THE DIENE SYNTHESIS REACTION AND SUBSTITUTIVE ADDITION WITH 2-PYRIDONES AND THEIR THIO ANALOGS (REVIEW)

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UDC 547.823.547.825

The literature on the reactions of 2-pyridones and their thio analogs with unsaturated compounds taking place by a mechanism of diene synthesis or of substitutive addition, depending on the structure of the initial components, has been systematized. The basic synthetic directions of the use of these reactions and also the stereochemistry of the diene synthesis with 2-pyridones and 2-thiopyridones are considered.

2-Pyrones are active dienes and are widely used in Diels—Alder reactions [1, 2]. It might be assumed that their nitrogen analogs — the 2-pyridones, containing a conjugated system of multiple bonds in the molecule — would also take part in the diene synthesis. However, the initial attempts to obtain 1,4-cycloadducts for these pyridine derivatives did not give satisfactory results [2-8]. In the first place, with dienophiles, pyridine unsubstituted at the nitrogen atom readily formed the products of substitutive (nucleophilic) addition, and if the rate of this reaction competing with the diene synthesis was high (particularly in the case of the thio analogs) no cycloadducts whatever were obtained [5-7]. Another reason for the initial lack of success was that the diene activity of the 2-pyridones is low because of their aromatic properties, which are expressed in them considerably more strongly than in the 2-pyrones [8-10].

However, in spite of these unfavorable factors, it was shown in the 1970's that with an appropriate choice of dienophiles and under comparatively severe conditions 2-pyridones can react by a 1,4-cycloaddition mechanism [2, 11-17].

Now, for pyridones substituted at the nitrogen atom, the diene synthesis has been performed with a wide range of unsaturated compounds [17-19], including azadienophiles [20-22], while for the NH pyridones the possibility has been shown of reactions by the 1,4-cycloaddition mechanism only with maleimide and its derivatives [2, 17, 23, 24].

The use of 2-pyridones of various structures — 1-alkyl- [15-19] and 1-vinyl-2-pyridones [25] and 1-alkyl-2-thiopyridones [16, 27], all substituted at the nitrogen atom — shows the general nature of 1,4-cycloaddition for these heterocyclic systems.

The diene synthesis with 2-pyridones and their thioanalogs has been used for the synthesis of bicyclic compounds with azocarbonyl bridges [15-19] and new nitrogen heterocycles [20-22], and for the production of azabarrelene [28] and bridged organosulfur compounds [27, 29, 30].

At the same time, the nucleophilic addition reaction of 2-pyridones unsubstituted at the nitrogen atom and, particularly, their thioanalogs with unsaturated compounds is of independent interest, since it permits extremely diverse pyridine derivatives to be obtained [5, 7, 19, 27].

In the present paper we have systematized the literature on the reactions of unsaturated compounds with 2-pyridones and their thioanalogs taking place by the mechanisms of substituted addition and of diene synthesis.

I. REACTIONS OF 2-PYRIDONES AND THEIR THIOANALOGS UNSUBSTITUTED AT THE NITROGEN ATOM

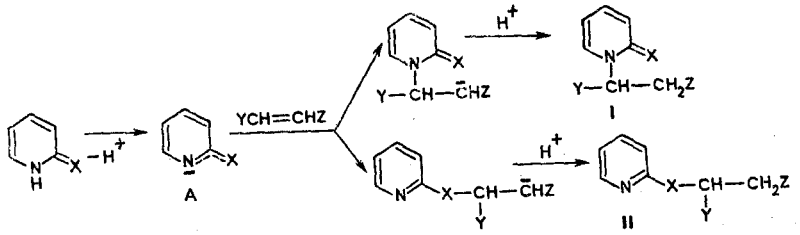
1. Substituted Addition

NH-Pyridones and their thioanalogs add to compounds with activated double bonds in the presence of catalysts of basic nature (or without them) by the mechanism of a Michael conden-

M. V. Lomonosov Moscow State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 3-20, January, 1984. Original article submitted November 9, 1982.

0009-3122/84/2001-0001$08.50

sation. The intermediate ambident anion A arising can add to the double bond with the formation of adducts – 2-pyridone (or 2-thiopyridone) derivatives (II) or 2-hydroxy- or 2-mercaptopyridine derivatives (II):

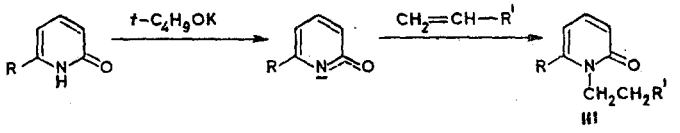


X=O, S; Y and Z=H or electron-accepting groups

The direction of the attack is determined, as in the alkylation of other ambident anions, by the ratio of the nucleophilicities and electronegativities of the N and X atoms in accordance with Kornblum's rule [31] and also steric factors.

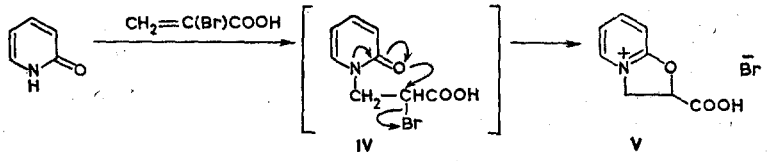
For the 2-pyridones, these reactions frequently take place at the nitrogen atom with retention of the pyridone structure (X = O) [6, 7], while for the thio derivatives they take place at the sulfur atom with the formation of 2-mercaptopyridine derivative (II) (X = S).

Catalysts are necessary for the performance of the reactions of unsaturated compounds with a C=C activated by one functional group. Thus, with 2-pyridones acrylonitrile and methyl acrylate form products of addition at the nitrogen atom (II) in the presence of bases [7, 32] of which the best results are given by potassium tert-butanolate

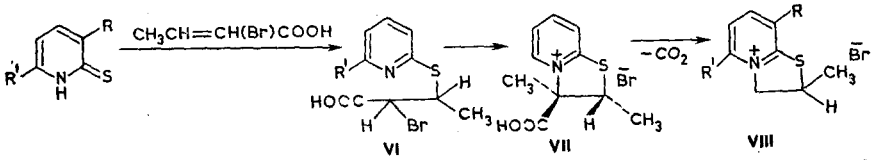


R=H, CH_3, C_6H_5; R¹=CN, $COOCH_3$

The reaction of 2-pyridones with 2-bromoacrylic acid [7, 33] likewise takes place in the manner of a Michael condensation with the formation of 2-bromo-3-[2-oxopyridin-1-yl]propionic acid (IV), which immediately cyclizes to the oxazolinium salt (V).



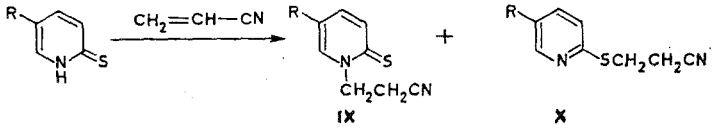
In contrast to the oxygen analogs, 2-thiopyridones interact with derivatives of α-bromo-α, β-unsaturated acids at the sulfur atom. The products of substitutive addition (VI) formed initially were readily converted into trans-dihydrothiazolo[3,2-a]pyridinium derivatives (VII) which were then decarboxylated [34-36].



