtain, namely by the addition of various reagents to the double bond in *N*-vinylpyrroles (Scheme 1):[25] alcohols and water add to the double bonds under the conditions of electrophilic catalysis, thiols add under the conditions of radical catalysis, and hydrosilanes add under the conditions of metal complex catalysis.

Scheme 1

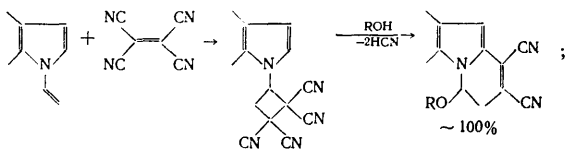


;

R^1 = H, alkyl, aryl, $CH_2C{\equiv}CH$; R^2 = alkyl, aryl; R^3 = alkyl.

Since the *N*-vinyl and *N*-α-alkoxyethyl groups can be removed without difficulty by means of hydrolysis (for example, in the presence of mercury acetate followed by treatment with sodium tetrahydroborate[71]), *N*-vinylpyrroles are now regarded as protected *NH*-pyrroles and are used increasingly as such.[71] The *N*-β-alkylthioethyl group, into which the *N*-vinyl group can be readily converted and which can be subsequently removed if necessary after oxidation to the sulphoxide group (by treatment with peracids and then with sodium hydride in dimethylformamide[71]) can also serve successfully as a protecting group.

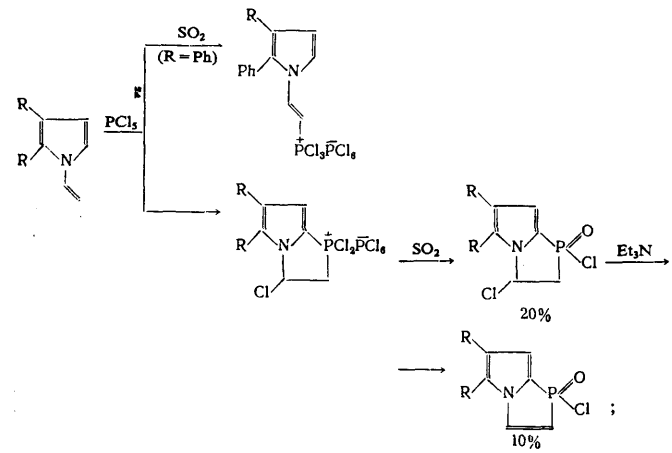
As expected,[25] *N*-vinylpyrroles have begun to be used for the synthesis of 1,2-fused condensed pyrrole systems. Thus they enter into [2 + 2] cycloaddition with tetracyanoethylene, forming *N*-(2,2,3,3-tetracyano-1-cyclobutyl) pyrroles, which are converted on heating with alcohols into 7,8-dicyano-5-organyloxy-5,6-dihydroindolizines in a virtually quantitative yield:[76,77]



;

R-alkyl, $CH_2CH{=}CH_2$, $CH_2C{\equiv}CH$, etc.

The phosphorylation of *N*-vinylpyrroles with phosphorus pentachloride opens up a pathway to new condensed pyrrole systems — pyrrolo[1,2-*a*]-1,3-dichloro-1-oxo-4,1-azaphospholans and pyrrolo[1,2-*a*]-1-chloro-1-oxo-4,1-azaphosphol-2-enes:[78]



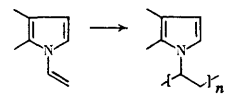
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R = H, alkyl, Ph; R − R = $(CH_2)_4$.

A very pronounced competition for the electrophile between the α-position of the pyrrole ring and the double bond is observed in phosphorylation. In the case of electron-donating (alkyl) substituents, which increase the electron density in the ring, the heterocycle is phosphorylated initially and this is followed by annelation via the double bond, while phenyl substituents, which deactivate the ring, promote the attack by the electrophile on the vinyl group and the formation of a phosphorylated olefinic fragment with the (*E*)-configuration, which is incapable of further cyclisation.

