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N-Acylpyridinium Salts and Corresponding Fused Benzo-derivatives

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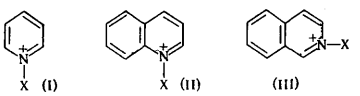
Published information on the preparation, structure, and reactions of *N*-acylpyridinium salts and the corresponding benzo-derivatives is summarised. They comprise purely ionic structures with the acyl group attached to the nitrogen atom, which bears a positive charge (partly delocalised through the ring), and a halide counter-ion. In individual cases (quinolinium and isoquinolinium) the electron of the anion may be transferred to a non-bonding orbital of the heterocycle with formation of a charge-transfer complex. *N*-Acylated heterocyclic cations contain more than one reaction centre, and are capable of *trans*-acylation, ring opening, hetarylation, one-electron reduction, etc. Processes involving hetarylation are especially interesting, and permit the preparation of various difficultly accessible derivatives of pyridine, quinoline, isoquinoline, and acridine. A list of 419 references is included.

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I. INTRODUCTION

A systematic survey is made of published data on the preparation, structure, and chemical reactions of *N*-acyl derivatives of six-membered nitrogen heterocycles—pyridine and its benzologues

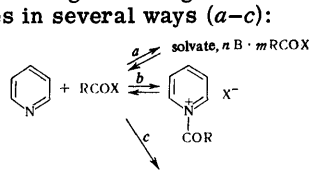


as well as their analogues—where X represents an electron-accepting group—RCO, $CONR_2$, COOR, sometimes CN, phosphoryl groups PO_3^-, PO_3R, $NH_3PO_2^-$, etc.

Although several reviews and monographs have been devoted to quaternary pyridinium, quinolinium, and isoquinolinium salts[1-4], the general aspects of *N*-acylated heterocyclic cations have not been considered: there are only brief summaries of already obsolete literature on *N*-acylpyridinium salts in papers on other topics[2,5,6]. During the past 10–15 years development of the acylation and phosphorylation of various nucleophilic compounds by salts of *N*-acylated heterocyclic cations (sometimes formed *in situ*) has been accompanied by elaboration of a method for introducing a heterocyclic ring into compounds containing an acidic methine group (ketones, dialkylanilines, pyrrole, furan, etc.), and several new reactions have been discovered. All this demands our attention.

II. PREPARATION AND STRUCTURE OF *N*-ACYL-PYRIDINIUM SALTS AND CORRESPONDING FUSED BENZO-DERIVATIVES

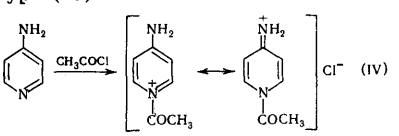
Pyridine and analogous nitrogen bases are able to react with acid halides in several ways (*a–c*):



When pyridine is carefully mixed with acetyl chloride in ether or petroleum ether, heat is evolved, and after cooling solid acetylpyridinium chloride is precipitated[7-9]. Other workers[10-12], however, were able to isolate only pyridine hydrochloride and keten, with part of the latter polymerising to dehydracetic acid[11,13,14]. Quinoline, 2-methylquinoline, and 2,6-dimethylpyridine under these conditions form mixtures of their hydrochlorides and the corresponding adducts with acetyl chloride[10,15]. If the reaction is conducted in chloroform, which dissolves pyridine hydrochloride, especially at low temperatures, *N*-acetylpyridinium chloride of greater purity can be obtained[12].

N-Acylpyridinium chlorides are prepared by adding pyridine to an equivalent quantity of the acyl chloride in anhydrous ether, benzene, petroleum ether, or dry nitrogen in the absence of a solvent[16-26]. Only pyridine hydrochloride is formed when the reactants are added in the opposite sequence. The method can be used to prepare quinoline and 2-methylquinoline salts[27,28]. Methylpyridines react with acetyl chloride in the cold to form compounds of variable composition, which are unstable on keeping[9,29].

The stability of *N*-acetylpyridinium salts is increased by the presence of substituents capable of helping to delocalise the positive charge[25,30,31]. Treatment of 4-aminopyridine in ether with acetyl chloride (as well as with benzoyl and toluenesulphonyl chlorides) produces salts of the type (IV):



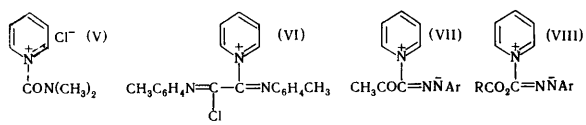
1-Acetyl-4-dimethylaminopyridinium chloride is evidently still more stable[25,30], but a very unstable quaternary salt is obtained by the action of acetyl chloride an 4-acetamidopyridine in oxolan[30].

Benzoyl chloride and quinoline form the adduct $C_9H_7N.2C_6H_5COCl$,[32] but equivalent quantities of the reactants generally yield a mixture of an *N*-benzoylquinolinium chloride and the hydrochloride of the base[33]†. It has not

†Reissert[34,35] was unable to isolate a product from the reaction of benzoyl chloride with quinoline, but obtained the corresponding "pseudobase" on attempting the Schotten–Baumann synthesis (with aqueous alkali).