R=R¹=H; R=H, R¹=CH_3; R=OH, R¹=H; R=OH, R¹=CH_3; R=OC_2H_5, R¹=CH_3

The rates of these reactions increase with a rise in the nucleophilicity of the sulfur atom, which depends on the nature and position of substituents in the thiopyridone ring, and also on the substituents in the β position of the α-bromoacrylic acid [34, 35]. The reactions of 2-thiopyridones with unsaturated compounds having activated multiple bonds may serve as a general method for the synthesis of dihydrothiazolo[3,2-a]pyridinium salts.

In contrast to the investigations described above, where, as a result of the reactions of 2-thiopyridones unsubstituted at the nitrogen atom with unsaturated compounds, only products of interaction at the sulfur atom were obtained, the cyanoethylation of 2-thiopyridones took place with the formation of both possible compounds. Thus, the action of acrylonitrile on 2-thiopyridone and its nitro derivative gave mixtures of the isomeric compounds (IX) and (X), the ratio of which depended on the nature of the substituent R [37, 38].



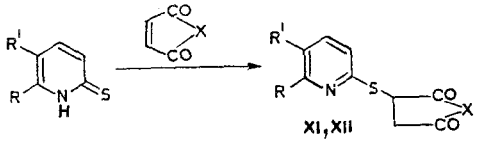
IX X

R=H, NO_2

The reaction of 2-thiopyridones with acrylonitrile is therefore the only known example of a dual reactivity of 2-thiopyridones unsubstituted at the nitrogen atom in reactions with unsaturated compounds.

The addition of NH-pyridones to a double bond activated by two acceptor groups has been studied for the cases of maleimide and N-phenylmaleimide. In these cases the main products were 1,4-cycloadducts (see below), with small amounts of the products of substitutive addition (3-4%) [23, 24].

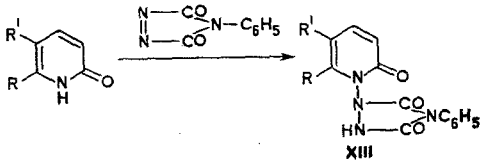
At the same time, 2-thiopyridones unsubstituted at the nitrogen atom reacted with maleic acid derivatives at the sulfur atom, forming at room temperature the N-phenyl(pyridin-2-ylthio)-succinimides (XI) and the anhydrides (XII) with quantitative yields [27, 39, 40].



XI,XII

XI X=NC_6H_5, XII X=O; R=H, CH_3; R′=H, CH_3; C_3H_7; R—R′=$(—CH_2—)_4$

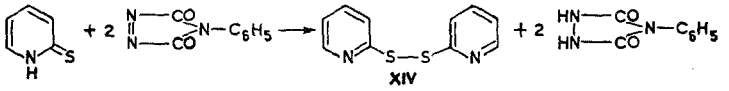
The interaction of the NH pyridones with the strongest azadienophile — 4-phenyl-1,2,4-triazoline-3,5-dione [41] — took place only by a Michael mechanism with the formation of the products of substitutive addition at the nitrogen atom of the pyridone ring ((XIII); yield 46-78%).



XIII

R=R¹=H; R—R¹=$(—CH_2—)_4$; R=R¹=CH_3; R=C_6H_5, R¹=H

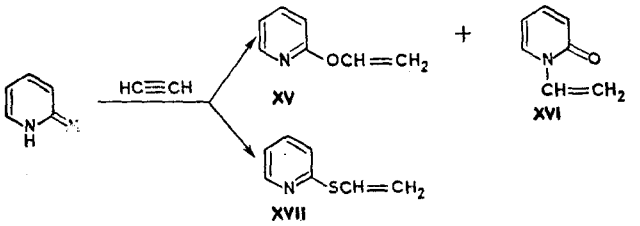
The 2-thiopyridones do not give addition products but are oxidized under the action of the phenyltriazolinedione to the corresponding disulfides (XIV) [39, 42].



XIV

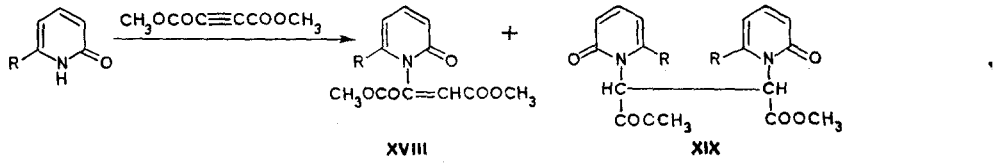
The reactions of pyridones with compounds containing a triple C—C bond have been studied most widely. In order to find methods for the synthesis of new vinyl monomers and to study their properties, the reactions of 2-pyridones and their thioanalogs with acetylene, phenylacetylene, and diacetylene have been studied [43-45].

Thus, acetylene reacts with 2-pyridone under pressure in the presence of heavy-metal chlorides and acetates. The ratio of the products of O- and N-vinylation (XV, XVI) depends on the nature of the catalyst. At the same time, 2-thiopyridone gives only 2-vinylthiopyridine (XVII), regardless of the catalysts used [45].



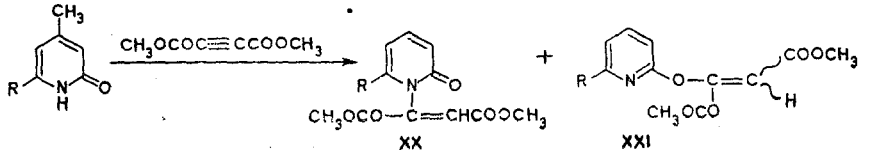
X=O, S

The reaction of 2-pyridones with acetylenedicarboxylic ester led to the formation of products of substitutive addition [11, 14, 46]. The rate of the reaction depended substantially on the structure of the initial pyridones. Thus, unsubstituted 2-pyridone reacted with acetylenedicarboxylic ester under severe conditions (with heating in a sealed tube to 190°C for 17 hours) with the formation of the mono- and bisadducts (XVIII) and (XIX) in a ratio of 26:1 [14]:



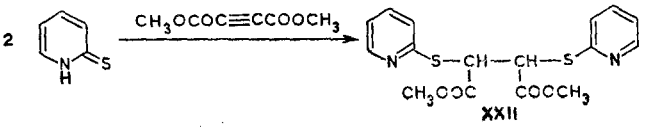
R=H, CH_3

Alkylpyridones reacted with this ester under considerably milder conditions [14, 46]. The nature of the substituent in position 6 of the pyridone ring has a strong influence on the rate and direction of the addition, which is apparently due to the steric hindrance arising in the approach of the unsaturated addend. Thus, the adduct with acetylenedicarboxylic ester from 6-phenyl-2-pyridone can be obtained only with the use of potassium tert-butanolate as catalyst [32]. In the reaction of 4,6-dialkyl-2-pyridones with acetylenedicarboxylic ester, depending on the volume of the substituent in position 6, the products of addition at the nitrogen atom (XX) or at the oxygen atom (XXI) are formed [47]. In the case where R = i-C_3H_7, the O-esters (XXI) are produced (in the form of a mixture of cis and trans isomers in a ratio of 2:3), while when R = CH_3, only the N-substituted enamido ester (XX) is formed:

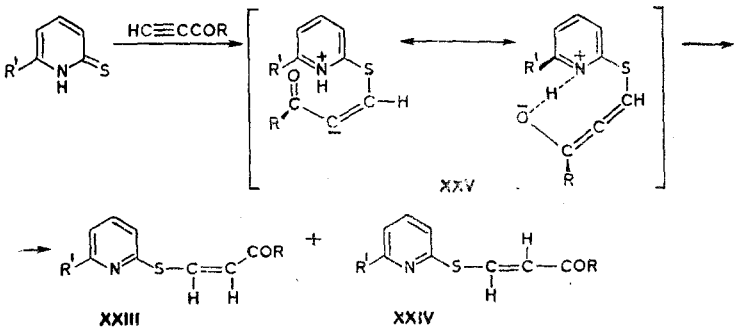


R=CH_3, $CH(CH_3)_2$

2-Thiopyridines react with acetylenedicarboxylic ester considerably more readily and only at the sulfur atom, which is explained by the greater nucleophilicity of the sulfur atom than of the nitrogen atom. Thus, the product of the addition of two molecules of thiopyridone to acetylenedicarboxylic ester (XX) is formed even at room temperature [39].

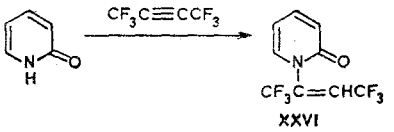


The amides and esters of acetylenecarboxylic acid and methyl ethynyl ketone also react with 2-thiopyridones to form solely derivatives of 2-mercaptopyridine (XXIII) and (XXIV). The stereochemistry of the reactions depends on the natures of the acetylenic compound and of the substituent in position 6. Thus, amides give mainly the cis isomers (III) and ketones the trans isomers (XXIV); the reactions with esters take place nonstereoselectively, leading to mixtures of isomers with a predominance of the cis forms [48]. The rate of the reaction is affected by the presence of stabilizing nonvalent interactions of the zwitterions (XXV) arising as intermediates [48].

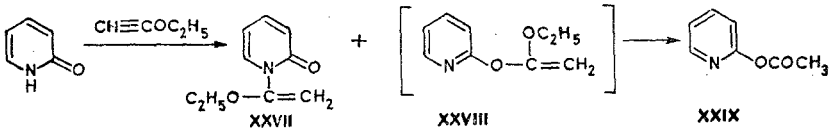


R=N(Alk)$_2$, Alk, OC$_2$H$_5$; R^1=CH$_3$, C$_3$H$_7$

A strong dienophile — hexafluorobutyne — also reacts with 2-pyridone only by the substitutive addition mechanism with the formation of the adduct (XXVI) [6].



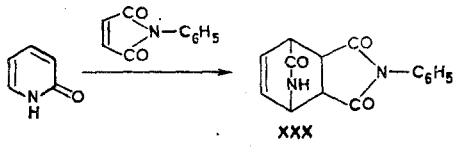
The reaction of 2-pyridone with ethoxyacetylene gave mainly the product of addition at the oxygen atom — 2-acetoxypyridine ((XXIX); 67%), arising by the hydrolysis of compound (XXVIII) — together with 1-(1-ethoxyvinyl)-2-pyridone ((XXVII); 33%) [5].



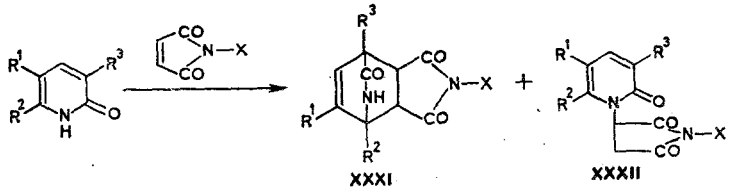
The triple bond in ethoxyacetylene is less capable of nucleophilic addition than those in the addends described above, and therefore the reaction is performed for a very long time (27 days), during which the isomer (XXVIII) undergoes conversion into the thermodynamically more stable adduct. Since the reaction is not kinetically controlled, it is impossible from this example to draw a conclusion from the factors usually determining O- and N-addition [49, 50].

2. Diels-Alder 1,4-Cycloaddition

As already mentioned, the initial attempts to perform the diene synthesis between NH-pyridones and the strongest of the known dienophiles (phenyltriazolinedione [41], hexafluorobutyne [6]) led to the formation of products of substitutive addition. All the more unexpected proved to be the result of the reaction of 2-pyridone with N-phenylmaleimide [4, 17]. In this case, the product of substitutive addition was not formed at all, and the 1,4-cycloadduct (XXX) in the form of a mixture of the endo and exo isomers was isolated in preparative yield (~50%).



It was then shown that mono- and dialkylpyridones also form with this dienophile the cycloadducts (XXI) as the main products and only traces (1-3%) of the products of substitutive addition (XXXII) [23, 24, 30].

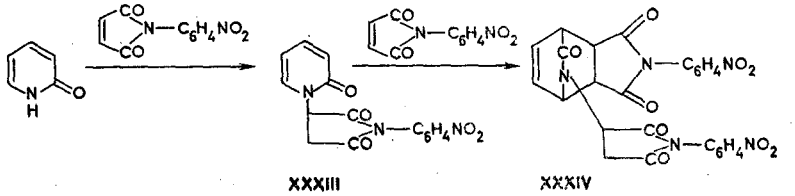


X=H, C$_6$H$_5$, C$_6$H$_4$Br-*p*; R^1=H, CH$_3$, C$_3$H$_7$; R^2=H, CH$_3$; R^1—R^2=(—CH$_2$—)$_4$; R^3=H, CH$_3$

The general nature of the diene synthesis of NH-pyridones was demonstrated by the use of, in addition to N-phenylmaleimide, p-bromophenylmaleimide and unsubstituted maleimide [24]. However, the latter polymerizes to a considerable extent under the reaction conditions, which complicates the isolation of the cycloadducts.

Thus, maleimide and its derivatives proved to be dienophiles for which the rate of the diene synthesis considerably exceeded the rate of the competing substitutive addition to N-pyridones, thanks to which it was possible to perform the diene synthesis with these heterocycles.

It has recently been shown that electron-accepting substituents in the aromatic ring of a N-arylmaleimide largely promote the occurrence of the Michael reaction, and not the diene synthesis, with 2-pyridone [51]. Thus, on reacting with N-p-nitrophenylmaleimide, 2-pyridone first gave the oxopyridinylsuccinimide (XXIII), which then reacted in the manner of the diene synthesis with one more molecule of the dienophile to form the 1,4-cycloadduct (XXXIV) [51].

