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REACTIONS OF POTENTIALLY TAUTOMERIC METHYL AND METHYLENE DERIVATIVES OF PYRIDINE AND DIAZINES WITH N-ELECTROPHILES (REVIEW)

O. A. Zagulyaeva and I. V. Oleinik

Data on the nitration, nitrosation, azo-coupling, and electrophilic amination of potentially tautomeric methyl and methylene derivatives of a series of pyridines, pyridazines, pyrimidines, and pyrazines in media of varying acidity and basicity are reviewed systematically.

Interest in alkyl and alkylidene derivatives of six-membered nitrogen-containing heterocycles is almost always linked to the possibility of using them as synthons for the preparation of a variety of functionally substituted heterocyclic systems, including condensed heterocycles [1]. The large number of chemical conversions of the potentially tautomeric alkyl- and alkylideneazines opens up the possibility of changing the chemoselectivity of their reactions via the aromatic or more reactive methylene tautomer or by the intermediate generation of mesomeric anions.

In this review we have systematized data on the reactions of potentially tautomeric methyl (A) and methylene (B) derivatives of azines for a series of pyridines (I, II), pyridazines (III, IV), pyrimidines (V-VII), and pyrazines (VIII) with N-electrophiles in various media. Nitration, nitrosation, azo-coupling, and electrophilic amination are examined, leading to products with aromatic or ylidene structures, in which regioselectivity of substitution is determined by the reagents and the nature of the substrate under the reaction conditions.

It was noted earlier [1] that it is characteristic for potentially tautomeric methyl and methylene derivatives of azines that, under conditions of kinetic control, the electrophile attacks the pyridine nitrogen atom in the aromatic tautomer (A) but it attacks the exocyclic α-carbon atom in the ylidene form (B). Further conversions during the course of the reaction can lead to the thermodynamically stable product in which the electrophile is found in an electron deficient position of the heterocycle or is contained in its substituent.

NITRATION OF METHYL- AND METHYLENEAZINES

Nitration of methyl and methylene derivatives of azines has been carried out with a variety of nitrating agents in various media, with the nitro groups inserting only into the heterocycle or only into the side chain. Depending on the acid–base properties of the substrates their interactions with nitrating agents in various media may occur in the form of: a) the free base of either tautomeric form (in neutral or even strongly acidic media with a substrate of low basicity); b) conjugated acids in the aromatic or ylidene form (in acid media although the form of the substrate may change with change in the pH or H_0 of the media); c) an anion generated by bases.

Criteria based on kinetic data for the reaction have been used to identify the nature of the reacting particles of the substrate [2]. For example, when 2,4,6-trimethylpyridine and 1,2,4,6-tetramethylpyridinium cation were nitrated with acid nitrifying mixture (conc. HNO_3 in H_2SO_4) to give the corresponding 5-nitro derivatives of pyridine the same profile of rates was observed, passing through a maximum at 90% H_2SO_4. It was therefore concluded that 2,4,6-trimethylpyridine reacted as the conjugated acid. Calculations of the rate of nitration via the free base showed that it would be about 2 orders greater than observed and that the reaction would occur under much milder conditions [3].

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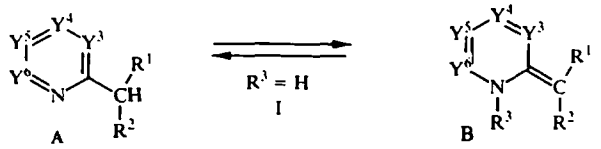
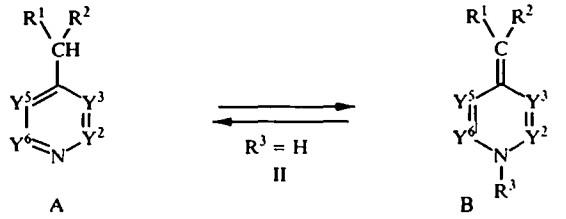
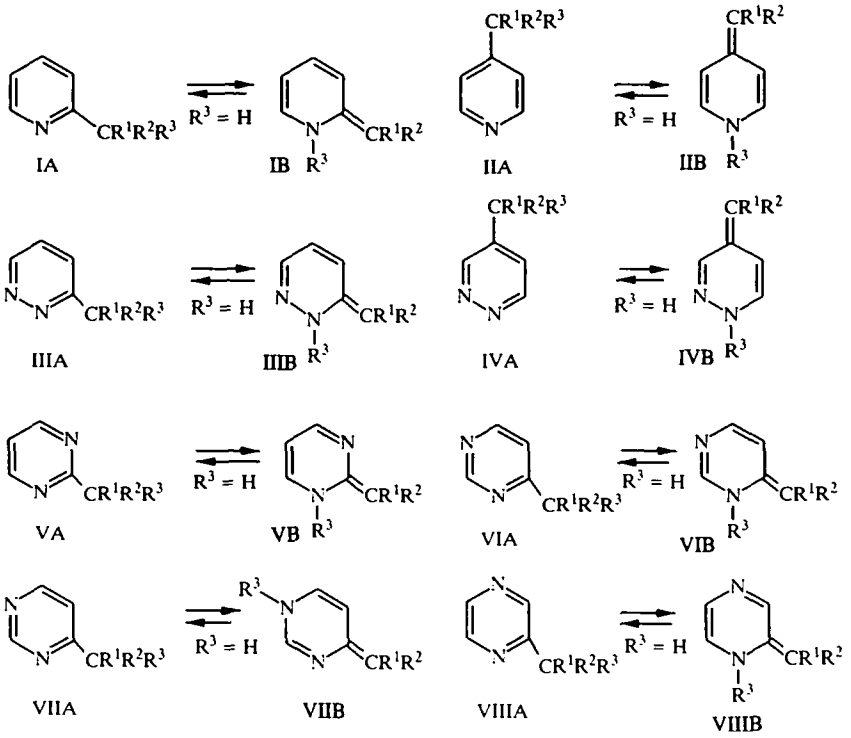


