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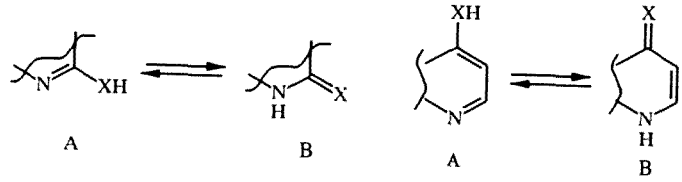
HYDROGEN EXCHANGE, ALKYLATION AND ACYLATION OF POTENTIALLY TAUTOMERIC METHYL AND METHYLIDENE DERIVATIVES OF PYRIDINE AND DIAZINES (REVIEW)

O. A. Zagulyaeva and I. V. Oleinik

Data on the deuteration, alkylation and acylation reactions of potentially tautomeric methyl and methylidene derivatives of pyridine, pyrimidine and pyrazine in media of varying acidity and basicity have been collated. Whether these reactions occur via the aromatic tautomers, the more reactive methylidene tautomers or predominantly by generation of mesomeric anions from both tautomers is examined.

The least well studied aspect of the family of azinyl–azinylidene tautomers of systems of the A ⇌ B type is the structure and reactivity of α- and γ-methylazines in which methyl-methylidene tautomerism is possible (X = CH_2) [1-4]. The topologically similar hydroxy- and aminoazines (X = O, NH) which play important roles in biological processes have been studied in greater detail. The general rules observed for the reactions of these compounds with electrophiles [5] help in understanding the chemical properties of the methylazines.



X = O, S, NH, CH_2 in positions α- or γ- to the nitrogen heteroatom

In comparing the properties of the various heterocyclic representatives of azinylidene systems of A ⇌ B type, note that they all have some general rules in common [2, 5, 6] despite the special properties of the exocyclic groups.

1. Under conditions of kinetic control an electrophile attacks the pyridine nitrogen in the aromatic tautomer A and the exocyclic atom X in the ylidene tautomer B. Further conversions during the course of the reaction may lead to thermodynamically stable products in which the electrophile is found in the electron deficient position in the heterocycle or in substituents attached to it.

2. The presence of a second pyridine nitrogen in the ylidene derivatives of diazines changes the regioselectivity of reactions with electrophiles so that the reaction direction depends on the positions of the ring atoms relative to one another.

Interest in methyl and methylidene stems principally from the possibility of using them as synthons for the preparation of a variety of functionally substituted azines and for the construction of other heterocyclic systems such as indolizines [7], pyrazoles [8], quinolizinium salts [9], etc. [10].

It is known that the tautomeric equilibrium A ⇌ B is shifted almost completely to the aromatic form (A) in the case of unsubstituted α- and γ-methylazines (X = CH_2) and their amino derivatives (X = NH). Data on the tautomeric equilibrium of α-mercapto-, α-hydroxy-, α-amino and α-methylpyridines are cited in Table 1.

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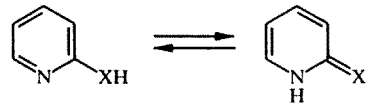
TABLE 1. Dependence of the Position of the Tautomeric Equilibrium for α-Mercapto-, α-Hydroxy-, α-Amino- and α-Methylpyridines on the Basicity of the Tautomers [3, 11]

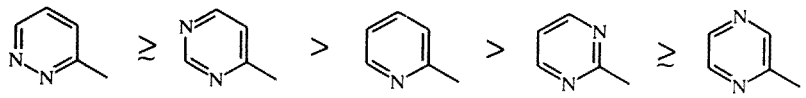


A B

X	lgK$_T$ (XH/X)	pKα(=X)*	pKα(XH)*
S	-4,8	-1,22	3,62
O	-3,0	0,32	3,28
NH	6,2	13,02	6,86
CH_2	13,3	20,0	5,97

*Basicity of the N- and O-methylated model compounds in water.