N-Vinylpyrroles are promising although little investigated systems for polymerisation. The interest in them as monomers has been growing rapidly. The principal results already achieved in this field have been surveyed in a review.[45]

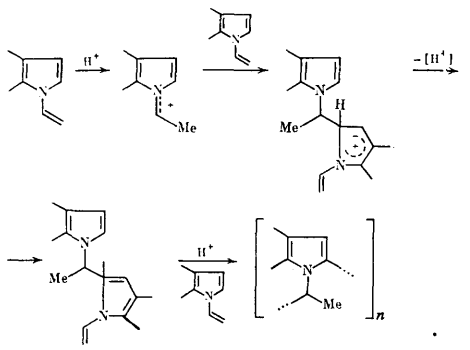
N-Vinylpyrrole polymers and copolymers synthesised by the traditional radical polymerisation in the presence of azoisobutyrodinitrile have the properties of photoconductors:[79]



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There are extensive possibilities for improving the properties of such polymers by altering the structural framework of the pyrrole ring and by its chemical modification. By means of the copolymerisation of *N*-vinypyrroles with other monomers, pyrrole fragments can be introduced into various polymers, imparting new properties to the latter.

The cationic oligomerisation of *N*-vinylpyrroles takes place in a non-traditional way — not as the usual vinyl polymerisation but as an alternative process — the carbonium ion, formed as a result of the addition of a proton to the *N*-vinyl group, attacks subsequently not the double bond but the heterocycle, converting it into the pyrrolium ion, which is stabilised by ejecting a proton:[80,81]



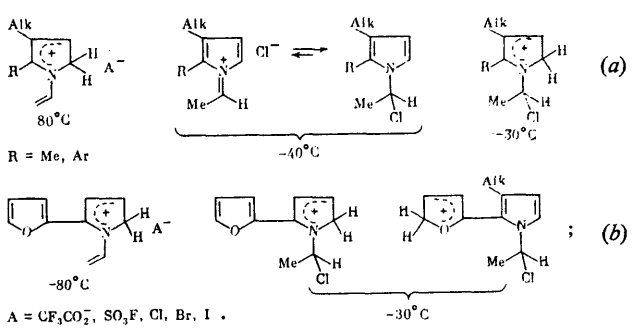
This process yet again illustrates clearly the competition between the double bond and the pyrrole ring in electrophilic reactions. The outcome of the reaction depends on the nature of the electron-deficient species: hard electrophiles (the proton) attack predominantly the double bond, while soft electrophiles (a delocalised carbonium ion) attack mainly the α-position in the pyrrole ring.

The protonated forms of *N*-vinylpyrroles — new types of stable carbonium ions and key intermediate species in the various electrophilic processes proceeding with participation of *N*-vinylpyrroles (polymerisation, addition, and substitution) — are being vigorously investigated.

The cations generated from *N*-vinylpyrroles in the presence of acids can find extensive applications in organic synthesis, in particular in the construction of new heterocyclic systems. Several examples of this kind were examined above.

The products of the protonation of *N*-vinylpyrroles both at the heterocycle and at the double bond and also both these nucleophilic centres simultaneously (Scheme 2, *a*) have been detected and characterised by NMR spectroscopy:[82]

Scheme 2



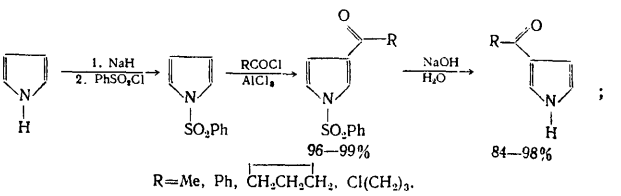
The mode of protonation and the ratio of the cations formed are determined by the strength and nature of the acid, the temperature, and the structure of the substituents in the pyrrole ring. Only the α-position of the pyrrole ring, regardless of the acid strength, is protonated at −80 °C. On raising the temperature to −30 °C in the presence of HCl taken in excess, the protonation of not only the ring but also of the double bond is observed. At −40 °C and in the presence of an equimolar amount of HCl, only *N*-α-chloroethyl derivatives are formed. It is of interest that 2-(2-furyl)-1-vinylpyrroles (Scheme 2, *b*) form selectively at −80 °C only the pyrrolium cations, whilst at a higher temperature (−30 °C) they form both pyrrolium and furanium cations at comparable concentrations. The products of the simultaneous protonation of the pyrrole and furan rings were not detected.[83]

Thus, in thermodynamically controlled electrophilic processes, the furan ring is not always significantly less reactive than the pyrrole ring, contrary to the established ideas.

