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Condensation of Oxazoles with Dienophiles—a New Method for the Synthesis of Pyridine Bases

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The condensation of oxazoles with dienophiles is of the diene synthesis type, the final reaction products being substituted pyridine bases. The review deals with the literature data concerning the preparative applications of the condensation and the elucidation of the theoretical features of this process. In conclusion of the review, the application of heterodiene synthesis with participation of oxazoles in the preparation of vitamin B_6 and its analogues is discussed. The bibliography comprises 38 references.

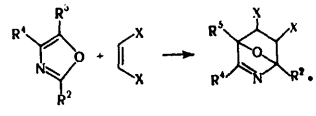
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I. INTRODUCTION

Towards the end of the 1950's, Kondrat'eva [1,2] showed that the azadiene system of oxazoles readily reacts with an activated double bond by the diene synthesis mechanism [Diels–Alder mechanism (Ed. of Translation)]. The final products of this reaction are substituted pyridine bases. The reaction constitutes a very promising method for synthesising substituted pyridines including biologically important compounds—derivatives of nicotinic and isonicotinic acids, i.e. B_6 vitamins and their analogues.

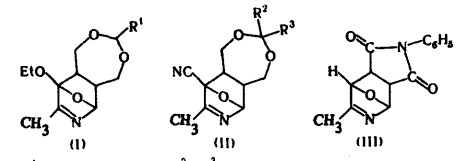
A series of papers have now been published on studies of the interaction between oxazoles and dienophiles both as regards the development of preparative methods for the synthesis of pyridine derivatives and the elucidation of the theoretical features of this interesting process. The synthesis of pyridine bases by the condensation of oxazoles with dienophiles consists of two stages. The first stage, the diene synthesis proper, results in the intermediate formation of bicyclic adducts:



Depending on the structure of the initial compound, the second stage can take place in several ways (see Scheme 1 and p. 37). Each of these stages has specific features and is of independent interest.

II. DIENE SYNTHESIS WITH PARTICIPATION OF OXAZOLES

The bicyclic adducts formed in the interaction between oxazoles and dienophiles are extremely unstable and usually cannot be isolated from the reaction mixture. Only three cases where the intermediate formation of the adducts has been rigorously established have been described. Thus in the reaction of 5-ethoxy-4-methyloxazole [3] and 5-cyano-4-methyloxazole [4,5] with substituted 4,7-dihydro-1,3-dioxepines. The racemates of the *endo*- and *exo*-isomers of compounds (I) and (II) were isolated:



(I) R^1 = H; iso-C_3H_7

(II) $R^2 = R^3 = H$; $R^2 = R^3 = CH_3$; R^2 = H; R^3 = iso-C_3H_7; R^2 = H; $R^3 = C_6H_5$

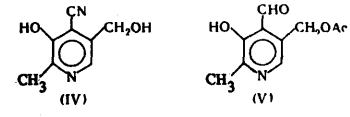
(III)

Similarly the condensation of 4-methyloxazole with *N*-phenylmaleimide yielded the adduct (III). [6] The stereochemistry of this compound was not studied.

As a result of the lability of the adducts produced in heterodiene synthesis, the characteristics of the individual reaction stages cannot be taken into account separately. Of the effects which should obtain mainly in the first stage of the heterodiene synthesis, it is necessary to consider in the first place the orientation of asymmetric dienophiles in the interaction with oxazoles.

In most cases the usual Diels–Alder reaction yields both possible isomers. In contrast, in heterodiene synthesis with participation of oxazoles only one of the products is formed as a rule. In her study of the interaction of alkyloxazoles with acrylic acid, Kondrat'eva [7] showed that this involves the formation exclusively of substituted isonicotinic acid and only in a few cases was it possible to detect traces of the second isomer–substituted nicotinic acid.

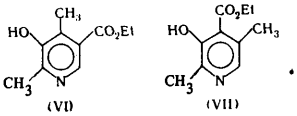
A similar observation was also made in the condensation of 5-ethoxy-4-methyloxazole with the nitrile of 4-hydroxycrotonic acid [8] and 4-acetoxycrotonic aldehyde [9]. Compounds (IV) and (V) respectively were isolated:



(IV) (V)

Thus, as a rule, the heterodiene synthesis takes place in such a way that the fifth position in the adduct is occupied by the most electronegative group of the dienophile.