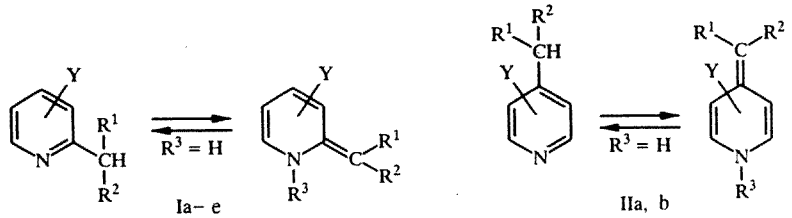
The relative tendency for derivatives of various azines (A) to transform into the ylidene tautomer (B) falls in the following series:



Non-polar solvents and the gas phase favor the aromatic form (A) while polar solvents favor the ylidene form (B). The presence of an acceptor substituent in the exocyclic CH group facilitates the appearance of the ylidene tautomer B. The effect of substituents in the heterocycle on the ease of formation of the ylidene tautomer has been little studied [1]. Examples of tautomeric equilibria with comparable amounts of the aromatic and ylidene tautomers of the methylazines are rarely encountered since a practically complete shift of the equilibrium in favor of the ylidene form (B) occurs with increasing acceptor power of the substituent on the CH unit, while the rate of interconversion of the tautomers is very slow under normal conditions [2].

The dependence of the tautomeric equilibrium of methylazines on structural factors, the nature of the medium and other reaction conditions has been discussed elsewhere [2]. It should be noted that the aromatic (A) and ylidene (B) tautomers of methylazines are very different in reactivity. In comparisons of neutral molecules of tautomers (A) and (B) for derivatives of the pyridine series, calculations [12] show that the ylidene form (B) is more polar and has a clearly expressed alternation of charges and bond orders characteristic of the reactive enamine system [13]. Methylidene structures have been postulated as active intermediates in the reactions of alkylazines with electrophiles in the presence of Lewis acids [14, 15]. A considerable range of chemical reactions of potentially tautomeric methylazines can be explained by migration of groups (e.g., acyl, arylsulfonyl, and other mobile groups [16]) introduced by the electrophile in tautomeric equilibria of the A ⇌ B type. N-Alkyl groups can migrate to the methyne carbon atom during thermolysis [17, 18].

Data on the reactivity with electrophiles in various media of potentially tautomeric methyl- and methylidene derivatives of azines (Ia-e, IIa-c) of the pyridine, pyridazine, pyrimidine and pyrazine series are reviewed here. Deuteration, alkylation and acylation are examined. Information on the chemical properties of these compounds has appeared in monographs and reviews [3-5, 15, 19] but this review is concerned with new information obtained over the last decade.



Ia– e IIa, b

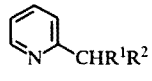
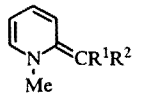
Ia Y = CH, b Y = N(3), c Y = N(4), d Y = N(5), e Y = N(6); IIa Y = CH, b Y = N(2), c Y = N(3). R^1, R^2 = H, Alk, Ar, COPh, COOR, SO_2Ph, CN, NO_2 etc.; R^3 = H, Alk, COR etc.

TABLE 2. Equilibrium and Kinetic Acidity of Methylazines

Compound	pK_a^{CH} ,*	pK_a^{CH} ,*2	pK_a^{CH} ,*3
Toluene	—	—	36
2-Methylpyridine	35,8	34	27
2-Benzylpyridine	—	28,4	—
4-Methylpyridine	34,0	32,2	25
4-Benzylpyridine	—	25,3	—
3-Methylpyrazine	31,7	—	23
3-Methylpyridazine	31,9	—	—
4-Methylpyridazine	27,6	—	—
2-Methylpyrimidine	30,8	—	—
4-Methylpyrimidine	27,4	—	—

*Determined using cesium derivatives of indicator CH acids in dimethoxyethane [21].
*2Measured in THF using lithium derivatives of alkylsilyl- and disilylamines [22].
*3Calculated from the relation $lgK = 14.26 - 0.84pK_a^{CH}$, where K is the rate constant for basic deuterium exchange in a solution of potassium ethoxide in deuteroethanol at 25°C [23].