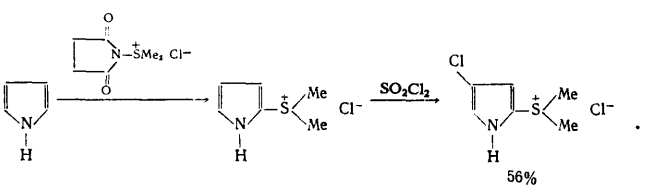
2. New methods for the introduction of functional groups into the pyrrole ring

Methods based on the alteration of the direction of attack by the reagent as a result of the introduction into the ring of polarising substituents (sulphonyl, sulphonium, etc.) have been developing to an increasing extent for the introduction of functional groups into pyrroles.[84]

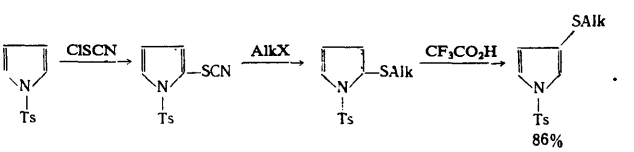
Reactions leading to electrophilic substitution in pyrroles take place predominantly in the α-position in the ring. However, in the case of *N*-sulphonylpyrroles, unprecedented regiospecific β-acylation takes place. The sulphonyl protecting and polarising group is removed just as readily as it is introduced. These preparatively simple operations constitute the basis of an effective method for the synthesis of β-acylpyrroles (in 84–98% yield):[85]



The α-dimethylsulphonium group, which can be readily introduced into the pyrrole ring with the aid of the adduct of dimethyl sulphide and *N*-chlorosuccinimide, similarly deactivates the heterocycle inductively and directs the electrophilic or radical substitution reaction (for example, chlorination[86]) to the 4-position:

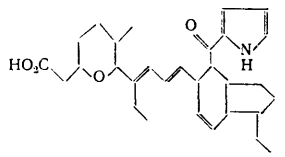


However, the redirecting effect of strong electron-accepting substituents is not always sufficient and is not sufficient for all electrophiles. For example, the direction of attack on the pyrrole ring by various sulphur chlorides cannot be altered in this way. In this case, the β-substitution products are obtained as a result of the acid-catalysed (CF_3COOH) migration of the alkylthio-group from the α- to the β-position:[87]



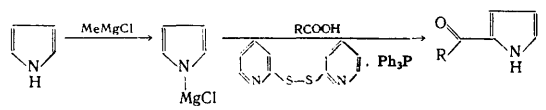
The HBr-catalysed migration of bromine from the α- to the β-position has been observed in the bromination of *N*-substituted pyrroles.[88]

In view of the important biological role of the 2-ketopyrrole structure and its role in the realisation of the programme designed for the complete synthesis of the antibiotic X-1457A, i.e.



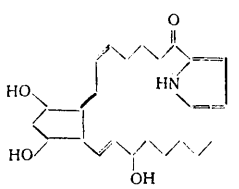
antibiotic X-1457A

a highly effective and highly selective method has been developed for the mild (−78 °C) acylation of pyrrolylmagnesium chloride by a 2-pyridyl thiolo-ester formed *in situ* from di(2-pyridyl) disulphide, triphenylphosphine, and a carboxylic acid:[89]



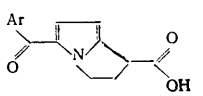
80—95%

The method is suitable even for complex polyfunctional and highly reactive compounds such as thromboxanes, prostaglandins, and monensin. For example, a ketopyrrole derivative has been obtained from prostaglandin $F_{2\alpha}$ in 95% yield:



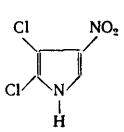
ketopyrrole derivative of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$).