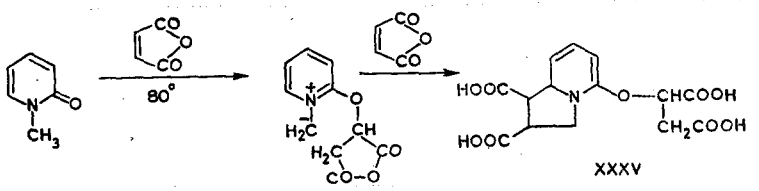


XXXIII XXXIV

II. DIENE SYNTHESIS WITH N-SUBSTITUTED 2-PYRIDONES AND THEIR THIO ANALOGS

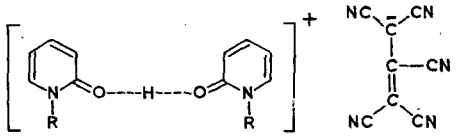
Since in the examples described above the main obstacle to performing the diene synthesis was the occurrence of the nucleophilic addition of the NH group of the pyridone to an activated multiple bond, it might be expected that 2-pyridone substituted at the nitrogen atom should react with dienophiles in the manner of a 1,2-cycloaddition.

However, the first experiments on the reaction of 1-methyl-2-pyridones with various dienophiles did not lead to the formation of cycloadducts [3, 4, 8]. On the reaction of 1-methyl-2-pyridones with a classical dienophile — maleic anhydride — at 80°C, a tetracarboxylic acid was obtained which was formed as the result of the addition of two molecules of maleic anhydride [3].



XXXV

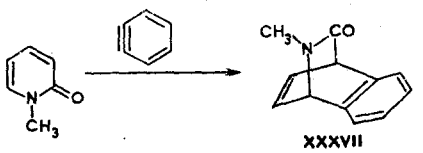
It was impossible to obtain the 1,4-cycloadduct with pentacyanopropene either, because of the formation of the salts (XXXVI) [4].



XXXVI

R=CH_3, C_2H_5, C_3H_7

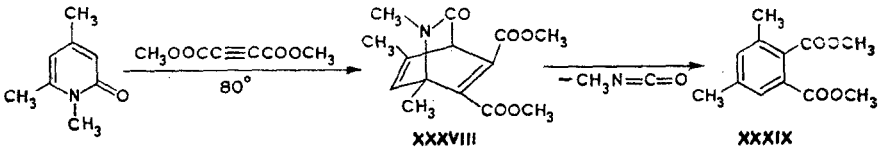
The possibility in principle of the diene synthesis for 1-alkyl-1-2-pyridone was first shown at the end of the 1960's [12, 13] for the case of the reaction of 1-methyl-2-pyridone with dehydrobenzene. However, the bridge adduct (XXXVII) was obtained in low yield (1-10%).



XXXVII

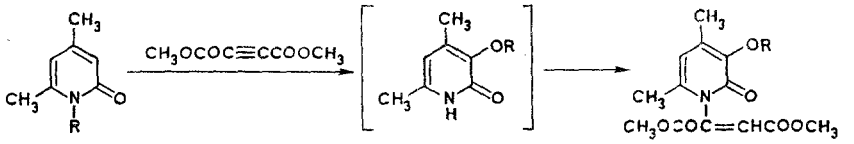
More successful was the use of this dienophile in a reaction with 1-styryl-2-pyridone (the yield of cycloadduct amounted to 40%) [25].

The possibility of using acetylenedicarboxylic ester as dienophile is determined by the structure of the initial pyridones. Thus, 1-methyl-2-pyridone did not react with this dienophile [14], while even at 80°C, 1,4,6-trimethyl-2-pyridone gave the diene synthesis adduct (XXXVIII) with preparative yield; this adduct, on heating, readily split out an alkyl isocyanate, being converted into an ester of dimethylphthalic acid (XXXIX) [47]. A similar lability of an azocarbonyl bridge has also been observed for adducts of other pyridones with acetylenedicarboxylic ester [19, 52].



XXXVIII XXXIX

It was then shown that the yields of cycloadducts depends greatly on the nature and position of the substituents in the pyridone ring [19, 47, 52]. In order to establish the reason for the influence of the substituents (mainly methyl and methoxy groups) on the rate of the reactions with acetylenedicarboxylic ester, 2-pyridones of various structures were studied [19, 52]. It was found that methyl groups in positions 4, 5, and 6 (particularly when they are present simultaneously in two of these positions) favor the occurrence of the reactions, while the same substituent in position 3 gave a negative result. It was assumed that in the latter case a "reverse" diene synthesis took place [2]. However, calculations by the MO method have shown that the dominant orbital interaction takes place between the HOMO of the 2-pyridone and the LUMO of the acetylene dicarboxylic ester, i.e., there is the classical type of cycloaddition [19] in which, in all cases, electron-donating methyl groups must promote the occurrence of the diene synthesis. It was therefore concluded that the observed change in yields is due to steric, and not electronic, factors. The steric effect that determines the high rate of the reaction for 1,5,6-trimethyl-2-pyridone consists in the removal, in the diene synthesis of the strain in the ring created by the departure of the 6-CH_3 group from the plane of the ring because of the closeness of the methyl groups in positions 1 and 5 [19, 52].

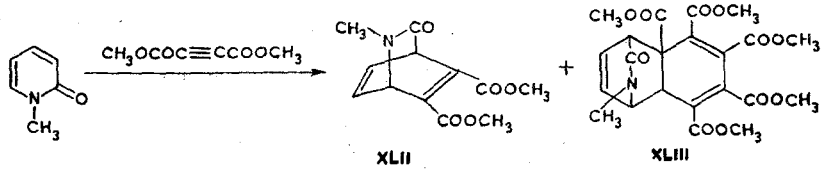


XL XLI

R= 2,4-dinitrophenyl

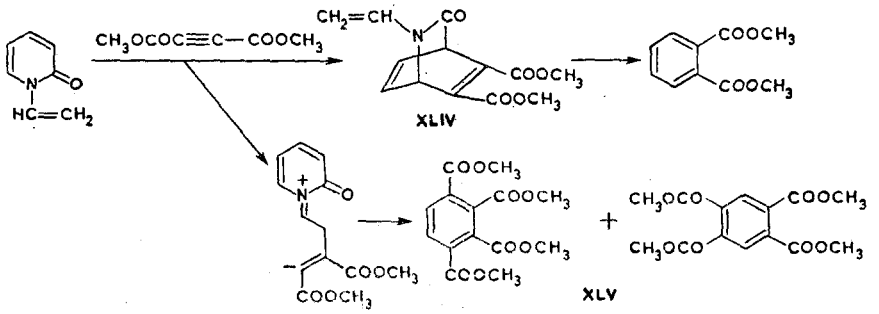
When a voluminous radical is present at the nitrogen atom in the initial pyridone, its interaction with acetylenedicarboxylic ester does not take place by the cycloaddition mechanism at all. After the migration of the substituent from the nitrogen atom into position 3, the corresponding NH pyridone (XL) is formed which interacts with the acetylenedicarboxylic ester to give the products of substitutive addition (XLI) [47].