TABLE 3. Basicity of Substituted 2-Methyl- and N-Methyl-2-methylidenepyridines in Water [24, 28, 29]

Structural formula	R^1	R^2	pK_a
 III	H	Ph	5,13
	H	COPh	5,03
	Ph	Ph	4,51
 IV	H	Ph	17,01
	H	COPh	7,38
	H	SO_2Ph	10,45
	Ph	Ph	17,33

ACIDITY AND BASICITY OF METHYLAZINES

The importance of the acid–base properties of various heteroaromatic compounds in their reactions with electrophiles has been noted in a review [20]

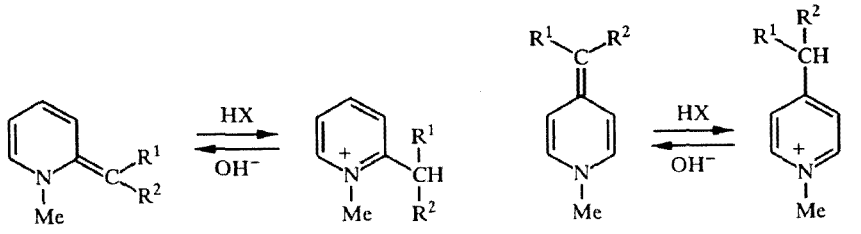
However there are not many quantitative estimates of the acid properties of methyl and methylidene derivatives of azines (CH and NH acids respectively). The kinetic and thermodynamic CH-acidity of methylazines in various solvents has been studied [21-23]. Unsubstituted methylazines are stronger CH acids than toluene (Table 2) which is apparent from their chemical properties since they readily generate anions capable of reacting further with weak electrophiles. The size of the acidifying effect of several cyclic nitrogen atoms is affected by their positions relative to one another and the methyl group [21].

The acidity of substituted methylazines is substantially increased by the introduction of substituents in the side chain. For example, the pK_a of 2- and 4-benzylpyridines are 5-6 orders of magnitude greater than those of the picolines (Table 2). The acidities of the keto forms of 2- and 4-phenacylpyridines are still greater (pK_a is 13.3 and 12.5 respectively [24, 25]). The content of the ylidene form (B) increases in parallel with the acidity, the acidity of ethyl 2-trifluoromethyl-1,4-dihydro-4-pyrimidinylidenecyanoacetate, which exists in the ylidene form (B) is so great that it exists as a practically completely ionized compound in ethanol or DMSO [26]. Strong bases such as sodium hydride or sodamide are frequently used in practice for complete generation of anions from unsubstituted methylazines before addition of the electrophile. With weaker bases (e.g.,

triethylamine or piperidine) traces of the reactive anion are formed which reacts rapidly with the electrophile and is then replenished via the equilibrium.

Examination of the basicity constants for model pyridine derivatives in Tables 1 and 3 shows that the pK_a values for all derivatives (X = O, S, NH, CR^1R^2) of the conjugated acids of the aromatic form (A) differ relatively little from one another. On the other hand the basicity of the ylidene form (B) changes considerably with changes in the tautomerized side chain. The methylidene derivatives of pyridine show the greatest basicity on varying X (the difference for the hydroxy derivatives is about 20 orders of magnitude). Introduction of an electron accepting substituent on the exocyclic carbon of the methyl group (Cα) has a smaller effect for the aromatic form. Values of the pK_a are cited in Table 3 for α-substituted derivatives of 2-methylpyridines III and N-methyl-2-methylidenedihydropyridines IV with electron acceptor groups in the side chain. The aromatic form is less stable for these than the ylidene form. There is no information available for compounds with two strong acceptor substituents.

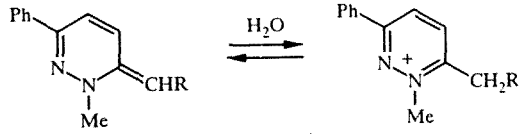
Methyl and methylidene derivatives of the azines form mesomeric cations of different structures in acid media. Study of the structure of products of protonation of methylidenedihydropyridines showed that fixed ylidene derivatives (anhydrobases of the pyridine series) Va-f and VIa-c form cations with aromatic structure VIIa-f and VIIIa-c in acid media, while derivatives Va and b, which have higher basicity, are partially protonated even in water [24, 27-31].