Non-steroid anti-inflammatory and analgesic agents with the structure of 1,2-dihydro-3*H*-pyrrolo-1,2-*a*]pyrrole-1-carboxylic acid are being actively developed:

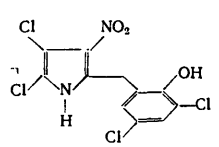


A series of novel methods for the cyclisation of pyrrole compounds have been developed for this purpose.[86,90]

The mode of halogenation and nitration of the pyrrole ring has now acquired special importance in connection with the isolation from natural substrates (*Streptomyces* SF-2080) of new chlorinated nitropyrrole antibiotics (pyrrolomycins A, B, etc.):[91,92]

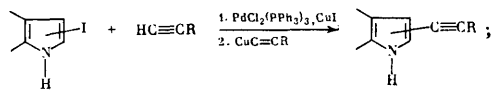


pyrrolomycin A (SF-2080 A)



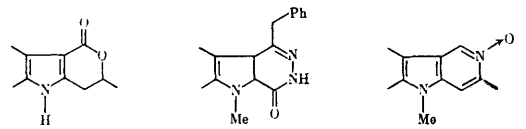
pyrrolomycin B (SF-2080 B)

The problem of the introduction of acetylenic substituents into the pyrrole ring has been solved.[93—101] Two mutually complementing versions of the condensation of iodopyrroles with acetylenes have been used for this purpose: catalytic [in the presence of $PdCl_2(PPh_3)_2$ or CuI] and acetylide. The yields of ethynylpyrroles are 50—96%:



R = H, alkyl, Ph, $C(OH)Me_2$.

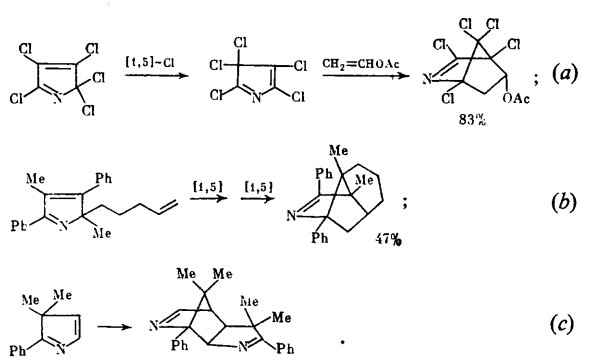
This reaction has important preparative consequences: the ethynyl substituent in the pyrrole ring provides new and unusually wide possibilities for the introduction of functional groups and the construction of complex heterocyclic systems, which has been demonstrated convincingly[102—105] in relation to the intramolecular cyclisation of functional pyrroles and indoles with ethynyl substituents, as a result of which pyran, pyridazine, and pyridine rings have been built onto the pyrrole ring:



3. 2*H*- and 3*H*-pyrroles as azadienes

The picture of the modern pyrrole chemistry would be incomplete if no mention were made of the enhanced interest in 2*H*- and 3*H*-pyrroles,[106] especially in the prospects for their employment in the Diels—Alder reaction as azadienes.[107] The first steps in this direction appear very promising. Examples of both intermolecular (Scheme 3, *a*) and intramolecular (Scheme 3, *b*) diene syntheses with participation of 3*H*-pyrroles, formed as a result of the rearrangement of 2*H*-pyrroles via a 1,5-shift, are known:[106—108]

Scheme 3



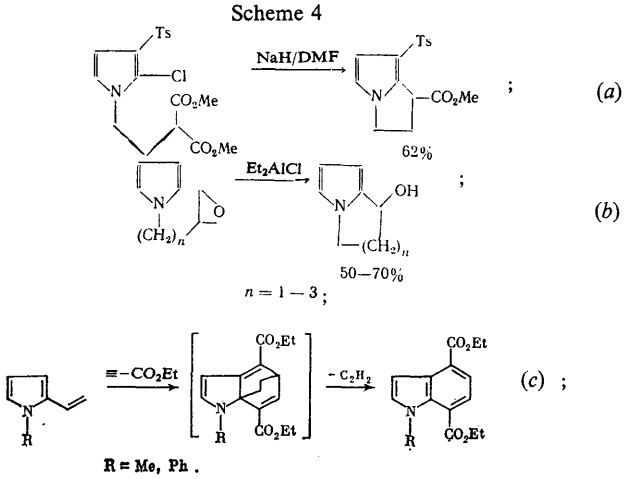
An interesting approach to new skeletal and condensed tetrahydropyridine systems may be provided by the diene autocondensation of the available 3,3-dimethyl-2-phenyl-3*H*-pyrroles (Scheme 3, *c*).[52]

IV. Pyrroles as intermediates in organic synthesis

Pyrroles have been recently investigated with increasing frequency not as objects of synthesis but as a means for the construction of particular complex molecules with a specified structure.[109] The most evident employment of pyrroles on these lines involves the synthesis of condensed heterocyclic systems by various annelation reactions.