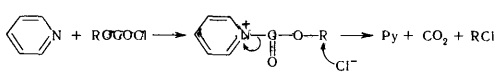
hitherto proved possible to isolate pure *N*-benzoylpyridinium chloride [8,12,17,32], but aroyl chlorides containing electron-accepting substituents in the ring form stable *N*-acylpyridinium salts [7,16]. Olah [36] has recently reported the preparation of *N*-acetyl-, *N*-propionyl-, and *N*-benzoylpyridinium hexafluoroantimonates by acylating pyridine with solutions of carboxonium salts in sulphur dioxide. *N*-Nitro- and *N*-nitroso-pyridinium fluoroborates have been prepared similarly [37]. Information on salts of pyridinium bases, benzoyl chloride, and Lewis acids will be found in Ref. 31.

The adducts formed by pyridine, quinoline, and isoquinoline with carbamoyl chlorides, e.g. (V), are very stable [38-43]. Similar salts have been obtained also with 4-methylpyridine, 3,5-dimethylpyridine, and nicotinamide [42,44,45].



Pyridine and its homologous react with imidoyl chlorides of the type (o-$CH_3C_6H_4N:CCl)_2$, $CH_3COCCl::NNHAr$, [46,47] and $ArNHN:CClCOOR$ [48] to form stable compounds (VI)–(VIII).

According to the patent literature [49-56] adding carbonyl chloride, perchlorocarbonates, or alkyl chlorocarbonates to pyridine or 2-methylpyridine in benzene results in the rapid formation of precipitates containing 2 moles of base per mole of acylating agent, which react smoothly with water and aliphatic alcohols to produce symmetrical or unsymmetrical carbonates [57]. Repeated observations have since been made of the formation of adducts of pyridine, 2-methylpyridine, and quinoline with ethyl chlorocarbonate [58-63], but the products could not be isolated in a pure form. The adducts decompose when the temperature is raised. Carré has studied the breakdown of various chlorocarbonates in pyridine and quinoline [60,64,65], and demonstrated the high catalytic activity of the first of them:

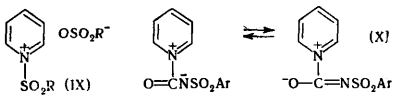


Information is available [66,67] on the reaction of carbonyl chloride with quinoline and 4,4′-bipyridyl.

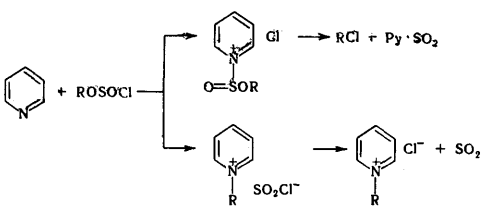
Similarly to the above example with acetyl chloride, treating 4-dimethylaminopyridine with t-butoxycarbonyl chloride in dry ether at 0°C yields the corresponding *N*-acyl salt [68].

Pyridine, quinoline, isoquinoline, and 4-methylpyridine readily form adducts with various substituted arenesulphonyl chlorides $RC_6H_4SO_2Cl$. [69-72] The stability of such salts diminishes in the sequence—isoquinoline, pyridine, quinoline [70]—and 2-methylpyridine probably does not react at all [69,74]. With polysulphonyl chlorides the reaction may cease on the replacement of one chlorosulphonyl group [71]. It has also been reported that *p*-acetamidobenzenesulphonyl chloride does not react with triethylamine and pyridine in anhydrous acetone [74,75]. The enhanced stability of *N*-arenesulphonylpyridinium salts in comparison with the *N*-acyl salts is shown in the possibility of obtaining adducts (IX) from anhydrides of methane- and benzene-sulphonic acids [73,76].

It is interesting that the condensation of isocyanatosulphonyl chloride $OCNSO_2Cl$ with pyridine involves only the sulphonyl group [78]. Yet the reaction of nitrogen bases with arenesulphonyl isocyanates usually leads to betaines of the type (X): [77,79]

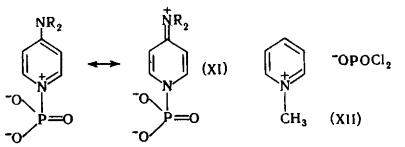


The reactions of pyridine and other tertiary amines with chlorosulphates $ROSO_2Cl$ have been surveyed in detail [80]. The normal products are alkyl halides and the complex $C_5H_5N.SO_3$, formed by breakdown of intermediate quaternary salts $ROSO_2\overset{+}{N}C_5H_5 + Cl^-$. [80,81] Pyridine reacts with alkyl chlorosulphinates to form mixtures of *N*-acyl and *N*-alkyl salts [82,83]:



The reactions of pyridine and its derivatives with thionyl chloride, sulphuryl chloride, chlorosulphuric acid, phosphoryl chloride, and other inorganic chlorides have also been studied [35,84,85].