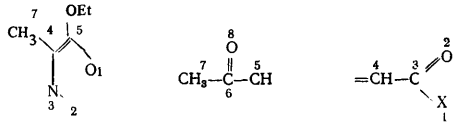
Exceptions to this rule were noted only with 4-methyloxazole. Thus in the reaction of this diene with ethyl crotonate the ester of 3-hydroxy-2,4-dimethylpyridine-5-carboxylic acid (VI) was obtained in 12% yield instead of the expected product (VII):[10]



(VI) (VII)

The sole attempt at a theoretical explanation of the first stage of the heterodiene synthesis was undertaken[11] in the study of the interaction between 5-ethoxy-4-methyloxazole and asymmetric dienophiles—β-acetylacrylic acid (VIIIa) and its ethyl ester (VIIIb). The authors[11] start with the hypothesis that the extreme polarisation of the azadiene oxazole system should favour reaction by a two-stage mechanism with separation of charges in the transition state. Then the orientation should be determined by the distribution of π-electron densities at the atoms participating in the transition state. To test this hypothesis, the parameters of the 5-ethoxy-4-methyloxazole molecule and its cation and also the anion and the ethyl ester of β-acetylacrylic acid were calculated. The calculations were performed by the LCAO-MO method in the Hückel approximation taking into account the effect of the hyperconjugation of the methyl group.

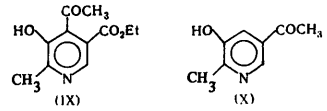
Distribution of π-electron densities



(VIIIa): X=O⁻
(VIIIb): X=OEt

Compound	q^{π} at different atoms							
	1	2	3	4	5	6	7	8
5-Ethoxy-4-methyloxazole	1.733	1.020	1.196	1.042	1.095	1.921	1.070	—
Cation of 5-ethoxy-4-methyloxazole	1.663	1.781	1.609	0.994	1.055	1.915	1.069	—
Ethyl β-acetylacrylate (VIIIb)	1.922	1.321	0.815	0.950	0.937	0.763	1.075	1.318
β-Acetylacrylate anion (VIIIa)	1.825	1.396	0.823	0.932	0.962	0.764	1.075	1.323

The Table shows that, in the product of the interaction of 5-ethoxy-4-methyloxazole with compound (VIIIb), the acetyl group must occupy the fourth position in the pyridine ring, while the opposite orientation should obtain in the reaction with the free acid (VIIIa), and the formation of substituted 5-acetylpyridine as the main product is to be expected. Indeed, after the condensation of 5-ethoxy-4-ethyloxazole with compound (VIIIb) only 4-acetyl-5-ethoxycarbonyl-3-hydroxy-2-methylpyridine (IX) was isolated, while in the condensation with compound (VIIIa) the only product obtained was 5-acetyl-3-hydroxy-2-methylpyridine (X).

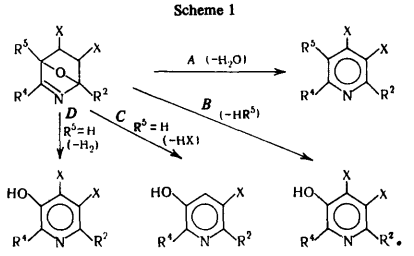


(IX) (X)

III. AROMATISATION OF THE ADDUCTS FROM DIENE SYNTHESIS

As already mentioned, the bicyclic adducts readily undergo aromatisation, particularly in acid media, and, depending on the structure of the starting compounds, the reaction can take place in four principal ways (Scheme 1).

Scheme 1

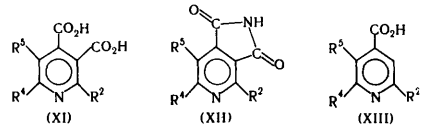


Usually all or several pathways operate simultaneously and heterodiene synthesis yields a more or less heterogeneous mixture of products. Analysis of literature data shows that the mode of aromatisation is determined by the nature of two substituents in the adduct—the substituent R^5 in the 4-position and the substituent X in the 5-position.

1. Aromatisation with Elimination of a Water Molecule (Kondrat'eva's Reaction)

The aromatisation of adducts via pathway *A* has been called Kondrat'eva's reaction. It resembles the aromatisation in acid media of the adducts obtained in the condensation of furan derivatives with dienophiles and usually takes place if the substituents R^5 and X in the adduct do not show a tendency to be eliminated in the form of anions.