Raising the pressure favors the occurrence of the diene synthesis reaction of acetylenedicarboxylic ester with the pyridones [53], as is also the case with other Diels–Alder reactions. Under these conditions it is possible to obtain the adduct (XLII) (yield 16%) from 1-methyl-2-pyridone (having no substituents on the carbon atoms of the ring); in addition to the diene synthesis, the self-condensation of the acetylenedicarboxylic ester to form hexamethyl benzenehexacarboxylate takes place and also the addition of another two molecules of the dienophile to the cycloadduct (XLII) to form the ester (XLIII).



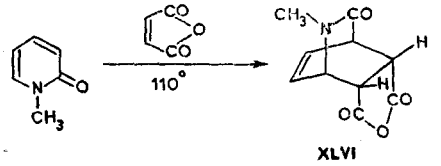
XLII XLIII

Using as examples the reactions of 1-vinyl- and 1-styryl-2-pyridones with acetylenedicarboxylic ester, it was also found that the formation of isomeric esters of benzenetetracarboxylic acids (XLV), taking place as side reactions, lowers the yield of cycloadducts (XLIV) [25].



XLIV XLV

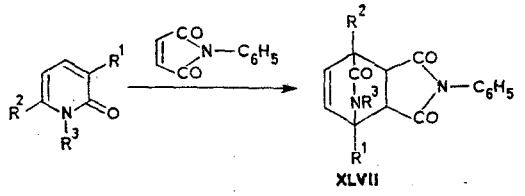
In 1969, the 1,4-cycloadduct of 1-methyl-2-pyridone with maleic anhydride (XLVI) was obtained for the first time in preparative yield (42%) by boiling a toluene solution of the reactants for 72 h [15, 16]:



XLVI

However, it has been impossible to extend this reaction to other 1-alkyl-2-pyridones because of the pronounced resinification of the mixtures, apparently as the result of the polymerization of the maleic anhydride [11]. At the same time, with this dienophile 1-vinyl- and 1-styryl-2-pyridones form cycloadducts with yields of 90-92% [25].

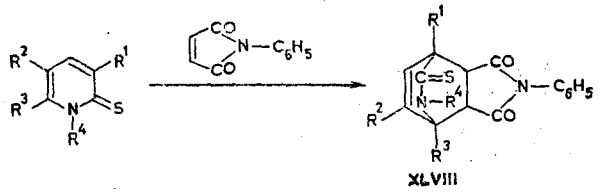
The general nature of the diene synthesis for 1-alkyl-2-pyridones has been shown by the use of N-phenylmaleimide as dienophile. Depending on the structures of the initial pyridones, either endo- or exo-1,4-cycloadducts (XLVII) were obtained with yields of 40-80% [11, 29, 39, 54, 55] (for more details on the stereospecificity of this reaction, see below).



XLVII

R^1, R^2=H, CH_3; R^3=CH_3, C_2H_5, C_3H_7, C_4H_9, $CH{=}CHC_6H_5$

By using N-phenylmaleimide as dienophile it was possible for the first time to effect a diene synthesis with 1-alkyl-2-thiopyridones having no substituents on the carbon atoms of the rings, and also with those containing methyl groups at the ends of the conjugated system of multiple bonds of the heterocycle, and to elucidate the influence of the positions of the alkyl groups on the stereochemistry of the reaction [26, 27, 30]. The previously unknown bicyclic adduct with an azothione bridge (XLVIII) was obtained with yields of 20-70%.



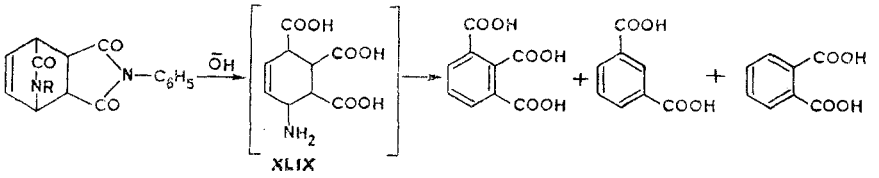
XLVIII

R^1, R^3=H, CH_3; R^2=H, CH_3, C_3H_7; R^4=CH_3, C_2H_5, C_3H_7

In these reactions of 2-pyridones and their thioanalogs with phenylmaleimide [27, 29, 39], as also in those with acetylenedicarboxylic ester described above, the yields of cycloadducts fell sharply when methyl groups were present in positions 3 and 6 of the initial heterocycle.

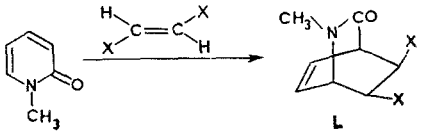
This phenomenon, which has not been observed previously for other cyclic dienes, is observable in these examples because of the comparatively low dienic activity of the pyridones, which raises their sensitivity to any type of deactivating influences. A methyl group at the head of the bridge of an adduct apparently leads to a greater rate of retrodiene decomposition (thanks to the stabilization of the biradical, arising as an intermediate; see below on endo, exo isomerization), and it also creates steric hindrance in the orientation of the components, which interferes with the occurrence of the diene synthesis.

The production of 1,4-cycloadducts of 1-methyl-2-pyridone with maleimide and its N-carbamoyl, N-(p-nitrophenyl), and N-(p-methoxyphenyl) derivatives has been described [49, 55], these adducts hydrolyzing in the cold with the formation of bicyclo[2.2.2]octane derivatives [29, 49]. In contrast to the adducts with acetylenedicarboxylic ester, the adducts with maleic acid derivatives did not split out the azocarbonyl bridge even on heating to the boiling point [49, 54, 55]. At the same time, under the action of an aqueous solution of alkali they opened the lactam bridge and the imide ring with subsequent aromatization of the intermediate amino acid (XLIX) formed [56, 57]:



XLIX

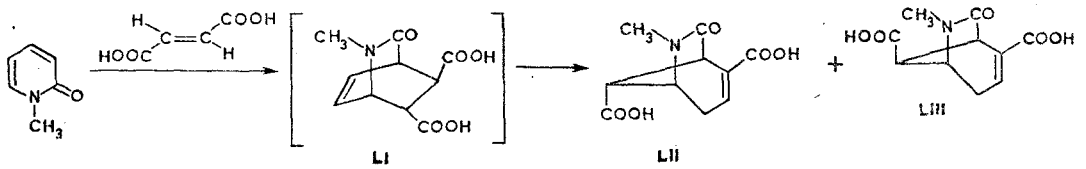
In 1978-1979, a series of papers by Japanese chemists appeared which was devoted to the use in the diene synthesis with 1-methyl-2-pyridone of fumaric acid and its derivatives, these taking part in the reaction only on very prolonged contact. Thus, the dinitrile and the dimethyl ester of fumaric acid react with 1-methyl-2-pyridone according to the normal scheme of diene synthesis regioselectively, forming the cycloadducts (L) in extremely low yields (3-4%) when the reaction mixtures are heated for 7 days [58, 60]:



L

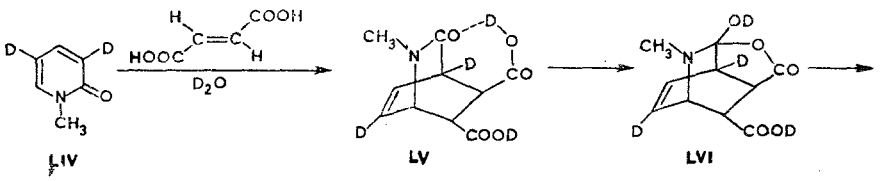
X=CN, $COOCH_3$

The prolonged boiling of 1-methyl-2-pyridine with fumaric acid itself in aqueous solution led to bicyclo[3.2.1]octene derivatives (yield 20%) in the form of a mixture of the stereoisomers (LII) and (LIII), which are produced as the result of a rearrangement of the initial cycloadduct (LI) under the reaction conditions [61-65].