Several quaternary pyridinium salts have been prepared containing a phosphoric-acid residue attached to the nitrogen atom. Treatment of 4-dimethylamino- and 4-morpholino-pyridines in benzene solution with excess of phosphoryl chloride and triethylamine followed by alkaline hydrolysis gave the salts (XI) as amorphous white powders [25,86]:



Analogous salts of 4-amino-, 4-isopropylamino-, and 4-dimethylamino-pyridines have been obtained by exchange with an *N*-phosphoryl salt of *N*-methylimidazole [25,87].

The possible formation of *N*-acyl derivatives also in the preparation of organophosphorus compounds by the reactions of acid chlorides and chloro-esters of phosphorus in the presence of pyridine and quinoline has been discussed [83,88], but few adducts have been isolated [84,89,90], and information on their structure is frequently lacking. The reaction may involve the O–R bond, not the phosphorus atom: thus the salt (XII) alone is formed from methyl phosphorodichloridate and pyridine [91].

A saltlike structure for the 1 : 1 adducts of pyridine with acyl chlorides was already suggested in the earliest papers [12,92]. Such a structure is indicated by the insolubility of the adducts in most non-polar solvents, the possibility of recrystallising the most stable compounds, the relatively high melting points, the reactions involving exchange of the anion, and the rapid and unambiguous acylations involving such adducts. Alternatively it was postulated that these adducts were complexes or even molecular compounds. It can now be accepted that the adducts are ionic structures with the acyl group attached to the nitrogen atom of the pyridinium ring and the halogen acting as counter-ion. This is based on the results of electrical conductivity measurements, polarography, heats of mixing, acid–base titrations, kinetic methods,

and ultraviolet, infrared, and nuclear magnetic resonance spectroscopy.

Paul and his coworkers [9,15,29,32,38,93] made visual and conductometric titrations of pyridine, methylpyridines, quinoline, and dimethylaniline in acetyl and benzoyl chlorides with titanium tetrachloride, tin tetrachloride, or arsenic pentachloride. The nitrogen heterocycles reacted with the Lewis acids (acceptors of the chloride ion) completely, giving one or two neutralisation points corresponding to the formation of "normal" and "acid" salts [15,29,93,94]. The same workers found appreciable electrical conductivity in solutions of the three methylpyridines and quinoline in acetyl chloride, although rather less than with benzyltrimethylammonium chloride. A mixture of pyridine and acetyl chloride in liquid sulphur dioxide at −30°C exhibited a complicated conductance corresponding in magnitude to the purely ionic salts $(C_2H_5)_3NH^+SbCl_6^-$ and $R_3O^+SbCl_6^-$. The strongly ionising solvent plays a definite part in this, of course.

Holeček [96] studied the electrical conductivity of solutions of pyridine, isoquinoline, quinoline, and acridine in acetyl bromide, and showed that they form adducts $[B.CH_3CO]^+Br^-$, which behaved as univalent electrolytes. The ionisation constants were 0.7×10^{-4} for the pyridine salt and $1.8–1.9 \times 10^{-4}$ for the quinoline, isoquinoline, and acridine salts. Korshak et al. [97] have recently determined potentiometrically the thermodynamic equilibrium constants for the reaction of benzoyl chloride with pyridine and triethylamine in acetonitrile. The higher value for pyridine than for triethylamine (1.2×10^{-4} and 2×10^{-5}), in spite of the less basic character of the former, was attributed to resonance factors enhancing the stability of the *N*-benzoylpyridinium salt.

The possibility of mesomerism is slight with unsubstituted *N*-acylpyridinium salts [95,98], and this is responsible for their relative instability.

1-Dimethylcarbamoylpyridinium chloride (V) behaves in aqueous solution as a strong electrolyte. This applies also to acetonitrile solutions, but the picture is then complicated by partial breakdown of the salt into its components as a result of solvolysis [42]. The conductance of solutions of *N*-diphenylcarbamoylisoquinolinium chloride in nitrobenzene has been studied recently [43]. A solution of benzoyl chloride and pyridine in 89% aqueous acetone conducts electricity and is able to benzoylate butylamine [99]. Although arenesulphonyl chlorides do not conduct electricity in nitromethane or liquid sulphur dioxide, considerable conductance is observed in the presence of pyridine and quinoline.

Paul [100,101] determined calorimetrically the heats of dissolution of 2-methylpyridine, quinoline, and dimethylaniline in acetyl and benzoyl chlorides, and also their heats of neutralisation by Lewis acids. The dependence of the enthalpy change on the concentration of the base showed in all cases a characteristic break at low concentrations, indicating increased dissociation of the solvates under these conditions.

On polarography in pyridine, acylpyridinium salts exhibit a typical reduction curve with two waves (half-wave potentials 0.1–0.7 and 1.3–1.7 V). [16,17,102] Similar results were obtained with mixtures of benzoyl or *p*-methoxybenzoyl chloride with pyridine, which suggests in these cases also the formation of acylpyridinium salts *in situ* [16,17].