Va -f VIIa -f VIa -c VIIIa -c

V—VII a $R^1 = R^2 = H$, b $R^1 = H$, $R^2 = Ph$, c $R^1 = H$, $R^2 = CN$, d $R^1 = H$, $R^2 = COPh$, e $R^1 = H$, $R^2 = -SO_2Ph$, f $R^1 = R^2 = COPh$, VI, VIII a $R^1 = R^2 = CO_2Et$, b $R^1 = H$, $R^2 = SO_2Ph$, c $R^1 = R^2 = COPh$

Like their pyridine analogs Va and b, the 1-methyl-3-phenyl-1,6-dihydro-6-methylidenepyridazines IXa-c exist in aqueous solution in equilibrium with the corresponding azaaromatic forms Xa-c. The latter are easily recognized by the appearance of signal for the CH_2 groups in the ^1H NMR spectrum [32].

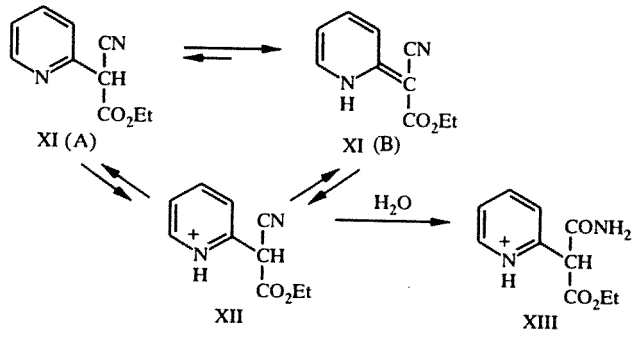


IXa -c Xa-c

IX, X a R = CO_2Et, b R = $COCH_3$, c R = COPh

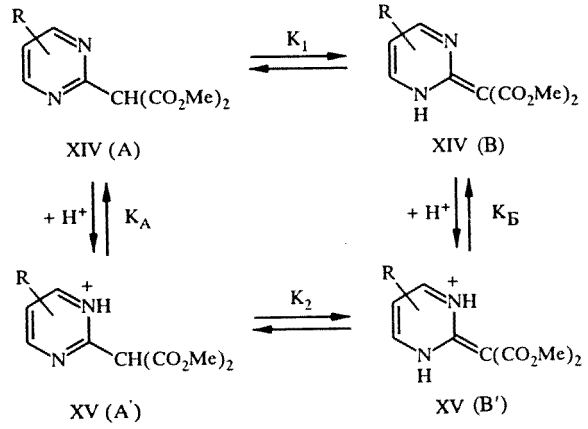
A high degree of protonation for mobile methylidene derivatives of pyridine with two strong acceptors in the side chain is only achieved by dissolving them in strong acids (CF_3COOH, conc. H_2SO_4, etc.). It was shown by ^{13}C NMR spectroscopy that ethyl 1,2-dihydro-2-pyridylidenecyanoacetate (XI) was about 50% protonated in CF_3COOH, whereas it was practically completely protonated in 95% H_2SO_4, but even in these conditions the spectrum contained additional signals resulting from further conversion of the protonation product XII into the corresponding monoamide of ethyl pyridylmalonate XIII.

An increase in the number of nitrogen atoms in the ring causes a decrease in basicity of the aromatic form (A) for all methyldiazines in comparison with the corresponding picolines [3]. To judge from the structure of the protonation products the effect of additional heteroatoms in the ring on the basicity of the ylidene tautomer of substituted methyldiazine is more complex [34].



As a result of studies by UV and ^{13}C NMR spectroscopy of the structure and stability of the products of protonation in conc. H_2SO_4 of various ethyl dihydroazinylidenecyanoacetates that protonation of ethyl cyanoacetates of the pyridazine series the equilibrium shifted towards the azaaromatic cation (as in the case of the fixed derivatives IX), whereas protonation of the analogous pyrimidine, pyrazine and S-triazine derivatives showed that the shift was to the ylidene structure [33, 34], it was established that cations of the latter type are the more stable in conc. H_2SO_4.

The most informative example is the equilibrium of derivatives of ethyl 2-pyrimidinylmalonate, XIV (R = H, Ph) which exist as form A and which show no tautomerism in neutral solvents like chloroform.