I a $Y^3 = Y^4 = Y^5 = Y^6 = CH$; b $Y^3 = N$, $Y^4 = Y^5 = Y^6 = CH$;
c $Y^3 = Y^5 = Y^6 = CH$, $Y^4 = N$; d $Y^3 = Y^4 = Y^6 = CH$, $Y^5 = N$;
e $Y^3 = Y^4 = Y^5 = CH$, $Y^6 = N$

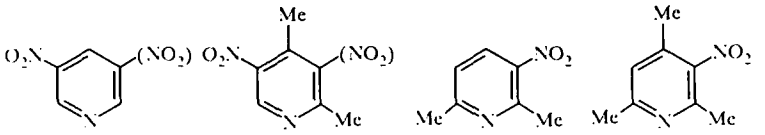


II a $Y^2 = Y^3 = Y^5 = Y^6 = CH$; b $Y^2 = N$, $Y^3 = Y^5 = Y^6 = CH$;
c $Y^2 = Y^5 = Y^6 = CH$, $Y^3 = N$; d $Y^2 = Y^3 = Y^6 = CH$, $Y^5 = N$



R^1, R^2 = H, Alk, Ar, COPh, COOR, SO_2Ph, CN, NO_2, etc.; R^3 = H, Alk, COR, etc.

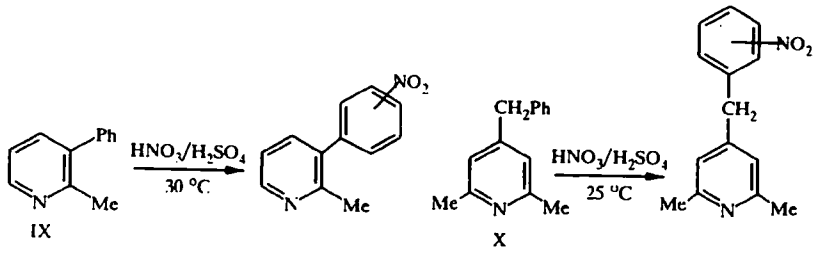
Study of the nitration of methylazines with nitrating mixture showed that introduction of additional methyl groups, or hydroxy and amino groups, increased the yields of nitration products [2]. For example nitration of 2-picoline with KNO_3 and H_2SO_4 at high temperature (160°C) gave a mixture 3- and 5-mononitro derivatives in low yield [4]. Increasing the number of methyl groups in the pyridine molecule sharply increased the yield of mononitro derivatives and the reaction temperature was decreased [4-6].



Overall yield of 3- and 5-isomers (%): 3, 50, 66, 90

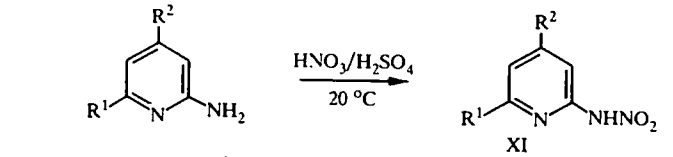
Nitric acid did not give high yields on nitration of picolines [7].

The substituted methylpyridines IX and X, which contain phenyl groups as substituents on the ring or in the side chain, reacted with HNO_3 and H_2SO_4 to give mixtures of *o*-, *m*-, and *p*-nitrophenyl derivatives of the methylpyridines [8-10].

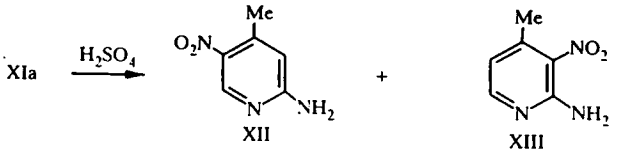


When picolines with amino groups in the ring were treated with the same nitrating mixture under mild conditions (T ≤ 20°C) nitration occurred at the amino group to give the nitraminopicolines XI which gave the corresponding 3- and 5-mononitro derivatives of aminopicolines XII-XV when the reaction mixture was raised to 50°C [11].

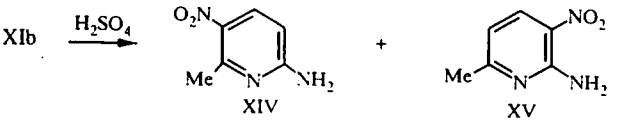
Kinetic data were obtained for the reactions of 4-methyl-2-nitramino- (XIa), 6-methyl-2-nitramino- (XIb) and 2-methyl-4-nitraminopyridine (XVI) in 92% H_2SO_4 to give the isomeric 3- and 5-nitro derivatives of the aminopicolines XI-XV, XVII, XVIII [12-14]. In the view of the authors of these papers, the mechanism for the conversion of the nitramines into products containing nitro groups was quite different from that for the analogous rearrangement in the benzene series. The ratio of the *o*- to *p*-nitroaminopicolines formed (relative to the amino group) is explained [13] by the difference in the electronic stabilization of the intermediates (*σ*-complexes) during the nitration with a presumed S_EAr mechanism. Steric factors are apparently relatively unimportant. Previously the preferential formation of the *p*-nitro product and the small percentage of incorporation of ^{15}N from the reagent into the heterocycle was interpreted as confirming a mixture of inter- and intramolecular rearrangements [15-17].