Detailed studies have been made of the infrared spectra of *N*-acetyl- and *N*-propionyl-pyridinium chlorides [16–18], acetyl-pyridinium, -quinolinium, -isoquinolinium, and -acridinium bromides [103], and adducts of acetyl and benzoyl chlorides with pyridine and 3- and 3-methylpyridines [104]. Several papers mention the positions of individual bands in the infrared spectra of other salts [30,31,42,66,105,106].

Most workers note a shift in the carbonyl-stretching band (1760–1800 cm^{-1}) to higher frequencies (1790 to 1804 cm^{-1}) with *N*-acylpyridinium chlorides derived from aliphatic and aromatic acids. Such displacement indicates the presence of a positively charged cyclic nitrogen atom beside the carbonyl group. Although a larger shift is to be expected from the difference in values of the Taft constants for NR_3^+ and Cl, the replacement of Cl in the acyl chloride by NR_3^+ has the opposite effect by increasing the C—C—N angle [18]. This has been found also with aliphatic acylammonium salts [95,107–109].

Data on the ultraviolet spectra of solid *N*-acylpyridinium salts are restricted to examples of 1-acetyl-4-dialkylaminopyridinium chlorides [30,31], 1-dimethylcarbamoylpyridinium chloride [42,68], and 4-alkylamino-1-phosphorylpyridinium salts [25,86]. Conversion of a nitrogen base into an *N*-acyl salt is accompanied by a considerable bathochromic shift, while the absorption characteristic of the aromatic ring is maintained. Kinetic studies of the hydrolysis of acetic anhydride and reactions involving the transfer of acyl [20,110] have recorded the ultraviolet spectra of *N*-acyl derivatives of alkylpyridines obtained *in situ*, the differential spectra corrected for absorption by pyridine and its salt giving for acetylpyridinium λ_{max} = 272 and 255 nm (ϵ = 4300 and 7000).

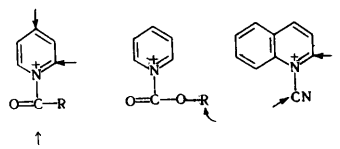
Data on the proton magnetic resonance spectra of these compounds are also fragmentary [25,30,36,37,42,68,86]. The chemical shifts of the 2-, 3-, and 4-protons of 1-acetyl-, 1-propionyl-, and 1-benzoyl-pyridinium fluoroantimonates in liquid sulphur dioxide (at −60°C) increase with increase in the accepting properties of the acyl group in this sequence [36] (cf. spectra of quaternary pyridinium salts [111]), which correlates with hetarylation experiments on these salts [112]. The chemical shifts also agree well with the expected values for pyridinium, *N*-nitrosopyridinium, and *N*-nitropyridinium fluoroborates [37].

On passing from 1-acetyl-4-dimethylaminopyridinium chloride to its analogue containing the less strongly electron-accepting 1-t-butoxycarbonyl group we observe the same decrease in chemical shift for both 2- and 3-protons [30,68], although the infrared spectra indicate that the charge on the former is more strongly delocalised (νCO = 1755 and 1770 cm^{-1}). It is more difficult to analyse the nuclear magnetic resonance spectra of 4-amino-1-phosphorylpyridinium [25,86]. The contribution of immonium forms to resonance stabilisation would probably be greater for the dimethylamino- than for the isopropylamino-group (cf. XI). This diminishes appreciably the deshielding of the 2-protons in the former case, which is shown in the chemical shifts (8.2 and 8.6 ppm). The opposite relation is found for the 3-protons.

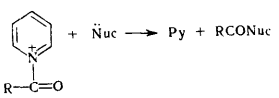
In view of the possible involvement of *N*-acylpyridinium salts in acylation by acid anhydrides, many attempts have been made to detect by infrared and n.m.r. spectroscopy their presence in solutions of pyridine and an anhydride [19,112–116]. In non-polar solvents such as carbon tetrachloride no significant changes are observed in the spectra when pyridine is mixed with acetic and trifluoroacetylacetic anhydrides [113,114,116]. Similarly, the ultraviolet spectra of pyridine–acetic anhydride mixtures in cyclohexane are additive [113]. In the acetic anhydride–1,4-diazabicyclo[2,2,2]octane system, however, formation of the corresponding *N*-acyl salt can be established from the infrared and n.m.r. spectra or refractometrically [114].

III. REACTIVITY OF *N*-ACYLPYRIDINIUM SALTS AND CORRESPONDING FUSED BENZO-DERIVATIVES

N-Acylpyridinium salts and the corresponding fused benzo-analogues contain more than one reaction centre both in the ring system and in the acyl group. In conformity with this their reactions can be divided into six main types.

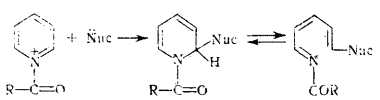


1. Attack by nucleophilic reagents on the exocyclic carbon atom attached to the heteroatom leads to elimination of the nitrogen base and transfer of the acylating group to a component of the medium (acylation of water, alcohols, amines, acids, etc.) or to the gegenion (solvolysis)[42,102]:



We must include here reactions in which the acyl group is transformed—hydrolysis of nitrile to amide[106], decomposition of acyl salts of chlorocarbonates, chlorosulphates, etc. effected by attack by the gegenion (Cl^-) on the C–O–R bond[55,65,80], formation of ketens (attack by the pyridine ring on an α-proton relative to the carbonyl group)[117,118].