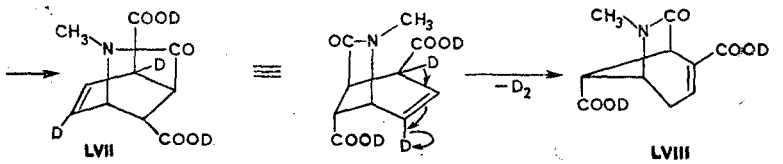


LI LII LIII

From 3,5-dideutero-1-methyl-2-pyridone (LIV) was obtained the deuterated analog of compound (LII), and a mechanism of its formation was suggested [60-62]:



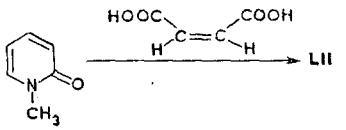
LIV LV LVI



LVII LVIII

In the opinion of the authors concerned, the isomerization of the cycloadduct (LV) into the bicyclo[3.2.1]octene derivative (LVIII) takes place as the result of the interaction of the lactam carbonyl group with the exo-carboxyl of the cycloadducts (LV) and the subsequent rearrangement of compound (LVI) [62], which, in the final account, amounts to an intramolecular transacylation of the nitrogen atom.

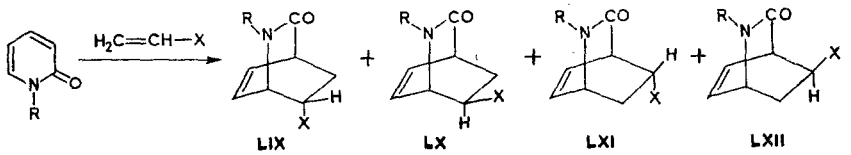
The formation of an adduct of the bicyclo[3.2.1]octene series also takes place when maleic acid is used as the dienophile [64].



LII

Thus, the study of the reactions of 1-methyl-2-pyridone with fumaric acid and its derivatives permitted the detection of the previously unknown thermal isomerization of compounds of the azabicyclo[2.2.2]octene series.

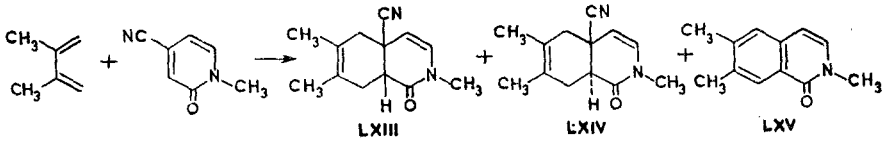
The interaction of 2-pyridines with unsymmetrical dienophiles takes place under severe conditions to form both possible regio- and stereoisomers [25, 66]. Thus, with methyl acrylate and with acrylonitrile, in each case, 1-methyl-2-pyridone forms a mixture of three isomeric adducts, and with methyl vinyl ketone 1-styryl-2-pyridone gives four compounds (LIX-LXII) with a total yield of 20-42%.



LIX LX LXI LXII

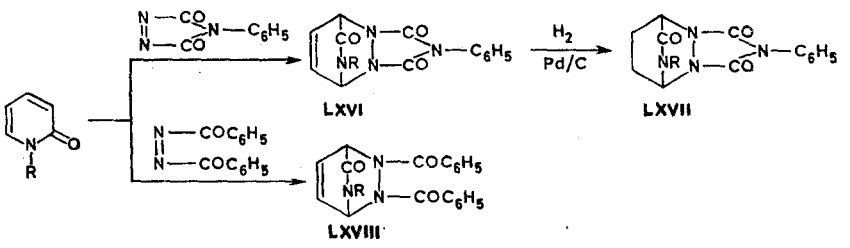
X=$COOCH_3$, CN, $COOH_3$; R=Alk, $CH{=}CHC_6H_5$

4-Cyano-1-methyl-2-pyridone has been used as dienophile in a reaction with 2,3-dimethylbuta-1,3-diene [67, 68]. This reaction enables tetrahydroisoquinoline to be obtained in preparative yield. The stereochemistry of the reaction depends on the temperature: at 170°C, only the cis isomer (LXIII) was formed (72%), and at 190°C a mixture of the cis and trans isomers (LXIII) and (LXIV) and of the product of their aromatization (LXV).



LXIII LXIV LXV

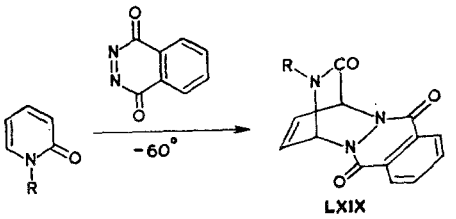
The use of azodienophiles in reactions with 1-alkyl-2-pyridones has been described. Thus, at room temperature 4-phenyl-1,2,4-triazoline-3,5-dione formed cycloadducts consisting of tetrahydropyridazine derivatives (70-80%), which were readily hydrolyzed with the formation of compound (LXVII) [20-22], while azobenzoyl reacted on prolonged heating.



LXVI LXVII LXVIII

R=CH_3, C_2H_5, C_3H_7

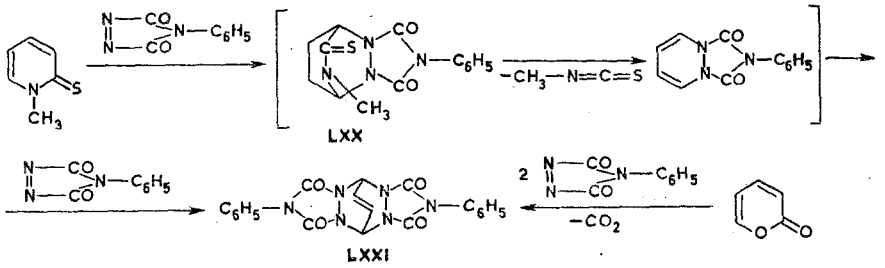
Phthalazinedione reacted with the pyridones at temperatures below 0°C [22].



LXIX

R=$CH_3C_6H_5$, CH_2, $C_6H_5CH_2CH_2$

At the same time, with phenyltriazolinedione (in the presence of an antioxidant*) 1-methyl-2-thiopyridone gave the unstable cycloadduct (LXX), which, splitting out the azothione bridge and adding one more molecule of the dienophile, was converted into the bisamide (LXXI) [39], identical with that obtained previously from 2-pyrone [20].