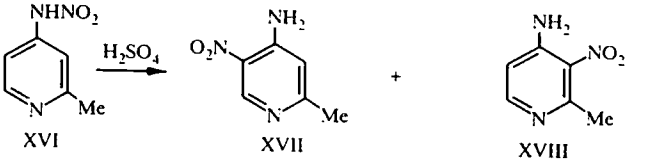
a R^1 = H, R^2 = Me; b R^1 = Me, R^2 = H



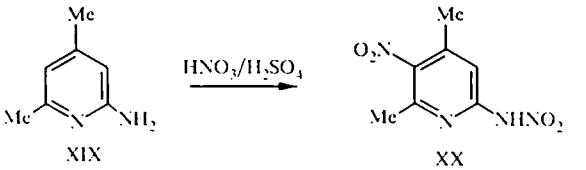
XII : XIII = 60 : 40



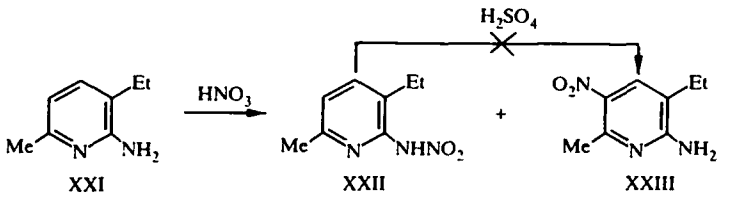
XIV : XV = 74 : 26



All possible mononitro derivatives of the four 2-aminopicolines were obtained in pure form using this reaction [11]. Nitration of 2-amino-4,5-lutidine (XIX) under the same conditions gave 2-nitramino-5-nitro-4,6-lutidine (XX) as the sole product [18].

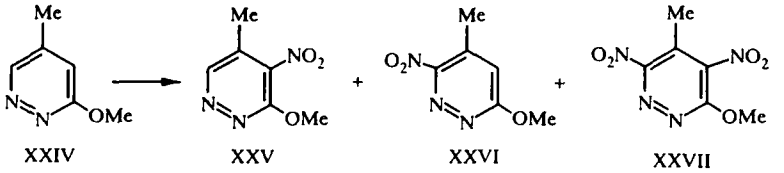


On the other hand a mixture of 2-nitramino-6-methyl-3-ethylpyridine (XXII) and 2-amino-5-nitro-6-methyl-3-ethylpyridine (XXIII) was obtained from 2-amino-6-methyl-3-ethylpyridine (XXI). Migration of the nitro group did not occur when the nitramine XXII was heated in conc. H_2SO_4 [19]. However nitration of aminopicolines is frequently complicated by hydrolysis of the nitramine group to give the corresponding hydroxy derivatives of picolines [20].

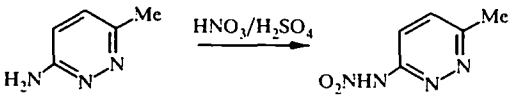


A single additional donor group in the heterocycle is frequently insufficient for successful nitration of methyldiazines with nitrating mixture. For example suitable conditions have not been found for the nitration of methylpyrazines containing hydroxy groups. These compounds react with HNO_3 in boiling acetic acid but no products retaining the pyrazine ring were isolated [21].

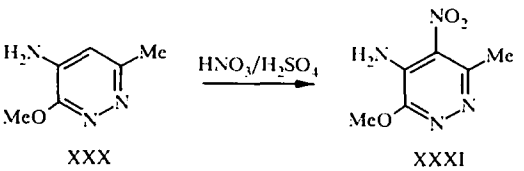
It was reported that a mixture of 4-nitro- (XXV), 6-nitro- (XXVI) and 4,6-dinitro-3-methoxy-5-methylpyridazines (XXVII) were formed on heating 3-methoxy-5-methylpyridazine (XXIV) [22]. The second nitro group was probably introduced into the nonprotonated mononitro derivatives XXV or XXVI [2].



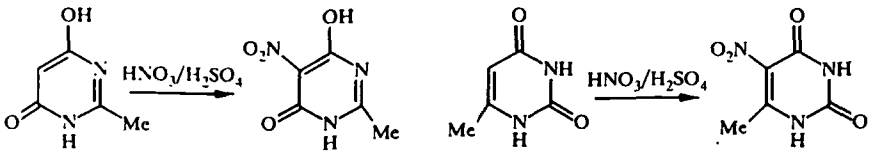
Treatment of 6-methyl-3(2H)-pyridazinone with hot nitric acid caused oxidation of the methyl group to give 3(2H)-pyridazinone-6-carboxylic acid [23]. Nitration of methylpyridazines containing phenyl substituents occurred exclusively at the phenyl ring [24]. Treatment of 2-amino-5-methylpyridazine (XXVIII) with nitrating mixture gave the 2-nitramine derivative XXIX which could not be converted to a C-nitro compound [25].



The substituted pyridazine XXX, which contains methyl, methoxy, and amino groups, was nitrated on the ring to give compound XXXI [26].

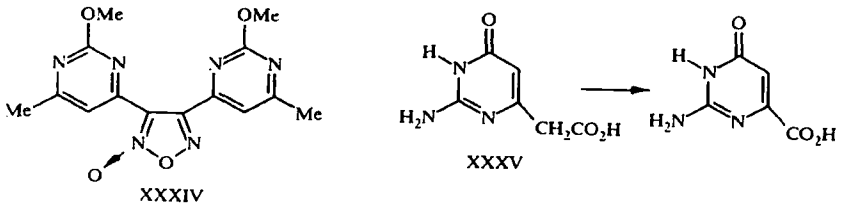


Methylpyrimidines with three substituents such as alkyl, amino, and hydroxy groups were successfully nitrated at $C_{(5)}$ of the heterocycle using the acid nitration mixture [27]. For example, 2-methyl-4,6-dihydroxypyrimidine (XXXII) and 6-methyluracil (XXXIII) were nitrated in position 5 of the rings in high yields [28].