In trifluoroacetic acid, the acidity of which facilitates monoprotonation of these pyrimidine derivatives, the equilibrium is shifted towards the protonated ylidene tautomeric form XV (B') which was confirmed spectroscopically [35]. The equilibrium constant for methylazine protonation is known to be linked to the basicities of the tautomers by the following expression [35]:

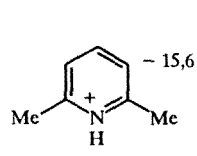
$$K_2 = K_1 \cdot K_B / K_A,$$

where K_2 and K_1 are the equilibrium constants for tautomerism of the protonated and neutral forms and K_A and K_B are the basicity constants of the neutral tautomers. According to this expression, if $K_B >> K_A$, then $K_2 > K_1$, i.e., protonation shifts the tautomeric equilibrium towards the protonated ylidene form if the neutral ylidene form B is more basic than the aromatic form A, and vice versa.

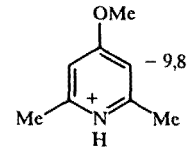
Thus, like the amino- and hydroxyazines, methylazines, depending on their acid–base properties, can react with electrophiles either as free bases of either tautomeric form in neutral or even strongly acidic media with substrates of low basicity ($pK_a < -2.5$ [5]), or as conjugate acids in the aromatic or ylidene tautomeric form in acid media (with basic substrates with $pK_a > 1$ [5]), or the reaction may occur with a change in mechanism with change in pH (H_0) of the medium for compounds with intermediate values of pK_a.

ACID AND BASE DEUTERIUM EXCHANGE OF METHYLAZINES

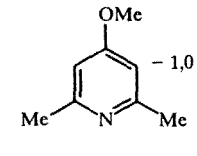
The rates of acid catalyzed deuteration (lg K_0) with exchange of the β-protons of the ring in the methylpyridines XVI-XVIII standardized to 100°C and pH 0 are as shown below [36].



XVI



XVII



XVIII

The deuterium isotope effect through one and two bonds ($^1\Delta$ and $^2\Delta$) on the ^{13}C shifts of the aromatic carbon atoms in methylpyrazines have been determined [37]. The rates of base catalyzed H/D exchange in the methyl groups of 2- and 4-picolines using a solution of sodium alkoxide in deuteroethanol at 120°C [38].

Only the methyl protons of 2-picoline undergo exchange with deuteromethanol and triethylamine at 180°C [39]. A comparison of the rate of deuterium exchange of the methyl hydrogens in 2- and 4-picolines on heating at 180°C in D_2O plus NaOD showed that the 4-methyl group is more reactive than 2-methyl group in this reaction [40]. Only the 4-methyl groups in 2,4-dimethyl- and 2,4,6-trimethylpyridine were deuterated on heating with D_2O-CD_3OD in sealed ampoules [41].

It was found that when 3- and 4-methylpyridazines were subjected to vigorous reaction conditions the 4-methyl group underwent deuterium exchange more readily than the 3-methyl group [42]. When pyridazinylmethyl lithium derivatives were prepared as a first step [43], the analogous deuterations occurred under milder conditions. Deuterium exchange in the methyl groups of 2- and 4-methylpyrimidines also occurred under mild conditions (D_2O at 33°C)in neutral or mildly acidic conditions [14, 44]. The exchange evidently goes via a methylidene intermediate of type B under these conditions, whereas in basic media the mesomeric anion is the intermediate [14].

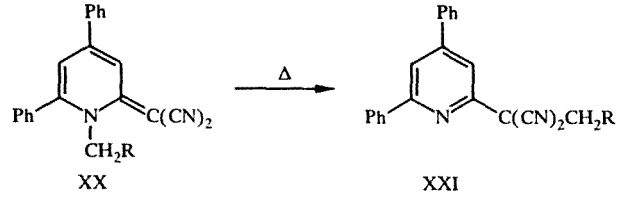
To investigate the mechanism of tautomerism in substituted methylazines containing two acceptor groups in the side chain, the kinetic isotope effect K_H/K_D was measured for ethyl 5-methoxy-2-pyrimidinylcyanoacetate (XIX) (in $CDCl_3$ at −4°C) [45].

ALKYLATION OF METHYLAZINES

Under kinetically controlled conditions methylazines, which exist in the aromatic tautomeric form, are alkylated at the pyridine nitrogen atom to give quaternary methylazinium salts [46]. Methods of synthesis, physico-chemical, chemical and biological properties and uses of N-substituted pyridinium salts (including salts from alkylpyridines) have been reviewed [47-51]. It was shown that for methylation of 2-R-pyridines with iodomethane the 2-methyl group slows the quaternization reaction by a factor of 2 to 4 in comparison with unsubstituted pyridine as a result of steric hindrance [46].