LXX

LXXI

III. STEREOCHEMISTRY OF THE DIENE SYNTHESIS WITH 2-PYRIDONES AND THEIR 2-THIO ANALOGS

For 2-pyridones, as for other cyclic dienes, two methods of orientation of the components in Diels–Alder reactions are possible, corresponding to the formation of stereoisomeric adducts with the endo and exo configurations. At the present time, the study of the laws of endo,exo-selectivity is being carried on widely and is enabling information to be obtained on the structure of the transition states and the mechanism of the diene synthesis [2]. Since a one-stage mechanism, in favor of which there are many pieces of evidence, cannot explain many experimental facts, other variants of 1,4-cycloaddition continue to be discussed [69, 70].

The stereochemistry is affected by the reaction conditions (temperature, solvent) and by the structure of the initial reactants, the characteristics of the reaction of which are being studied at the present time.

As a result of kinetic investigations, it has been shown that for unsubstituted dienes and dienophiles the formation of the endo isomers takes place at a considerably greater rate than of the exo adducts [69, 71]. This is explained by the overlapping of the π-orbitals of the multiple bonds of the diene and of the dienophile, which is possible only with the endo orientation of the components (Alder's "endo" rule [72]). However, the exo isomers are more stable thermodynamically, and, therefore, under severe temperature conditions adducts with the exo configuration are frequently obtained as a consequence of the retrodiene decomposition of endo isomers initially formed. This type of isomerization can also take place under mild temperature conditions if there is little difference in the activation energies of the two stereoisomers [71]. For example, the endo adduct of furan with maleic anhydride isomerizes even at 20°C, which has led to errors in the determination of configurations.

An investigation of the structure of the components with respect to stereochemistry can be carried out only in those cases where endo,exo-isomerization is excluded under the conditions of synthesis, i.e., when the reaction is kinetically controlled.

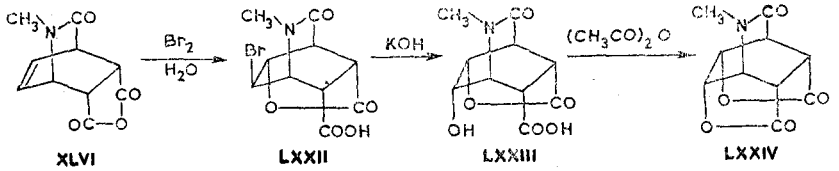
Together with the π-orbital interactions described above, the orientation of substituted dienes and dienophiles may be determined by the electrostatic forces of attraction and repulsion of the substituents with one another and with the sp^2-carbon atoms of the diene [2, 73-

*Without an antioxidant, the thiopyridone catalyzed the quantitative conversion of phenyltriazolinedione into the bisimide 3,7-diphenyl-1,3,5,7-tetraazabicyclo[3.3.0]octa-2,4,6,8-tetraone [39].

77], by steric factors [78, 79], and also by secondary π-orbital interactions between the unsaturated groupings of the diene and the p-electrons of the azadienophile [80]. Furthermore, isolated examples have been described of the influence of solvents on the endo,exo-stereoselectivity of the diene synthesis [56, 81, 82]. The investigation of the control of the factors described above on the stereochemistry of cycloaddition reactions is made difficult by the fact that it is not always possible to detect one or another type of interaction separately.

Diene synthesis reactions with 6-membered heterocyclic dienes — 2-pyridones — have proved to be extremely convenient for the study of the relationships between the structures of the components and the stereochemistry of the diene synthesis, since these reactions are, as a rule, kinetically controlled.

The assignment of the configurations of the adducts to the endo or the exo series has been performed chemically and spectrally. Thus, to establish the configuration of the anhydride (XLVI), the classical method of bromolactonization was used. Conversion of the cycloadduct into the bromolactone (LXXII) and then into the bislactone (LXXIV) showed its endo configuration [15, 16].

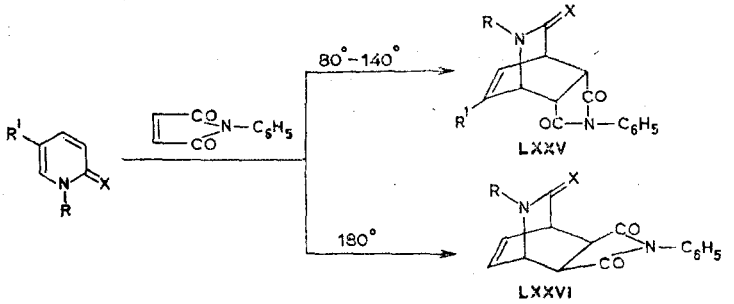


XLVI LXXII LXXIII LXXIV

For amide adducts, the bromolactonation method does not give unambiguous results [83], and therefore to establish their configurations use is made of characteristics of their PMR spectra, in which regular changes have been observed in the values of the spin–spin coupling constants for the protons at a bridgehead with the neighboring protons on passing from the endo to the exo adducts* [27, 54].

An investigation of the configurations of the adducts of 1-alkyl-2-pyridones and their thio analogs without substituents at the ends of the conjugated system with maleic anhydride [15, 16] and phenylmaleimide [26, 27, 53, 54] showed that the reactions take place endo-stereoselectively with the formation of the adducts (LXXV), in spite of the comparatively severe conditions (80-140°C, time up to 72 h).

With a rise in the temperature to 180°C in the case of the reaction of 1-methyl-2-pyridone with phenylmaleimide, the exo adduct (LXXVI) was obtained [39].



LXXV

LXXVI

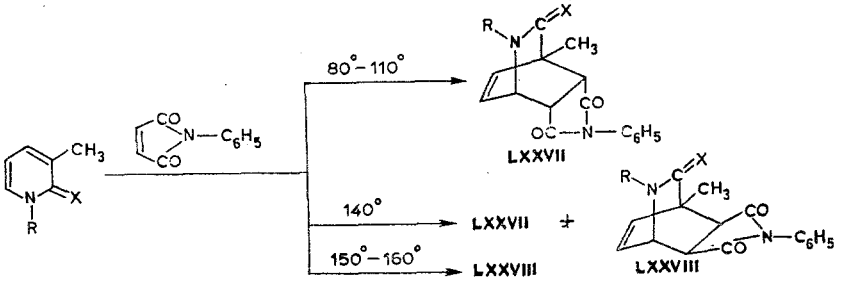
R=CH3, C2H5, C3H7; R1=H, CH3; X=O, S

These results indicate, in contrast to known examples of the isomerization of endo adducts of furans, cyclopentadienes, and fulvenes [82], that the transition of the endo isomers of the 2-pyridones and thiopyridones into the exo adducts requires a far higher activation energy, and therefore stereoselectivity of the reactions is observed at the given temperatures.