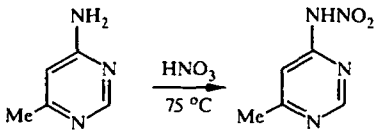
XXXII XXXIII

Raising the temperature to 100°C during the nitration of 6-methyluracils led to oxidation of the methyl groups to carboxyl [28]. A derivative of furoxane (XXXIV) was isolated from treatment of 2-methoxy-4,6-dimethylpyrimidine with the same nitrating mixture [29]. Nitration of isocytosine-6-acetic acid (XXXV) with KNO_3 in conc. H_2SO_4 caused oxidation of the acetic acid moiety to carboxyl [30].



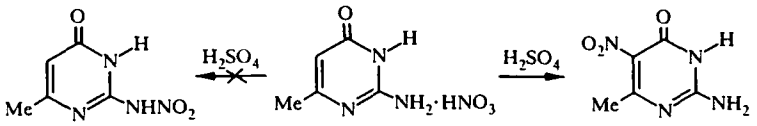
XXXIV XXXV

Treatment of 4-amino-6-methylpyrimidine (XXXVI) with fuming nitric acid gave 6-methyl-4-nitraminopyrimidine (XXXVII) the structure of which was proved unambiguously by conversion to 4-hydrazino-6-methylpyrimidine [31].



XXXVI XXXVII

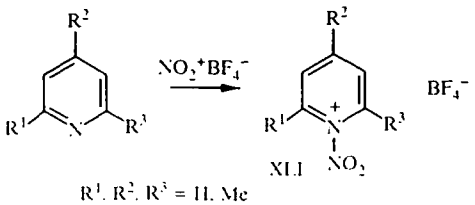
The product of the reaction of 2-amino-4-methyl-6(1H)-pyrimidone nitrate (XXXVIII) with conc. H_2SO_4 was initially erroneously described as the 2-nitramino derivative XXXIX [32] but the same authors [33] showed that the product was the 5-nitro derivative XL



XXXIX XXXVIII XL

As these examples show, in all cases nitration of methyl derivatives of azines with nitrating mixture in media of varying acidity leads to introduction of the nitro group into the heterocycle or into another substituent (e.g., phenyl or amino groups) but not into the methyl group.

The use of another reagent for the nitration of methyl derivatives of azines — nitronium tetrafluoroborate in neutral solvents — led to a relatively stable intermediate, the N-nitro derivative. By using UV and ^1H NMR spectroscopy the formation of N-nitropyridinium ions XLI was demonstrated on mixing solutions of 4-picoline and 2,6-lutidine with nitronium tetrafluoroborate in sulfolane at 30°C in a stream of dry nitrogen [34].

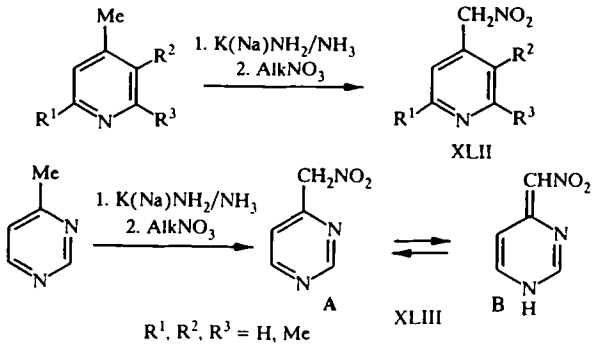


XLI

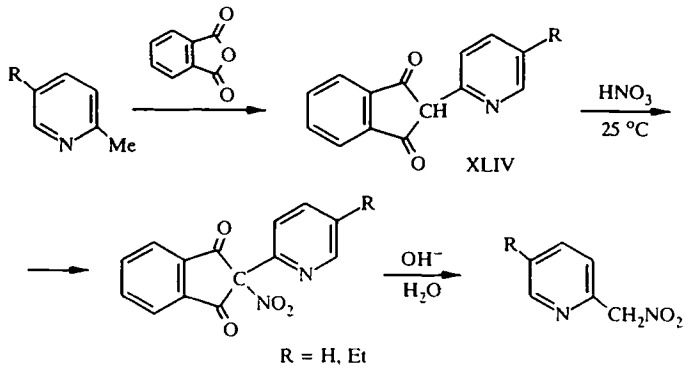
R^1, R^2, R^3 = H, Me

In subsequent papers [35, 36] various N-nitropyridinium tetrafluoroborates XLI were proposed as effective nitrating agents with high selectivity for aromatic and aliphatic substrates. In contrast to inorganic nitronium salts, the pyridinium salts made it possible to carry out nitration readily in homogeneous conditions. Moreover the acid formed is bound to the alkylpyridine which is very important as a nitrated compound which is sensitive to acid [37].

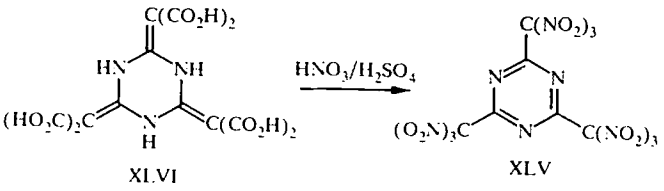
The 2- and 4-picolines and 4-methylpyrimidine are readily converted into the corresponding α-nitroalkyl derivatives XLII and XLIII by consecutive treatment with alkali metal amides and alkyl nitrates in liquid ammonia. The authors [38] proposed two "standard" systems: picoline/sodamide/liquid ammonia = 1.0/2.5/3.1 and picoline/sodamide/liquid ammonia = 1.0/2.0/2.5. Yields of nitration products of up to 75% were obtained by using these systems. Exclusive mononitration was observed exclusively for 2,4- and 2,3-lutidines and 2,4,6-collidine, the reactivity of the methyl groups decreasing in the order 4 > 2 > 3 [38]. According to IR, UV, and ^{1}H NMR spectra, 4-(α-nitromethyl)pyrimidine (XLIII) exists as a mixture of the tautomers (A) ⇄ (B) [38].