Alkyloxazoles react in this way with maleic anhydride and maleic acid[2,12], forming alkyl-substituted cinchomeronic acids (XI); the reaction with maleimide[12-14] yields under these conditions the imides of cinchomeronic acids (XII) while the reaction with acrylic acid[7] gives analogues of isonicotinic acid (XIII):



(XI) (XII) (XIII)

where $R^2 = R^5$ = alkyl and R^4 = alkyl or aryl.

With other dienophiles, alkyloxazoles having an unsubstituted 5-position react via pathways *C* and *D* (see Section III, Subsection 3). Kondrat'eva[14] studied the behaviour in diene synthesis of oxazoles substituted in the 2- and 5-positions by electronegative groups. Dienes of this type do not react with maleic anhydride, but do react with maleimide via pathway *A*, forming normal products with yields lower by approximately 50% than for the corresponding alkyl-substituted oxazoles. Thus 2,4-dimethyloxazole gives the product (XII) in 93% yield, while with

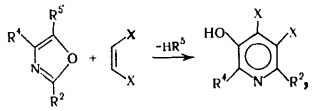
5-acetyl-4-methyl- and 5-ethoxycarbonyl-4-methyl-oxazoles, the yields of compound (XII) are 45 and 37% respectively.

The introduction of a phenyl group in the 4-position of oxazole has almost no effect on the interaction with dienophiles but 2- and 5-phenyloxazoles do not take part in heterodiene synthesis. On the basis of these data, the substituents of the oxazole ring can be arranged in the following sequence in terms of their effect on the reaction: alkyl ≃ 4-phenyl > $COCH_3$ > $COOC_2H_5$ ≫ 2- and 5-phenyl, the activity of oxazoles in the diene synthesis decreasing from left to right.

The occurrence of the reaction by pathway *A* is favoured when the diene synthesis is carried out in aprotic solvents. Japanese workers [12] have shown that the replacement of acetic acid by benzene in the reaction of 4-methyloxazoles with maleic anhydride leads to an increase of the yield of 2-methylcinchomeronic acid from 40 to 65%.

2. Aromatisation with Elimination of a Molecule of Alcohol or Hydrocyanic Acid

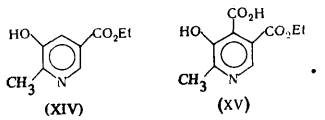
If a substituent which is readily eliminated in the form of an anion is present in the 4-position of the adduct, aromatisation takes place via pathway *B*, the final products being substituted 3-hydroxypyridines:



where R^5 = Oalkyl, $OCOOC_2H_5$, or CN. This reaction is characteristic of 5-hydroxyoxazoles with a protected hydroxy-group or of 5-cyanooxazoles.

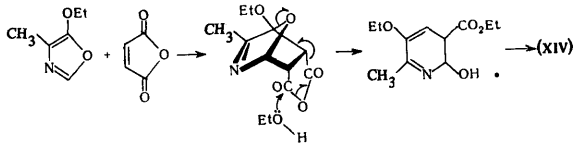
It is noteworthy that 5-alkoxyoxazoles, which are the most active dienes among oxazole derivatives, are comparable in their reactivity with carbocyclic dienes, the yields of the final products being usually high.

Firestone et al. [15], who studied the reaction of 5-ethoxy-4-methyloxazole with maleic acid anhydride in ether at 0°C, isolated 5-ethoxycarbonyl-3-hydroxy-2-methylpyridine (XIV) and the monoethyl ester of 3-hydroxy-2-methylpyridine-4,5-dicarboxylic acid (the main reaction product) after the aromatisation of the adduct with a solution of dry hydrogen chloride in absolute ethanol. The relative positions of the carboxy- and ethoxycarbonyl groups in the second product were not established rigorously, but the authors suggest the structure (XV) for this compound:



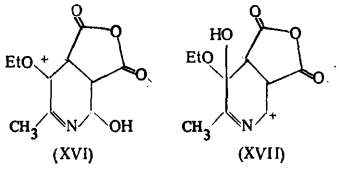
(XIV) (XV)

According to the authors, compound (XIV) is formed by the mechanism



Naito and Yoshikawa [6] did a lot of work on the determination of the composition of the reaction mixtures formed in the interaction between 5-ethoxy-4-methyloxazole and a number of dienophiles and showed that the main product is always accompanied by a certain amount (frequently traces) of a side product—3-hydroxypyridine with a free 4-position [a derivative of type (XIV)].