2. Attack by a nucleophilic reagent at the 2-carbon atom of the heterocycle, yielding so called "pseudobases" or more often opening the ring (Zincke–König reaction)[3,119]:



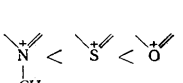
3. Addition of nucleophilic reagents at the 2- and 4-positions of the heterocyclic ring results in the formation of 1-acyl-1,2(or 4)-dihydro-derivatives or, if these are unstable, to substituted heterocycles (after detachment of the acyl groups and aromatisation). These reactions, which can be combined under the name "hetarylation", are of the greatest interest, since they permit the preparation of various compounds, including naturally occurring substances, that are often inaccessible by other methods.

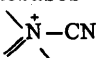
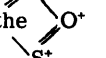
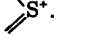
4. Reactions involving one-electron transfer to the *N*-acyl salts followed by dimerisation of the radicals (Dimroth reduction)—or radical hetarylation.

5. Reactions involving methyl or methylene side-groups activated by the presence of the *N*-acyl group[17,28,120,121].

6. Electrophilic substitution in salts of *N*-acylated heterocyclic cations[122,123].

Reactions of types 3–5 are known for various aromatic and heterocyclic cations—tropylium, cyclopropenylium, pyrylium, thiapyrylium, etc.—which is evidence of the similarity of their π-electron systems. The effect of substituents is transmitted through the positively charged nitrogen atom[111,124], although probably not by conjugation but purely by induction. In this connection the sequence of increasingly strong electron-accepting properties of the heteroatoms



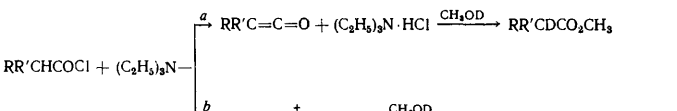
found for pyrylium, thiapyrylium, and pyridinium salts[125] should change significantly if a strongly electron-accepting substituent is attached to the cyclic nitrogen atom. By comparing values of pK_{ROH} for a series of pseudobases Johnson has shown[126] that the acceptor effect of the  group in *N*-cyanoquinolinium approaches that of the  group in benzopyrylium and exceeds the effect of .

1. Acylation in the presence of Pyridine Bases

Examples of the use of pyridine in the acylation of alcohols and phenols date from the 1890s (bibliography in Ref. 127), but pyridine was regarded initially merely as a substitute for alkali. The advantages and limitations of this method were studied on many hydroxy-compounds and acylating agents by Einhorn and Hollandt[127], and hence the term "Einhorn acylation" is encountered in the literature[128,129a–131a].

Acylation in pyridine is effective for alkali-sensitive compounds. Pyridine is a good solvent, and therefore acid chlorides can be replaced by acids with subsequent addition of chlorinating agents (e.g. carbonyl, thionyl, and benzoyl chlorides) or the experimentally more convenient acid anhydrides (especially acetic anhydride). Acylation in the presence of pyridine takes place also in acid media. Even under these conditions the acylpyridinium chloride is evidently formed[127]. The use of acetic formic anhydride or a mixture of formic acid with acetic anhydride and pyridine has recently been recommended for the formylation of aliphatic and cycloaliphatic alcohols[132]. Pyridine compounds also play an important part in the preparation of chlorocarbonic esters, carbonates, chlorosulphates, and several other compounds having mixed functions[51,55,80,133]. If the hydroxy-compounds are replaced by their alkoxides, only traces of pyridine are required, since it is regenerated in the course of the exchange reaction.

The high acylating power of individual *N*-acylpyridinium salts towards alcohols and phenols is confirmed by direct experiments[23,51,53,57]. Addition products of carbonyl chloride and pyridine bases[53,54,86] effectively phosgenate alcohols, phenols, naphthols, anilines, and cyclic imines. Although *N*-nitropyridinium fluoroborate is unsuitable for the nitration of aromatic compounds, it does *o*-nitrate water and alcohols[37]. There is indirect confirmation of the involvement of acylammonium salts in acylations[134,135]. Aliphatic acid chlorides react with CH_3OD in triethylamine to form a mixture of $RR'CDCOOCH_3$ and $RR'CHCOOCH_3$, produced by two competitive reactions[136]:



Path (*a*) predominates or is the sole reaction with acid chlorides that are sterically hindered at the reaction centre, since they have less effect at the stage of elimination of the α-hydrogen atom (acid–base equilibrium) than on formation of the quaternary acyl salt. The percentage inclusion of deuterium in acetyl halides falls in the sequence $Cl > Br > I > CH_3COO$, i.e. with improvement in the so called "leaving group"[137–139].