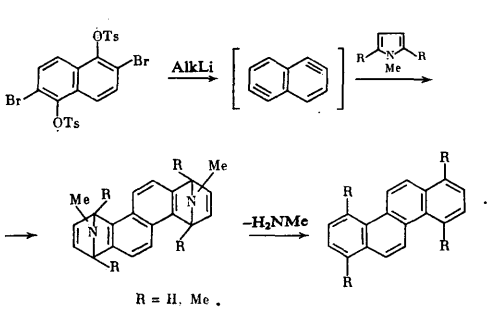
Intramolecular nucleophilic substitution of a halogen in the pyrrole ring, facilitated by the tosylate group (Scheme 4, *a*),[110] the electrophilic cyclisation of *N*-epoxyalkylpyrroles (Scheme 4, *b*),[111] and the diene condensation of 2-vinylpyrroles with electron-deficient acetylenes (Scheme 4, *c*)[109,112] are developing. *N*-Vinylpyrroles, which are now available, have led to new interesting prospects in this respect (see Section III, subsection 1).

Scheme 4



The use of the pyrrole ring itself as the 1,3-diene component in the Diels—Alder reaction for the construction of bicyclic structures with a bridging nitrogen atom is more traditional (Scheme 5).[109] Here pyrroles frequently play the role of butadiene synthons, because the adducts are capable of being deaminated. A typical example is provided by the synthesis of carcinogenic polycondensed aromatic hydrocarbons: pyrroles undergo the Diels—Alder condensation with 1,5-naphthodiyne generated *in situ* and subsequently give rise to chrysenes (in 33—49% yield) as a result of the splitting off of methylamine from the diadducts (Scheme 5):[113]

Scheme 5

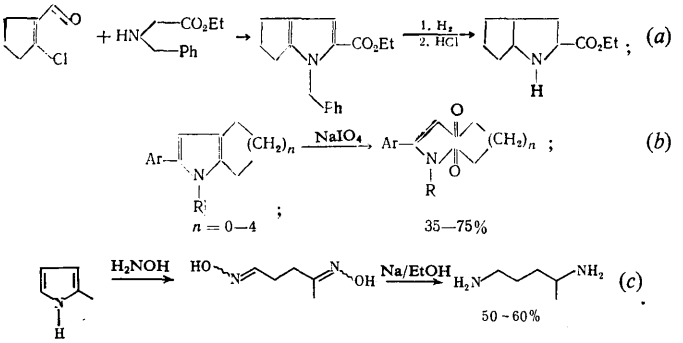


In many multistage specific syntheses, pyrroles are converted into pyrrolidine structures, for example, in the synthesis of 2-azabicyclo[3.3.0]octane-3-carboxylic acid—a key precursor of a highly active enzyme inhibitor (Scheme 6, *a*).[109,114]

The opening of the pyrrole ring is used successfully in the solution of certain synthetic problems. Thus macrocyclic ketolactams are obtained by the regiospecific oxidation of pyrroles annelated to alicyclic systems (Scheme 6, *b*).[115]

Dioximes formed from pyrroles on treatment with hydroxylamine have been used recently to synthesise 1,4-diaminobutanes, which participate, together with putrescine, spermidine, and spermine, in protein synthesis and cell proliferation (Scheme 6, *c*).[116]

Scheme 6



V. Conclusion

The chemistry of pyrroles continues to develop vigorously at the present time. In particular, this development has been stimulated by advances in the chemistry of porphyrins and organic metals. New approaches to the construction of the pyrrole ring and the introduction of functional groups into the latter are being vigorously developed. Pyrroles are being used increasingly as building blocks in organic synthesis. A close interaction and interpenetration of studies designed to seek and develop general synthetic reactions and methods, whose aim is the specific synthesis of complex structures, are characteristic of modern pyrrole chemistry.

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