Firestone proposed two alternative mechanisms of the formation of the main product (XV) of heterodiene synthesis, differing in the position of the hydroxy-group and the localisation of the positive charge in the key intermediate (XVI) or (XVII). Both cations may arise in the heterolysis of the bonds of the oxygen bridge in the adduct by each of the possible pathways:

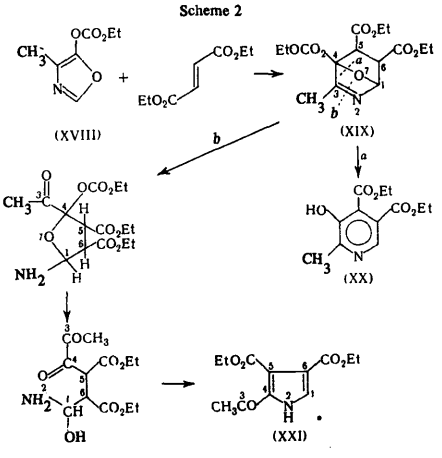


(XVI) (XVII)

Interesting results were obtained by Murakami et al. [16] in the study of the interaction of 5-ethoxycarbonyl-4-methyloxazole (XVIII) with diethyl fumarate (Scheme 2, below). The authors believe that, depending on the aromatisation conditions, the process may begin either with the dissociation of the C–O bond of the adduct (XIX), which leads to the diester of 3-hydroxycinchomeronic acid (XX), or with the dissociation of the C=N bond. In the latter case 2-acetyl-3,4-diethoxycarbonylpyrrole (XXI), the structure of which was demonstrated rigorously by proton magnetic resonance spectroscopy and by preparative synthesis, is obtained via a number of intermediates.

The particular pathway of the aromatisation of the adduct probably depends on the presence of water in the reaction mixture. Thus, by treating the adduct with a solution of dry hydrogen chloride in absolute ethanol, Murakami et al. [16] obtained 50% of the "normal" product (XX) and only 5% of the "anomalous" product (XXI), while treatment with concentrated hydrochloric acid gave the reverse proportions—5 and 54% respectively.

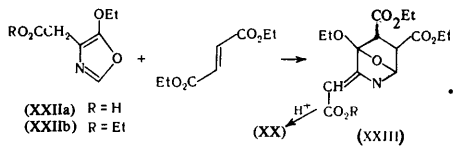
Scheme 2



(XVIII) (XIX) (XX) (XXI)

The above finding requires serious attention and further investigation in other instances of heterodiene synthesis via pathway *B*.

Miku and Matsuo [17] studied the interaction with dienophiles of 5-ethoxyoxazole-4-acetic acid (XXIIa) and its ethyl ester (XXIIb):



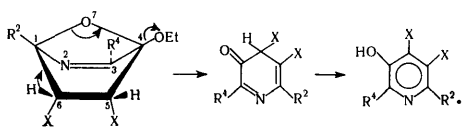
(XXIIa) R = H
(XXIIb) R = Et

The condensation of the ester (XXIIb) with diethyl fumarate leads, according to Miku and Matsuo [17], to the adduct (XXIII) with an exocyclic double bond. The structure of the latter was demonstrated by proton magnetic resonance and mass spectroscopy. The aromatisation of the adduct under the influence of acids is accompanied by the hydrolysis of the α'-ester group and the decarboxylation of the intermediate substituted pyridine-1-acetic acid, which is a β-imino-acid.

In the interaction of the free acid (XXIIa) with various dienophiles the aromatisation and decarboxylation take place directly during the reaction. Miku and Matsuo [17] do not associate this interesting phenomenon with the heterodiene synthesis but, referring to Doering and Pasternak [18], attribute it to the extremely ready decarboxylation of pyridine-1-acetic acids in an acid medium.

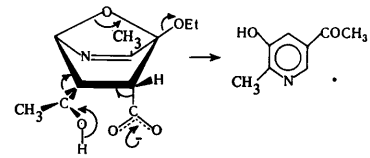
The following fact may be mentioned in connection with further consideration of the mechanism of the aromatisation of the adducts via pathway *B*: none of the investigators succeeded in isolating or demonstrating the presence in the reaction mixture of products corresponding to Kondrat'eva's reaction—substituted 3-alkoxypyridines.