Such data are lacking for esterification in pyridine, but the weakness of pyridine bases compared with triethylamine, together with the greater resonance stabilisation

of *N*-benzoylpyridinium than of benzoyltriethylammonium [95,97,98], leads us to expect reaction (*b*) alone, at least with sterically unhindered acid chlorides. Individual monographs, however, have hitherto assigned to pyridine bases the role merely of participation in acid–base equilibria (proton acceptor) [140].

The preparation of arenesulphonates of alcohols and phenols is also often conducted in pyridine [6,129b,130a,131b,141,142], again with intermediate formation of arenesulphonylammonium salts [70,71,73,75,76]. In most cases higher yields are obtained than with aqueous sodium hydroxide. Sometimes, however, the resulting esters (especially of lower alcohols) alkylate the pyridine to form alkylpyridinium salts, which lowers the yield. It has therefore been recommended that pyridine should be replaced by 2,6-dimethylpyridine, although this slows down the process significantly [143]. In the arenesulphonylation of 1,4- and 1,5-diols, certain amino-alcohols, and γ-hydroxy-amides the intermediate monosulphonate may be cyclised with the formation of various oxygen and nitrogen heterocycles (see Refs. 131b, 144, and 145 and the bibliography given there). Kröhnke has prepared aldehydes via quaternary pyridinium salts [6,141].

Systems comprising a carboxylic acid and pyridine with benzenesulphonyl or toluene-*p*-sulphonyl chloride have an acylating, not an arenesulphonylating, action [145]. They yield esters with primary and secondary alcohols, phenols, and polyphenols. This method is mostly used for the acylation of tertiary alcohols liable to dehydration. The reaction is assumed to involve the formation of acid anhydrides *in situ*, with regeneration of the arenesulphonyl chloride:

$$(RCO)_2O \xrightarrow[\text{TosCl + Py}]{R'OH} RCO_2H + RCO_2R'$$

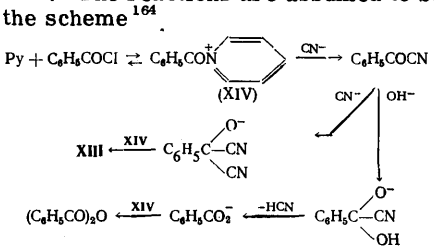
For the analytical application of acylations see Refs. 114, 128, 140, and 146–150.

Similarly, *N*-acylpyridinium salts react with carboxylic acids to form anhydrides or mixed anhydrides:

$$\left[RCO\text{-}\langle\text{pyridinium}\rangle\right] Cl^- + R'CO_2H \rightarrow RCOOCOR' + Py \cdot HCl$$

This reaction, discovered as early as 1892, [92,151–153] has not lost its importance for the preparation of anhydrides even at the present time. To obtain symmetrical anhydrides it is sufficient to act with water on a mixture of the acid chloride and pyridine (better in an inert organic solvent). No advantage is generally obtained by using a mixture of the acid chloride and the carboxylic acid or alkaline additives (sodium carbonate, barium carbonate, sodium hydrogen carbonate) to combine with the hydrogen chloride. At various times this method has been used to obtain anhydrides of substituted benzoic acids [8,92,151,154–157], cinnamic acid [151], several aliphatic acids [8,40,151,154,156] including α-chloro-acids, and certain heterocyclic acids [8]. Acid chlorides can also be employed *in situ*, by introducing into a solution of pyridine and the acid either carbonyl chloride or thionyl chloride [53,158,159] or a mixture of an arenesulphonyl chloride and an acid [145]. The possibility that solid adducts of acyl chlorides and pyridine are involved in these condensations has been demonstrated many times [8,22,23,40,53,160]. Mixed anhydrides are usually prepared by adding acetyl and benzoyl chlorides or chloroformic esters to a mixture of a relatively unreactive acid and pyridine in ether or benzene, and then treating with ice [153,161,162].

Still greater simplifications have recently been introduced into the preparation of anhydrides [163]. If the acid halide and the reaction product are comparatively stable towards water, the chloride can simply be added to an aqueous solution of an equivalent quantity of the sodium salt of the acid in the presence of catalytic quantities of pyridine, 3-aminopyridine, or pyridine *N*-oxide. Some decrease in yield occurs with methylpyridines, while the reaction is not catalysed by 2- and 4-aminopyridines, 2-fluoropyridine, or any pyridinecarboxylic acid. Aqueous *N*-benzoylpyridinium chloride acylates also salts of certain inorganic acids: e.g. benzoyl azide is obtained in 85% yield with sodium azide. An analogous reaction was described [8] with hydrogen sulphide in petroleum ether at −20°C. When benzoyl chloride is shaken with aqueous potassium cyanide and pyridine (1 : 1 : 1), however, the resulting benzoic anhydride is accompanied by the so called "dimer of benzoyl cyanide" $R.C_6H_4CO.O.C(CN)_2.C_6H_4.R$ (XIII); with chlorides of substituted benzoic acids dimeric products are formed as byproducts or as the main products [163,164]. The reactions are assumed to be represented by the scheme [164].