3- and 4-methylpyridazines are monoquaternized by alkyl halides at $N_{(1)}$ or $N_{(2)}$ with different ratios of the alkylated isomers [52]. Methylpyrimidines and methylpyrazines behave similarly [53-55]. Diquaternized salts of methyldiazines can be obtained by using oxonium salts as alkylating agents [56].

Alkylation of the highly basic N-substituted methylidenehydropyridines (anhydro bases) with various alkylating agents gave mono- and dialkylation at Cα of the side chain [15]. The basicity of N-substituted methylidenehydropyridines is apparently reduced considerably by introduction of strong electron withdrawing substituents at Cα and products of secondary reactions may be produced by alkylation under vigorous conditions. For example, when the N-substituted 2-dicyanomethylene-1,2-dihydropyridines (XX) were heated above their melting points, rearrangement occurred to the corresponding substituted 2-pyridylmalononitriles XXI with an alkyl group in the side chain [17].

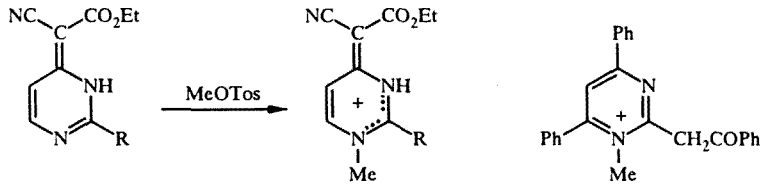


XX XXI

R = H, C_2H_6, $CH{=}CH_2$

Accumulation of electron withdrawing groups in the side chain of methylidene derivatives of diazines reduces their basicity so much that alkylation at the pyridine nitrogen is hindered. The high basicity of ethyl 2-methylsubstituted 1,6-dihydro-6-pyrimidinylidenecyanoacetate XXII relative to the 2-H and 2-Ph compounds allows the formation of the quaternary salt XXIII

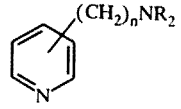
(R = CH_3) on heating with methyl tosylate. The structure of XXII has been confirmed by spectroscopic analysis [57]. The quaternary salt XXIV was obtained by alkylating substituted 2-phenacylpyrimidine under vigorous conditions [58].



XXII XXIII XXIV

R = H, CH_3, Ph

Alkylation of methylazines occurs readily if the ambident mesomeric anions are first generated. Alkylation of methylpyridines unsubstituted in the side chain occurs practically completely at the exocyclic Cα atom to give products of mono-, di- and tri-substitution in the CH_3 group [59, 60]. This reaction has been used successfully to prepare a variety of alkylpyridines, including some with functional groups in the side chain. For example, the method has been developed for the synthesis of 2-, 3-, and 4-dialkylaminoalkylpyridines XXV by reaction of the corresponding picolyl lithiums with dialkylaminoalkyl chlorides [61].



XXV

n = 3...5

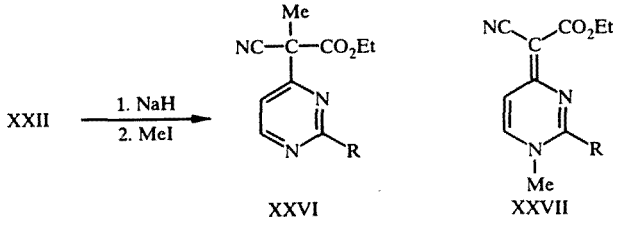
2-Picoline iodomethylate and its derivatives can be converted to the corresponding isopropylpyridines and the 4-methylpicoline analog to 4-*tert*-butylpyridine with iodomethane using phase transfer catalysis and subsequent dequaternization [62].

It has been found that the C=N bond of the heterocycle in the anions generated from methyldiazines has high activity with respect to the addition of organolithium compounds [3,4]. Sodium hydride and amide are frequently used for anion generation at low temperature. For example, treatment of 4,6-dimethyl-1-phenyl-2(1H)-pyrimidinone with alkyl halides in the presence of sodium hydride with cooling by solid carbon dioxide gave excellent yields of products of alkylation at position 6 only [63].