The following mechanism was proposed for the adduct aromatisation stage [11]:



According to the authors the isomerisation of the adducts begins with the dissociation of the C^1–O bond. This conclusion is based on the following main postulates: (1) the C^1–O bond is in fact the one weakened to the greatest extent due to σ–π conjugation with the C^3=N bond. Under the isomerisation conditions (usually a solution of dry hydrogen chloride in alcohol), the heterolysis is favoured by the protonation of the adduct both at the nitrogen and at the oxygen atom; (2) the dissociation of the C^4–O bond with subsequent hydrolysis is unlikely if only because the diene synthesis and the isomerisation are most often carried out in complete absence of water. The validity of this hypothesis is confirmed by the examination of the diene synthesis with participation of 5-ethoxy-4-methylthiazole (see p. 544), the products of which are always 3-alkoxypyridines despite the fact that the aromatisation conditions (heating with concentrated hydrochloric acid) favour hydrolysis. (3) Finally, if the dissociation of the C^4–O bond is assumed, it is difficult to explain the exclusive formation of 3-hydroxypyridines in the interaction of dienophiles with 5-cyano-oxazoles.

In support of this mechanism, the authors quote the fact that the condensation of 5-ethoxy-4-methyloxazole with β-acetylacrylic acid is always accompanied by decarboxylation regardless of the reaction conditions, which results in the formation of 5-acetyl-3-hydroxy-2-methylpyridine:



Although the mechanism of heterodiene synthesis described above [11] is to a considerable degree speculative, it nevertheless accounts for the characteristics of this interesting reaction known at the present time.

As far as one can judge from the literature data, solvents do not have much effect on diene synthesis by the above mechanism. There is an indication [15] that small amounts of acids (for example, trifluoroacetic acid) catalyse heterodiene synthesis.

The reaction constitutes a very convenient method for the preparation of substituted 3-hydroxypyridines. The high reactivity of azadienes permits condensation with a wide range of dienophiles. Among the latter, the following compounds have been used: maleic anhydride [15,19], maleimide [19], esters of maleic and fumaric acids and fumaronitrile [9,15–17,20], 1,4-diacetoxy- and 1,4-dimethoxy-but-2-ene and 2,5-dihydrofuran [9,15,20–22], 2-substituted 4,7-dihydro-1,3-dioxepins [3,5], and a number of other compounds.

It is noteworthy that the limitations consisting in the low availability of the initial oxazoles which initially arrested the development of this method have now been to a large degree overcome as a result of a number of successful investigations of the synthesis of oxazoles [9,23–27].

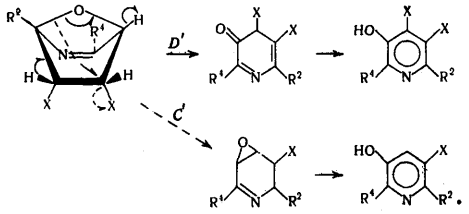
3. Other Pathways of the Aromatisation of Adducts

The aromatisation of adducts via pathways *C* and *D* is characteristic of the interaction of 5-unsubstituted oxazoles with dienophiles the substituents of which tend to be eliminated as anions. This type of aromatisation was investigated in the interaction of 4-methyl-, 4-phenyl-, and 2,4-dimethyl-oxazoles, with acrylonitrile [28], fumaronitrile and the diesters of maleic and fumaric acids [6,12], and a number of other dienophiles (see Scheme 1). As for pathway *B*, the final reaction product is 3-hydroxypyridine. In most cases both pathways operate simultaneously and, depending on the reaction conditions and the structure of the initial compounds, both products are obtained in various proportions.

We believe that the aromatisation of the adduct includes a stage in which the anion is displaced from the 3- or 4-position. This hypothesis is confirmed by the following findings. (1) According to the hypothesis, the reaction via pathway *C* should include the displacement from the 4-position of the substituent in the form of an anion, i.e. the substituent which previously belonged to the dienophile. Indeed, it has been shown [12] that, in the reaction of 4-methyloxazole with a series of dienophiles (fumaronitrile, acrylonitrile, diethyl fumarate, diethyl maleate, and ethyl acrylate), the yields of products via pathway *C* decrease from left to right in parallel with the capacity of the substituent of the dienophile to be eliminated as an anion. (2) The reaction via pathway *D* should include a stage in which an anion, i.e. a hydride ion, is displaced from the 3-position. Since this type of process is energetically unfavourable, the product of the reaction via pathway *D* is usually obtained in insignificant amounts, as an admixture to the product formed via pathway *C*. However, when the

reaction is carried out in the presence of hydride ion acceptors (hydrogen peroxide [12,29] or nitrobenzene at elevated temperatures [30]), pathway *D* becomes the main one and the yields of products reach 50–60%.