The controlled hydrolysis of acid chlorides in the presence of pyridine has been employed also in the preparation of tetra-alkyl pyrophosphates and mixed anhydrides of phosphoric acid [88,165–167]. Pyridine can be replaced by isoquinoline; both the yield and the quality of the products diminish with 2-methylpyridine; and no reaction occurs with quinoline.

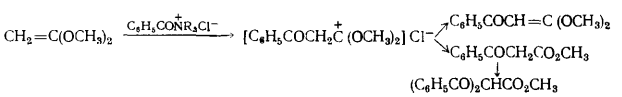
Acyl salts of pyridine and other tertiary amines are able to split off the acyl group under the influence of ethers [168], which resembles the process occurring in alkylpyridinium salts. Thus veratrole, anisole, and diphenyl ether are smoothly decomposed when heated with acylpyridinium chlorides to 220°C, with the formation of esters of the phenols [7]. An interesting preparation of an acyloin has been described, from benzothiazol-2-aldehyde in the presence of acetic anhydride and pyridine, which evidently involves the intermediate *O*-acylation of the *N*-acetylpyridinium ion. Under these conditions chloral forms chloral hydrate diacetate in quantitative yield [169]. The reaction of benzoyl halides with aldehydes in the presence of pyridine has been described [170].

The acylation of amines by acylpyridinium salts is of no great preparative interest, since reactions with acid anhydrides usually proceed satisfactorily even in the absence of a catalyst, but aroylation in pyridine is applicable to amines of enhanced NH acidity [128,129c,130b]. Acylation by acetic anhydride in pyridine is used more widely in the analysis of amines [128,147,150,171,172]. Application of the method to the preparation of sulphonamides has been discussed [173,174]. Both pyridine and triethylamine have an unfavourable effect on the molecular weight of the products in the preparation of polyamides from isophthaloyl and terephthaloyl chlorides and diaminodiphenols [175], which was attributed to catalysis of *NO*-transacylations. The part played by individual *N*-acyl- and *N*-arenesulphonyl-pyridinium salts in the acylation of amines has been discussed [22,39,53,68,76].

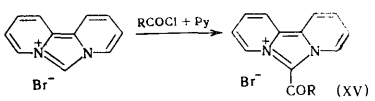
The considerable acylating power of acylpyridinium chlorides is especially clearly developed in reactions

with amides of carboxylic acids: mono- and di-acylation of the amide or dehydration to the nitrile takes place depending on the nature of the acyl halide and the amide [176]. Chlorides of weak acids usually form monoacyl derivatives, those of stronger acids diacylate the amide, and chlorides of strong acids exert only a dehydrating action. For example, 3,5-dinitrobenzoyl chloride in pyridine has been proposed for the quantitative dehydration and hence analysis of amides [128,177]. The reaction goes especially smoothly with benzenesulphonyl and toluenesulphonyl chlorides [145,178]. Sulphonamides can be acylated similarly [179].

Organic compounds can undergo *C*-acylation by acid chlorides in the presence of pyridine, although in most cases the reaction is not regarded as involving initial formation of *N*-acylpyridinium derivatives‡. The action of benzoyl chloride on 1,1-dimethoxyethylene in triethylamine or pyridine, for example, yields a mixture of three products [181]:



Certain nucleophilic heterocyclic nitrogen compounds readily undergo acylation at a carbon atom [182,183]:



The product (XV: R = C_6H_5) can also be obtained by cyclising 1-phenacyl-2-pyrid-2′-ylpyridinium bromide by the action of toluene-*p*-sulphonyl chloride in boiling pyridine [182]. Information has been published on the possible acylation of alkyl groups by certain heterocycles [184,185].

Various β-dioxo-compounds and ketones capable of keto–enol tautomerism generally give *O*-esters—not the *C*-acyl derivatives usually obtained by the acylation of sodium enolates—by the action of *N*-acylpyridinium salts *in situ* [186,187]. Reaction takes place under very mild conditions, sometimes at room temperature or even in the cold. However, Dieckmann et al. [188,189] observed that a *C*-derivative was also present in the acylation of cyanoacetic ester and dihydroresorcinol in pyridine. β-Aminocrotonic ester and its analogues yield *N*-acylated and/or *C*-acylated products depending on the acyl chloride [190]. The use of other tertiary amines generally leads to the formation predominantly of *C*-acylated products [98,181,191,192].

The first attempts to explain the role of pyridine in such reactions were made by Doering and McEwen [98,192,193]. The interaction of benzoyl chloride, pyridine, and acetophenone yielded 1-benzoyl-1,4-dihydro-4-phenacylpyridine (XVI) and *C*-benzoylacetophenone. It was suggested that the *N*-benzoylpyridinium salt attacks acetophenone simultaneously at $C_{(2)}$ and $C_{(4)}$, forming the stable (XVI) and 1-benzoyl-1,2-dihydro-2-phenacylpyridine, which rearranges to the *O*-adduct via a geometrically favourable quasi-six-membered transition state [98,193]. Results of a kinetic investigation of this system were interpreted similarly [194].