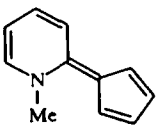
A method for nitrating the side chain of picolines has been developed [39] in which a temporary electron withdrawing substituent is introduced into the methyl group as follows:



The authors [39] did not provide data on the structure of the intermediate XLIV which with two carbonyl acceptor groups in the side chain is possibly a stable ylidene derivative of pyridine which readily reacts with electrophiles at the α-carbon atom [40]. An analogous reaction is the method of obtaining tris(trinitromethyl)-1,3,5-triazine XLV [41] in which nitration of the ylidene derivative of triazine XLVI is accompanied by decarboxylation.

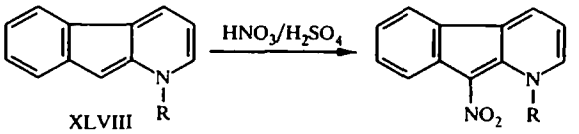


The ylidene derivative of pyridine XLVII, which contains no stabilizing acceptor groups, is polymerized by electrophilic reagents [42].



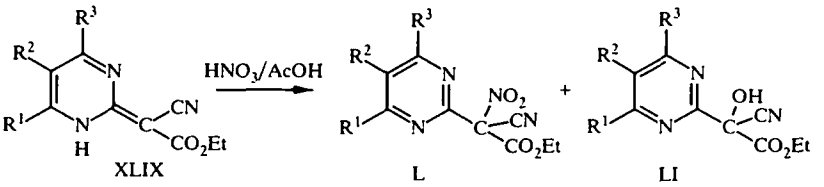
XLVII

Ylidene derivatives of azines undergo normal nitration at the α-carbon atom in the absence of acceptor substituents if they are part of a stable condensed system, e.g., XLVIII [43].



XLVIII

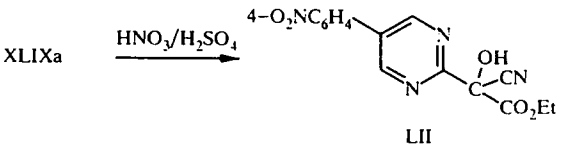
It has also been shown [44] that various monocyclic ylidenes — dihydroazinylidenecyanoacetate esters — react with nitric acid in media of varying acidity to initially give products of nitration at the exocyclic α-carbon atom which may then undergo further reactions. For example, nitration of the ylidene derivatives of pyrimidine XLIX with fuming nitric acid in acetic acid gave yields of about 90% of the ethyl α-nitro-α-(pyrimidinyl)cyanoacetates (L). Small amounts of the corresponding α-hydroxy derivatives LI [44] were isolated from the reaction mixture. It seems that these were formed by radical reactions of the initially formed nitration products L [45].



XLIX L LI

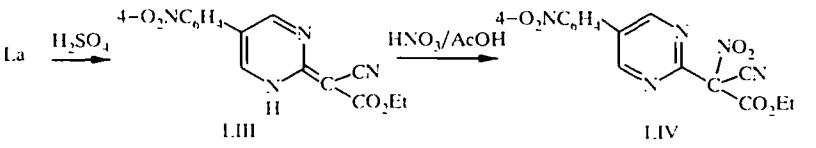
a $R^1 = R^3 = H$, $R^2 = Ph$; b $R^1 = Ph$, $R^2 = R^3 = H$;
c $R^1 = R^3 = Ph$, $R^2 = H$; d $R^1 = R^3 = H$, $R^2 = Me$

Nitration of the ylidene derivative of 5-phenyldihydropyrimidine XLIXa with excess HNO_3 in conc. H_2SO_4 gave the *p*-nitrophenylpyrimidine LII with an α-hydroxycyanoacetate ester in the side chain [44].



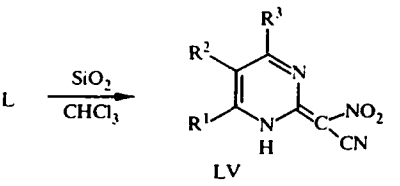
LII

The α-nitro pyrimidine derivative La, which contains a 5-phenyl substituent, was converted in conc. H_2SO_4 into the isomeric product LIII in which the nitro group is in the *p*-position of the phenyl ring. Subsequent nitration of compound LIII with fuming nitric acid in acetic acid gave the dinitro derivative LIV [44].



LIII LIV

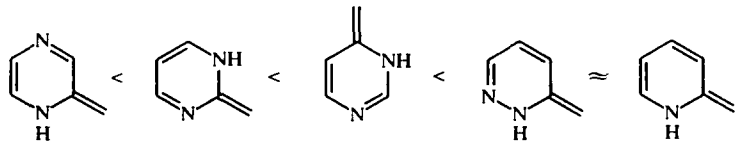
During chromatographic separation of a mixture of compounds L and LI on silica gel, the α-nitro derivatives L underwent dealkoxycarbonylation to give new methylenedihydroazine compounds — α-nitro-α-(dihydropyrimidinylidene)-acetonitriles LV — in quantitative yield [44].