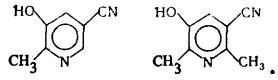
We believe that all these findings can be explained if it is postulated that the isomerisation of the adduct begins with the dissociation of the C^1–O bond of the oxygen bridge:



The liberated electron pair may attack either C^4 or C^5 atoms, displacing by a mechanism of the nucleophilic type either an X anion or a hydride ion.

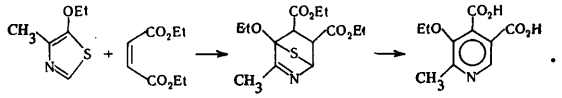
When the reaction is carried out in acid media, the yields of the products of heterodiene syntheses via pathway *C* are improved [1]. Thus, in the reaction of 4-methyloxazole with acrylonitrile [28] in benzene, 3-hydroxy-2-methylpyridine is obtained in 12% yield, while in acetic acid the yield is 28%.

The above pathway of heterodiene synthesis is not of particular value for synthetic purposes because of the low yields (usually 5–25%). An exception is the reaction of fumaronitrile with 4-methyloxazole [12,31] and 2,4-dimethyloxazole [6], which leads to substituted 5-cyano-3-hydroxypyridines (XXV) and (XXVI) in yields of 71 and 55% respectively:



(XXV) (XXVI)

In conclusion of the discussion of the diene synthesis of oxazoles, we shall describe the only study so far of the interaction with dienophiles of a derivative of thiazole—an oxazole heteroanalogue [32]. On heating for 8 h at 200°C with diethyl maleate, 5-ethoxy-4-methylthiazole (XXVII) forms the adduct (XXVIII), which undergoes aromatisation on heating with concentrated hydrochloric acid, hydrogen sulphide being eliminated:



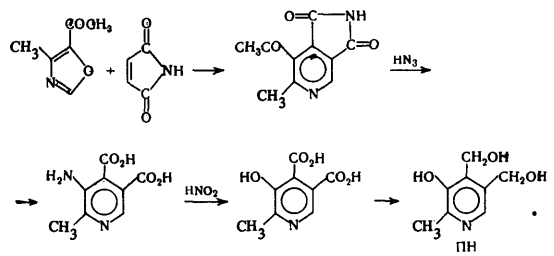
(XXVII) (XXVIII) (XXIX)

It is interesting to note that, in contrast to 5-alkoxyoxazoles, the isomerisation takes place in this case by a process of the type of Kondrat'eva's reaction and the final product is 3-ethoxy-2-methylpyridine-4,5-dicarboxylic acid (XXIX). The same product was obtained [32] by the reaction of compound (XXVII) with diethyl fumarate and maleic anhydride.

IV. APPLICATION OF HETERODIENE SYNTHESIS WITH PARTICIPATION OF OXAZOLES IN THE PREPARATION OF VITAMIN B_6 AND ITS ANALOGUES

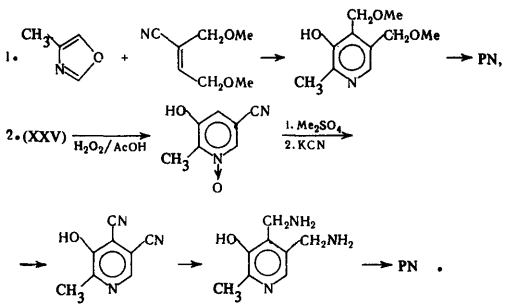
The interaction of oxazoles with dienophiles has been successfully used for the preparation of vitamin B_6 (pyridoxine) and its analogues. Methods for the synthesis of pyridoxine—3-hydroxy-4,5-bis(hydroxymethyl)-2-methylpyridine (PN) using heterodiene synthesis via pathways *A*, *B*, and *C* (Scheme 1) have been proposed. Kondrat'eva's reaction is not of great interest for the synthesis of pyridoxine, since the introduction of a hydroxy-group in the 3-position of the pyridine ring involves considerable difficulties. The sole attempt on these lines [33]—the synthesis of pyridoxine via Scheme 3—cannot be regarded as successful because of the complexity of the method and the low yields in the first two stages:

Scheme 3



In the series of pyridoxine analogues, this scheme can be used only to obtain products modified in the 3-position of the pyridine ring.