Generation of pyrazinylmethyl sodium from methylpyrazine with sodamide in liquid ammonia followed by treatment with alkyl halides gave up to 80% yields of side-chain alkylated products [64]. Considerably lower yields were obtained when methyl- and butyl-lithium were used as bases [65].

Moderate yields of products of mono- and dialkylation in the methyl group were obtained when the bulky isopropyllithium was used to lithiate 3- and 4-methylpyridazines with subsequent alkylation with alkyl halides [43].

When the Na(K) salts of ethyl 1,2-dihydro-2-pyridylidene-[66], -2-pyrimidinylidene- and 6-pyrimidinylidenecyanoacetate [57] reacted with methyl iodide the alkylation occurred predominantly at the "soft" carbon of the side chain (e.g., compound XXVI, R = CH_3). When the more powerful alkylating agent dimethyl sulfate was used the amount of products of alkylation at $N_{(3)}$ increased (e.g., XXVII, R = H, CH_3, Ph) [57].



XXVI XXVII

R = H, CH_3, Ph

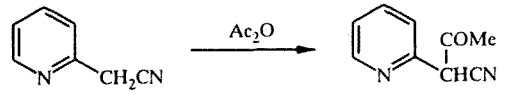
ACYLATION OF METHYLAZINES

Picolines react with acetyl chloride at low temperatures to give solid compounds of variable composition which are unstable on storage [67].

Methylazines react with acyl halides or other acylating agents in anhydrous solvents or in an atmosphere of dry nitrogen to give N-acylazinium salts. The latter can readily decompose (dissociate) with elimination of ketene to give a methylazinium halide. N-Acylheterocyclic cations readily undergo reduction and dimerization and also react readily with various nucleophiles [68].

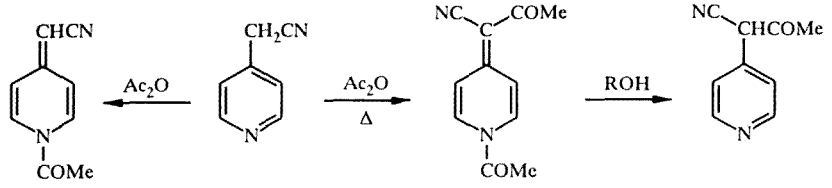
Formation of N-acyl salts of methylazines has been proposed [69] for activation of the methyl group (best for activating a methyl group *para* to the heteroatom) in reactions with aromatic aldehydes and other electrophiles [69].

When 2-picoline was boiled with benzoyl chloride at 130°C benzoylation occurred in the side chain to give 2-phenacylpyridine, apparently via initial acylation at the heteroatom [70]. The product from the reaction of 2-pyridylacetonitrile XXVIII with acetic anhydride at various temperatures was also the corresponding C-acetyl derivative XXIX [71, 72].



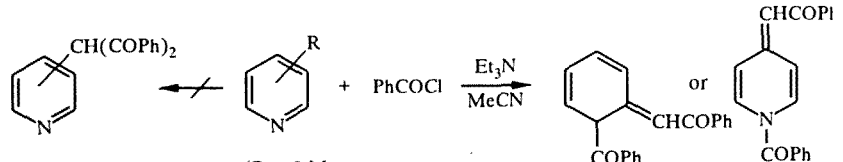
XXVIII XXIX

Acylation of 4-pyridylacetonitrile XXX with cold acetic anhydride gave the N-acetyl derivative XXXI, whereas on heating the C,N-diacetyl derivative XXXII was isolated. Treatment of the latter with methanol gave the C-acetyl derivative XXXIII [71].



XXXI XXX XXXII XXXIII

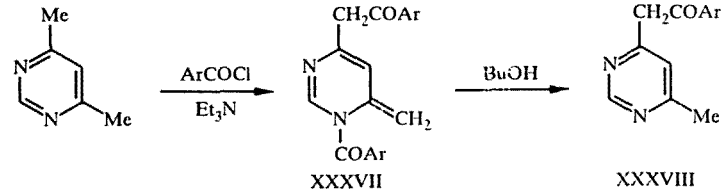
2- and 4-Picolines are readily dibenzoylated with benzoyl chloride with excess triethylamine (in refluxing acetonitrile or chloroform) [73]. The authors showed that 1-benzoyl-2-phenacylidene-1,2-dihydropyridine XXXIV or 1-benzoyl-4-phenacylidene-1,4-dihydropyridine XXXV were formed respectively, but not the isomeric dibenzoylmethylpyridines XXXVI.