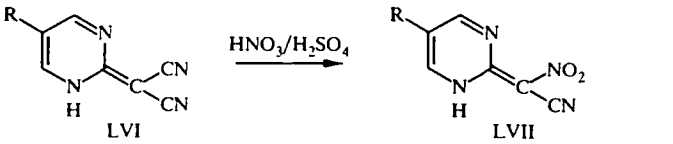
LV

R^1, R^2, R^3 = H, Me, Ph

It has been established [46] that nitration of other dihydroazinylidenecyanoacetate esters of the pyridine, pyridazine, and pyrazine series with fuming HNO_3 in acetic acid also occurs at the α-carbon of the side chain and may be accompanied by formation of α-hydroxycyanoacetate esters and α-nitroacetonitriles. The ease of the latter reaction depends on the type of heterocyclic nucleus and the acidity of the medium and increases in the order [46]:



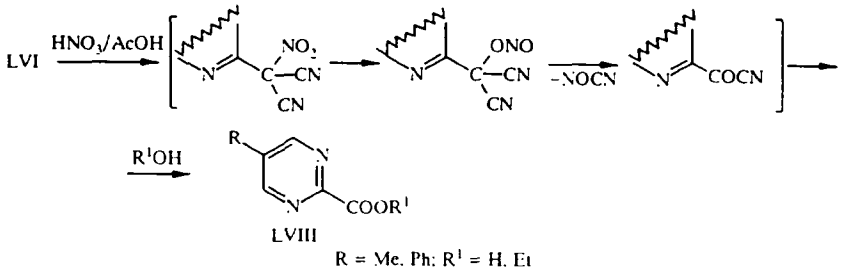
The nitration of 5-methyl(phenyl) substituted 2-dihydropyrimidinylidenemalononitriles LVI with nitric acid in different media was studied to elucidate the influence of the form of side chain tautomerizing fragment on the position of nitration [47]. The presence of a second nitrile group in the side chain (in place of a carbethoxy group) caused a decrease in stability of the initial nitration products. Substituted 2-pyrimidinylidenemalononitriles LVI, like the analogous cyanoacetate esters, reacted with nitric acid under mild conditions. However when nitration was carried out with nitric acid in conc. H_2SO_4 nitro derivatives LVII were obtained with only one cyano group on the side chain [47].



LVI R = Me, Ph

LVII R = Me, $C_6H_4NO_2$-4

The conversion of substituted pyrimidinylidenemalononitriles LVI into the corresponding 2-pyrimidinecarboxylic acids or their esters LVIII with fuming nitric acid in acetic acid has been described. The following mechanism for the formation of the acids and their derivatives has been proposed by the authors [47]:

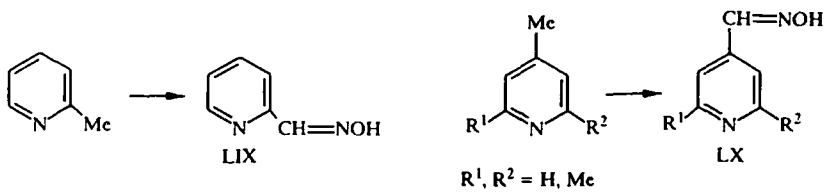


LVIII

R = Me, Ph; R^1 = H, Et

NITROSATION OF METHYL- AND METHYLENEAZINES

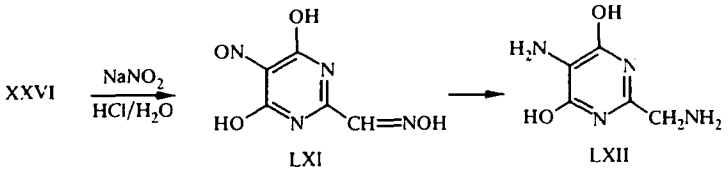
Nitrosation of 2- and 4-picolines and 2-methylpyrazine, like nitration of the methyl group, was effectively carried out with alkyl nitrites and alkali metal amides in liquid ammonia. The products were the corresponding pyridinealdoximes LIX and LX [48-51].



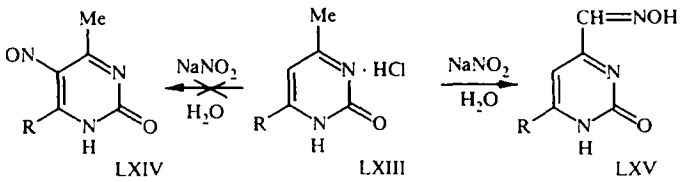
Nitrosation of 2- and 4-ethyl-, 2- and 4-benzylpyridines with amyl nitrite in liquid ammonia in the presence of potassamide gave the corresponding ketoximes [52]. Under these conditions nitrosation of 2,4-dimethyl- and 2,4,6-trimethylpyridines gave exclusively the 4-aldoximes LX [53].

Methyl groups in active positions on the pyrimidine ring were also readily converted into aldoxime groups with various organic and inorganic nitrites. It is important to note that in the pyrimidine series this reaction can be carried out not only in the presence of strong bases in liquid ammonia (via a mesomeric carbanion) [53-55] but also with an excess of hydrochloric acid or by using methylpyrimidine hydrochlorides in acetic acid or ethanol [56-61]. The authors [58] connect the ease of electrophilic attack by the nitroso cation in the latter case with the easier formation of quasi-*p*-quinoid (methylidene) structures of the substrates from the various substituted methylpyrimidines. Nitrosation of the side chain of 4-methylpyrimidines is a valued preparative procedure for the preparation of 4-cyanopyrimidines via the 4-oximino derivatives [61].

When two donor groups are present in addition to a methyl group a nitroso group can be introduced into the heterocyclic ring. For example, nitrosation of 4,6-dihydroxy-2-methylpyrimidine XXVI in aqueous hydrochloric acid gave the dinitroso derivative LXI in high yield. Its structure was proved by reduction to the corresponding diamine LXII [62].

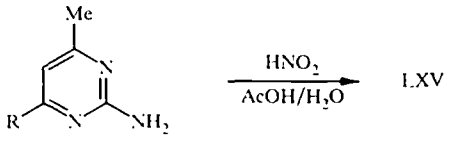


However in many cases of methylpyrimidines with amino-, hydroxy-, or mercapto groups in positions 2 and/or 4(6), nitrosation or reaction with aryldiazonium salts occurs at the amino-, mercapto-, or methyl substituent and not at position 5 of the ring [57, 63-65]. For example, the nitrosation products from the methylpyrimidines LXIII were erroneously said to be the 5-nitroso compounds LXIV, but in fact, as was shown later [57, 63, 64] only nitrosation of the methyl group occurs to give the oximino compounds LXV. When acetic acid was used as the solvent nitrosation at both methyl groups of dimethylpyrimidines was possible [64].