Thus, the stereochemistry of the diene synthesis of 1-alkylpyridones and their thio analogs without substituents at the ends of the conjugated system of multiple bonds under conditions of kinetic control followed Alder's "endo" rule and is consequently determined by the secondary π-orbital interaction.

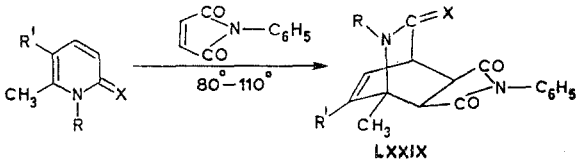
*A change in the values of the spin–spin coupling constants for bridge protons and neighboring protons was found previously for adducts of 2-pyrones with maleic anhydride and with N-phenylmaleimide [84].

It was then established that the stereochemical result depends on the presence of methyl groups at the ends of the conjugated system of the initial heterocycle, which favor the formation of the exo isomers. The presence of a methyl group in position 3 of the N-alkylpyridones and their thio analogs lowers the temperature of formation of the exo isomers as compared with unsubstituted 1-alkylpyridones (see above), which leads to a nonstereoselective course of the reaction even at 140°C. Thus, the 1-alkyl-3-methyl-2-pyridones and their sulfur analogs form the endo isomers at 80-100°C while when the temperature is raised by 30-40°C (to 110-140°C), mixtures of endo and exo isomers are obtained. At a higher temperature (160°C), only the exo adducts (LXXVIII) (for the oxygen analogs) are obtained [29, 39].



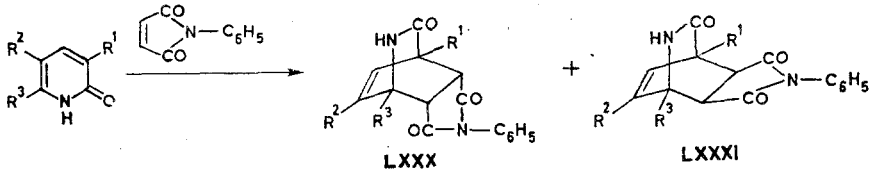
$R=CH_3, C_2H_5, C_3H_7$; X=O, S

A methyl group at the other end of the conjugated system of multiple bonds — in position 6 — shows an unambiguous exo-orienting action. Thus, with phenylmaleimide the 6-methyl-2-pyridones and their thio derivatives gave only the exo isomers (LXXIX) at considerably lower temperatures than for the 6-unsubstituted pyridones [11, 29, 30].



$R=CH_3, C_2H_5$; R^1=H, CH_3, C_3H_7; X=O, S

The predominant (or exclusive) formation of the exo isomers also takes place for 2-pyridones unsubstituted at the nitrogen atom but with methyl groups in position 3 or 6. While the simplest pyridone reacts with phenylmaleimide nonstereospecifically with the formation of both possible isomers in a ratio of 3:2* [17], 3-methyl- and 6-methyl-2-pyridones form mainly as the exo isomers (LXXXI) [23, 24, 30] (see Table 1).



R^1, R^3=H, CH_3; R^2=H, CH_3, C_3H_7; R^2—R^3=—$(CH_2)_4$—

As can be seen from Table 1, the use of p-bromophenylmaleimide in place of phenylmaleimide does not change the ratio of the isomers. At the same time, there is information on an increase in the proportion of exo isomers when electron-accepting groups are present in the phenyl ring of this dienophile [56].

The influence of methyl groups in position 3 and 6 on the stereochemistry may be due to a lowering of the energy barrier of endo,exo-isomerization through a facilitation of the retrodiene breakdown of the endo isomers (see p. 10) (isolation of both isomers for 1-alkyl-3-

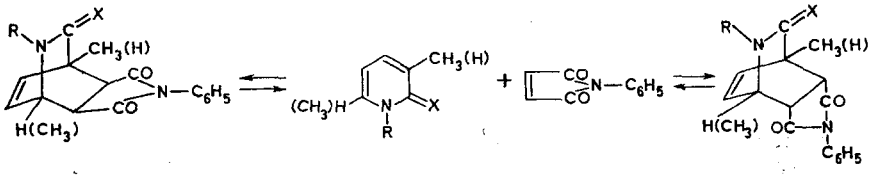
*The nonstereospecific occurrence of the diene synthesis for 2-pyridone with phenylmaleimide may be determined by the presence in this diene of a second center of unsaturation (the unshared pair of electrons of the nitrogen atom), which in the substituted pyridones is blocked by the alkyl group, which leads to the endo-stereoselective occurrence of the reactions.

TABLE 1. Ratio of the Stereoisomers in the Adducts of 2-Pyridones with N-Arylmaleimides

Initial pyridone	Aryl	Cycloadduct		endo/exo ratio	Literature
		configuration	yield, %		
2-Pyridone	Phenyl	endo	30,0	1,5	[17]
		exo	20,0		
	p-Bromophenyl	endo	35,0	1,59	[24]
		exo	22,0		
3-Methyl-2-pyridone*	Phenyl	endo	7,0	0,17	[23]
		exo	40,0		
6-Methyl-2-pyridone*	Phenyl	endo	4,9	0,12	[23]
		exo	40,6		
5,6-Dimethyl-2-pyridone	Phenyl	endo	0	0	[30]
		exo	30,0		
6-Methyl-5-propyl-2-pyridone	Phenyl	endo	0,7	0,03	[30]
		exo	20,0		

*Together with the cycloadducts, the products of substitutive addition are obtained in small yield (see p. 9).

methyl-2-pyridones) or to an increase in the rate of formation of the exo isomers directly from the pyridones because of the stabilization of the transition states as a consequence of nonvalent interactions between the methyl groups of the diene and the carbonyl groups of the dienophile [73, 74].



X=O, S; R=CH_3, C_2H_5, C_3H_7

Apparently, both these factors determine the observed stereochemical result. Thus, an investigation of the configuration of the diene-synthesis adducts of 2-pyridones and 1-alkyl-2-pyridones and their thio analogs with phenylmaleimide has revealed a general phenomenon — the influence of methyl groups at the ends of a conjugated system of multiple bonds of a heterocyclic diene on the stereochemistry of the reaction.

A similar exo-orienting action of methyl groups has been observed for 2-pyridones with a methyl group in position 6 [2, 84].

The material on the Diels—Alder reaction with 2-pyridones and their thio analogs that has been discussed shows that the main advances in the development of this field of synthesis have been achieved in the last decade. At the present time it is obvious that in spite of a number of peculiar features, these heterocycles are typical dienes that can react with various dienophiles.

Together with extremely important preparatory results (synthesis of bicyclo[2.2.2]octene derivatives with azocarbonyl and azothione bridges), great interest is presented by the stereochemical laws of the diene synthesis that have been found and also by the skeletal rearrangements of the cycloadducts and the formation of new organic sulfur compounds from 2-thiopyridones.

The investigation of the reactions of 2-pyridones and their thio analogs with unsaturated compounds has also enabled new information to be obtained on the dual reactivity of these ambident systems and has also permitted their use for the synthesis of pyridine and of some other heterocyclic compounds.

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