Two schemes based on heterodiene synthesis via pathway *C* have now been proposed for the synthesis of pyridoxine [10,34]:



The first synthesis is of exclusively theoretical interest, since the yield of 3-hydroxy-4,5-bis(methoxymethyl)-2-methylpyridine is very low. The second synthesis, despite the large number of stages, may find application in the synthesis of pyridoxine labelled at a carbon atom.

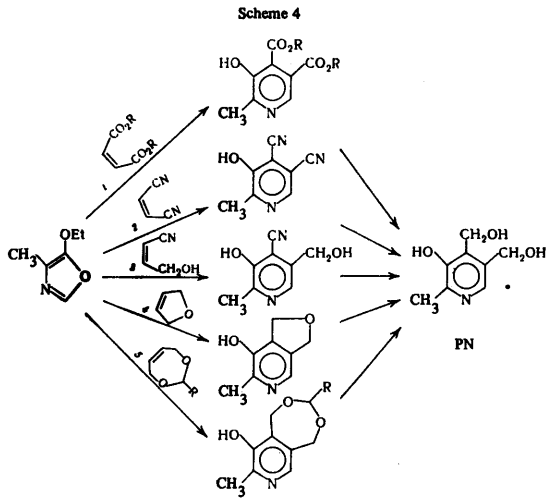
The most successful synthesis of pyridoxine and its analogues is heterodiene synthesis via pathway *B*. Its advantages include the following: high reactivity of 5-alkoxyoxazoles as dienes, high yields of final products, and simplicity. It is therefore not surprising that the efforts of investigators have been concentrated on the development of precisely this reaction (Scheme 4).

In syntheses *1–3* oxazole undergoes condensation with active dienophiles, which makes it possible to carry out the reaction under mild conditions (usually at 60–110°C). The yields of the final products amount to 75–86%. Further conversion of the compounds into pyridoxine does not present difficulties.

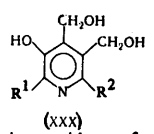
Since direct interaction of oxazole with but-2-ene-1,4-diol gives a low yield of pyridoxine, various butenediol derivatives have been used as dienophiles. Best results were obtained with 2,5-dihydrofuran [9,15,20–22] and 4,7-dihydro-1,3-dioxepine [3–5] (Scheme 4, pathways *4* and *5*). In this case the diene synthesis is carried out under more severe conditions than for pathways *1–3* (usually in an autoclave at 170–200°C) and the yields of the primary reaction products are somewhat lower (50–60%). However, the simplification of the process and the very high yields

of the final products give approximately the same yield of pyridoxine as in syntheses *1–3* of Scheme 4.

Scheme 4



The type of heterodiene synthesis considered above is very promising for the preparation of pyridoxine analogues. It makes it possible to modify virtually any position of the pyridine ring, with the exception of the third. A number of alkyl analogues of pyridoxine [compounds (XXXa)–(XXXf)] have been obtained by the interaction of 2- and 4-alkyl substituted 5-ethoxyoxazoles with diethyl maleate followed by the reduction of the esters of cinchomeronic acids with lithium aluminium hydride [35–38]:



(XXX)

a: $R^1=R^2=H$;
b: $R^1=H$; $R^2=CH_3$;
c: $R^1=R^2=CH_3$;
d: $R^1=C_2H_5$; $R^2=H$;
e: $R^1=$ iso-C_3H_7; $R^2=H$;
f: $R^1=$ n-C_4H_9; $R^2=H$.

Thus, the interaction of oxazoles with dienophiles constitutes a promising method for the synthesis of pyridine bases, in particular substituted 3-hydroxypyridines.

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During the preparation of the review for the press, a communication dealing with the condensation of 5-ethoxy-4-methyloxazole with *cis*- and *trans*-2,5-dimethoxy-2,5-dihydrofuran was published [39]. The authors isolated diene synthesis adducts and showed that the ratio of the *endo*- and *exo*-adducts is 2 : 1 in both cases. Aromatisation with an alcoholic solution of alkali gave 3-hydroxy-2-methylpyridine-4,5-dialdehyde.

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