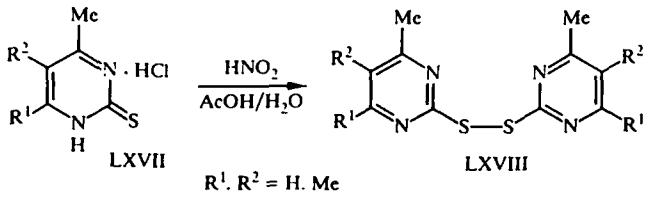
R = H, Me, Ph

Nitrosation of the methylpyrimidines LXVI which contact an amino group on the ring gave simultaneous conversion of the latter into an oxo group to give compound LXV [64].



R = H, Me, Ph R = H, Ph, CH=NOH

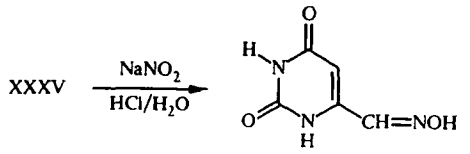
2-Mercapto-4-methylpyrimidines LXVII form bipyrimidinyl disulfides LXVIII on nitrosation and the methyl groups remain unchanged [65].



LXVII LXVIII

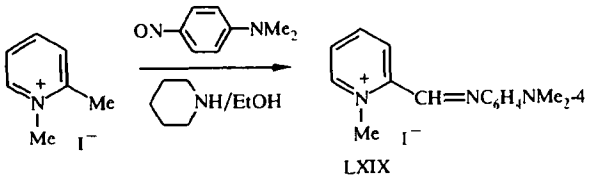
R^1, R^2 = H, Me

Isocytosine-6-acetic acid (XXXV) was nitrosated at the methyl group with simultaneous decarboxylation [30].



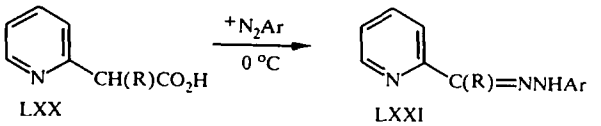
REACTIONS OF METHYL- AND METHYLENEAZINES WITH OTHER N-ELECTROPHILES

2-Picoline iodomethylate condensed with N,N-dimethyl-4-nitrosoaniline in the presence of piperidine to give the Schiff's base LXIX. 2-Picoline itself did not react with nitrosoaniline under these conditions [66].



LXIX

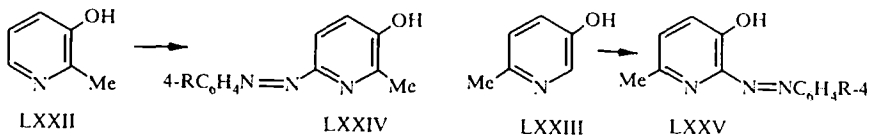
2-Pyridylacetic acid and its α-propyl derivative LXX gave good yields in the Japp-Klingemann reaction [67] to give 2-acylpyridine phenylhydrazones LXXI.



LXX LXXI

R = H, *n*-Pr; Ar = $C_6H_4NO_2$-4; $C_6H_4NH_2$-4; $C_6H_4SO_3H$-4; $C_6H_4CO_2H$-4

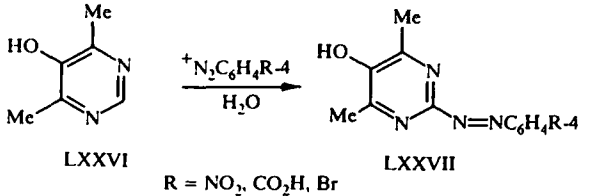
2-Picoline with a less activated methyl group did not undergo azo-coupling with diazotized sulfanilic and *p*-aminobenzoic acids and gave only 7% of pyridine-2-aldehyde *p*-nitrophenylhydrazone with *p*-nitrophenyldiazonium salt [67]. A study of the orientation of azo-coupling with 2-methyl- (LXXII) and 6-methyl- (LXXIII) 3-hydroxypyridines showed that in acidic and basic media 6-phenylazo-2-methyl- (LXXIV) and 2-phenylazo-6-methyl- (LXXV) 3-hydroxypyridines respectively were the sole products. 2,6-Dimethyl-3-hydroxypyridine did not react [68].



LXXII LXXIV LXXIII LXXV

R = H, NO_2

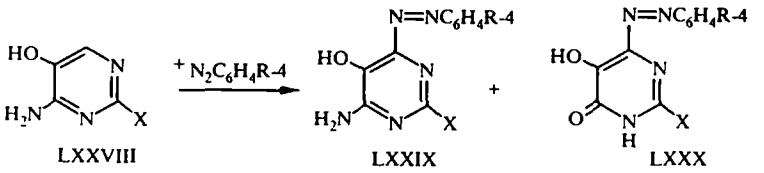
Azo-coupling of pyrimidines usually gives the 5-azoderivative on the ring, which is very important as a route for functionalization of pyrimidine precursors of purines, pteridines, and other condensed pyrimidines, although the reaction does not always work. Moreover the presence of other substituents on the pyrimidine ring may lead to the insertion of the phenylazo group in other positions on the ring of methylpyrimidines. For example, a study of the azo-coupling of 4,6-dimethyl-5-hydroxypyrimidine (LXXVI) in alkaline media showed that 2-arylazo derivatives LXXVII were obtained with the most reactive diazonium salts as predicted by the authors [69]:



LXXVI LXXVII

R = NO_2, CO_2H, Br

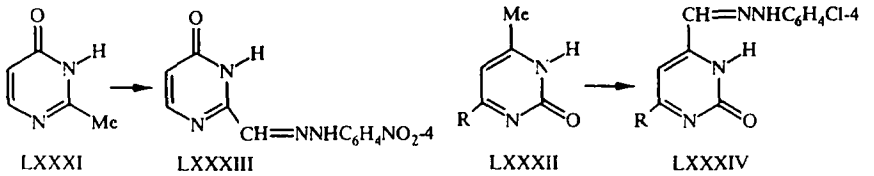
The 6-arylazo derivatives LXXIX and LXXX were isolated from the same reaction with 4-amino-5-hydroxy-pyrimidines LXXVIII [70].