XXXVI (R = 2-Me or 4-Me) XXXIV XXXV

Reactions of picolines with benzoyl chloride in the presence of triethylamine were carried out with initial reagent ratios of 1:2:2, 1:4:4 and 1:6:6. 4-Picoline responded most to this change: with the last ratio it was converted quantitatively to the dibenzoyl product XXXV in 2 h. Picolines did not react with benzoyl chloride in the absence of triethylamine under these conditions. A scheme for the mono- and dibenzoylation of 4-picoline was proposed [73].

Benzoylation of methylpyrimidines under analogous conditions are in good agreement with the results discussed above. For example, ketones of the pyrimidine types XXXVII and XXXVIII were obtained from 4,6-dimethylpyrimidine and acid chlorides in the presence of triethylamine [74].



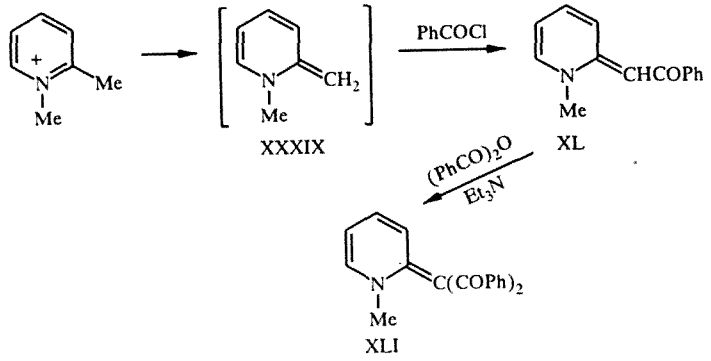
XXXVII XXXVIII

Ar = Ph, *p*-ClC6H4, *p*-CH3OC6H4

By changing the ratio of reagents, the authors synthesized 4,6-phenacylpyrimidine [75]. Under analogous conditions 2-methylpyrimidine reacted only with trichloro- and trifluoroacetyl chlorides [76]. It has been shown [77] that reaction at the methyl group of methylpyrimidines is facilitated by donor substituents in the ring and made more difficult by acceptor substituents [78].

Acylation of 2- and 4-picolines via the intermediate picolinyllithium, picolinylsodium and other salts gave 2- and 4-acylmethylpyridines in good yield [79, 80]. α- and γ-methyl derivatives of diazines, particularly pyrimidines [58, 81] and pyridazines [82] are also acylated at the methyl groups after preliminary treatment with bases.

N-Substituted methylidene derivatives of pyridine, generated under the reaction conditions (e.g., the methylidenedihydropyridine XXXIX), react with benzoyl chloride under mild conditions to give the C-alkylation product XL [83]. Diketones with structures XLI and VIc respectively were obtained from the reactions of 1-methyl-1,2-dihydro-2-phenacylidenepyridine and 1-methyl-1,4-dihydromethylidenepyridine with benzoic anhydride in the presence of triethylamine at 140°C [27]. These results show that the acylation reactions of these compounds are analogous to those of other enaminoketones [84].



Reactions with other C-electrophiles (carboxylation, Claisen condensation, reactions with CS_2, PhNCO and other reagents) in the presence of various acids and bases have been reviewed [3, 5, 15]. The successful use of Lewis acids as catalysts should be noted. For example, the use of BF_3, which forms trifluoroboride complexes with picolines, considerably facilitates the reaction between picolines and p-RC_6H_4CHO (R = H, NO_2, OCH_3. $N(CH_3)_2$) in acetic anhydride or without a solvent to give styrylpyridines in high yield [85].

We have discussed in this review the general behavior of azinyl−azinylidene tautomeric systems with electrophiles. In particular the characteristics of methyl and methylidene derivatives of azines in deuteration, alkylation and acylation have been noted. Because of the great lability of the acyl group, acylation reactions frequently lead to unexpected products. Further examination of halogenation, nitration and amination reactions may demonstrate new possibilities for the synthesis of a variety of functional derivatives of the azines.

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