LXXVIII LXXIX LXXX

X = NH_2, OH, Me; R = Cl, NO_2

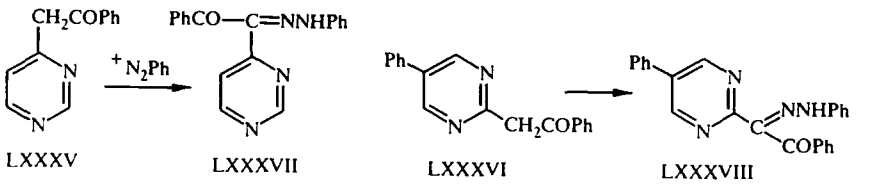
Examples of azo-coupling at the methyl group are the reactions of 2-methyldihydropyrimidine-4- (LXXXI) and 4-methyldihydropyrimidin-2-ones (LXXXII), which are capable of forming energetically favorable methylidene intermediates [70, 71] with subsequent conversion to compounds LXXXIII and LXXXIV respectively.



LXXXI LXXXIII LXXXII LXXXIV

R = H, Me

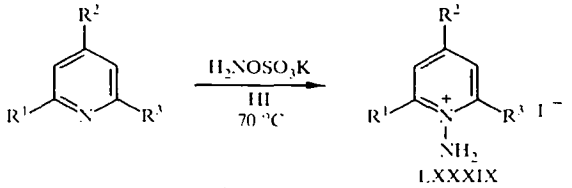
The two phenacylpyrimidines LXXXV and LXXXVI reacted with phenyldiazonium salts in alkaline media at the exocyclic CH_2 group to give the phenylhydrazones LXXXVII and LXXXVIII respectively. The structures of these compounds were studied by IR and ^1H NMR spectroscopy and X-ray crystallography [72].



LXXXV LXXXVII LXXXVI LXXXVIII

As the authors [70, 73] concluded, the results of a large number of studies of nitrosation and azo-coupling of derivatives of methylpyrimidines can be best explained if it is concluded that, for these reagents, electrophilic addition to the methylene intermediate in the side chain occurs more readily than aromatic electrophilic substitution in the ring. Other reactions are possible during the course of azo-coupling such as free radical arylation [74] or interaction with other substituents in the ring such as mercapto or amino groups [73, 75].

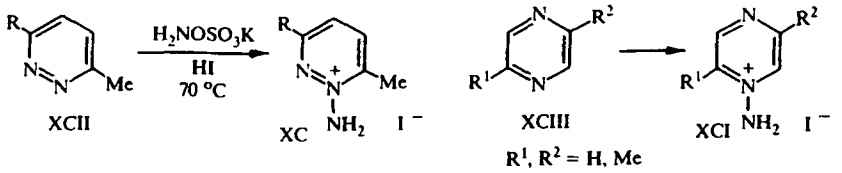
Alkylpyridines are readily aminated at the hetero-atom with potassium salts hydroxylamine-O-sulfonic acids and O-mesitylenesulfonylhydroxylamines. Products of N-amination (LXXXIX) were obtained in moderate yield under mild conditions with 2-picoline, 2,6-lutidine, 2,4,6-collidine [76], and other methylpyridines [77, 78] in order for further cyclization to pyrazolopyridine derivatives [79, 80].



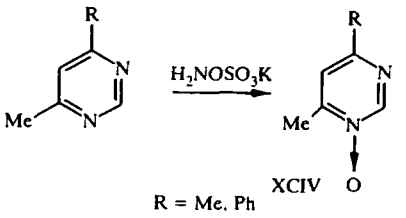
LXXXIX

R^1, R^2 = H, Me; R^3 = H, Me, Et, CH_2OH

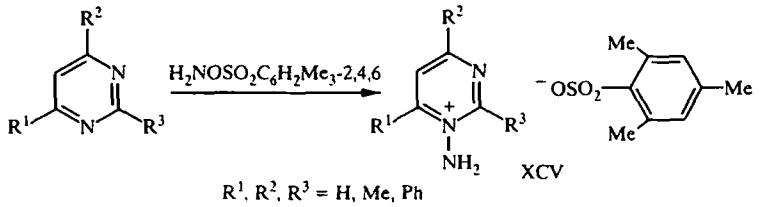
Methylpyridazines XCII and XCIII gave analogous N-amination products XC and XCI with the same reagents [81].



However 2-methyl- and 4-methylpyrimidines did not give N-aminopyrimidinium salts with hydroxylamine-O-sulfonates. Reaction with this reagent unexpectedly gave the corresponding N-oxide XCIV with 4,6-dimethylpyrimidine [81]. A probable mechanism for its formation was discussed in this paper.



Reasonable yields of the N-aminopyrimidinium salts XCV were obtained by treating N-methylpyrimidines with O-mesitylsulfonylhydroxylamine at room temperature [81].



The cited examples of the reactions of methyl and methylene derivatives of pyridine, pyridazine, pyrimidine, and pyrazine with N-electrophiles demonstrates the possibility for using these practically important heterocyclic systems for a variety of functionalizations [82].

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