Recent results indicate [195,196] that the reaction of acetoacetic ester with benzoyl chloride in pyridine, triethylamine, 2-methylpyridine, and 2,6-dimethylpyridine gives only the *O*-benzoate (but the yield decreases in the above sequence). The reaction is of the first order with respect to both components with inverse proportionality to the chloride-ion concentration. All reactions are slower in non-polar solvents. Acylation is assumed to proceed via the keto-form of acetoacetic ester without involving intermediate products of addition to the pyridine ring; in the case of benzoylation the slow stage is formation of a benzoylammonium salt, which is hindered when the nitrogen atom is shielded. Further research is obviously necessary before a final solution will be obtained to the problem of the mechanism of the *O*-acylation of β-keto-enols.

2. Nucleophilic and General Base Catalysis by Pyridine Bases

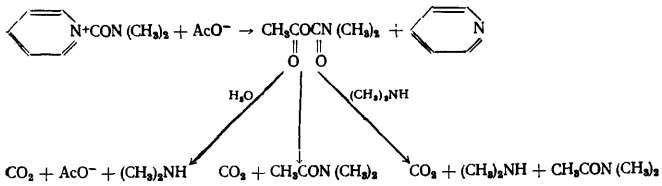
The study of reactions involving the migration of an acyl or a phosphoryl group in systems comprising an *N*-acylpyridinium ion and a nucleophile not only has enabled the kinetic and thermodynamic factors governing the stability of salts of *N*-acylated heterocyclic cations to be estimated (although such data are still too few), and the influence of structural and steric factors in nucleophilic reagents on their reactivity to be assessed, but has also introduced some clarity into our understanding of the mechanisms of nucleophilic reactions and certain problems of nucleophilic catalysis [137–139]. Furthermore, *trans*-acylations and *trans*-phosphorylations are directly involved in problems of biochemistry and bio-organic chemistry [137,138,197].

Nucleophilic catalysis implies attack by a nucleophile on a substrate (ester, anhydride, acid chloride), leading to the formation of an unstable intermediate structure, which then breaks down either spontaneously, catalytically, or under the influence of a weaker nucleophile to give the final product and regenerate the catalyst. General base catalysis covers the exchange of a proton between a base and a substrate at the rate-determining stage of a reaction. The former type of catalysis is regarded as typical of acid derivatives having a "good" leaving group (halide, acetate, radical of an alcohol of high pK_a) [198–200], and the latter of so called inactivated esters [198]. Among tertiary amines nucleophilic catalysis is typical of pyridine, its 3- and 4-methyl (polymethyl) derivatives, and isoquinoline; 2-methyl derivatives of these heterocycles and often quinoline itself are weak catalysts, despite their high basicity, because of steric hindrance of the nitrogen atom. The applicability of Brønsted's relation between lg k_B and pK_a to pyridines substituted at all positions in the ring is usually interpreted as evidence of general base catalysis [139]. The isotope effect on passing from water to deuterium oxide as solvent is k_H/k_D = 2–3 for most reactions, including acid–base equilibrium, and is close to unity for the nucleophilic hydrolysis of derivatives of organic acids [201–204].

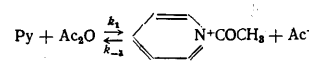
N-Dimethylcarbamoylpyridinium chloride (V) is stable in acidified aqueous solutions (pH 1–5), but undergoes rapid decomposition catalysed by the hydroxide ion when the solution is made alkaline [102]. On the addition of hydroxylamine hydrochloride, imidazole, sodium azide, sodium fluoride, or the formate ion, direct nucleophilic

‡The Dakin–West reaction involves *C*-acylation at an intermediate stage [180].

substitution occurs at the nitrogen atom. Hydrolysis of (V) is accelerated also by components of the buffer solution (e.g. the acetate ion):



Comparing the behaviour in aqueous solutions of solid *N*-acetylpyridinium chloride and of systems formed by acetic anhydride with pyridine bases, Jencks and Fersht[20,110,205] conclude that appreciable quantities of the *N*-acylpyridinium and its homologues may accumulate in aqueous buffer solutions. Increasing the concentration of the acetate ion lowers the quantity of acetylpyridinium formed by raising the rate k_{-1} of the reverse reaction. Pyridine has the opposite effect:



4-Substituted pyridines show a dependence on the basicity of the nitrogen atom (Table): the quantities $\lg k_1$ and $\lg K_{eq}$ correlate satisfactorily with pK_a of the base.

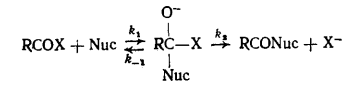
Relations between structure and reactivity in *N*-acetylpyridinium ions[20].

Base	pK_a of base	k_1, mole^{-1} s^{-1}	K_{eq}	Hydrolysis rate const. k_2, mole^{-1} s^{-1}		$-\Delta F^{\circ}$ of hydrolysis
				water	acetate ion	
Pyridine	5.51	84	0.092	6.9	910	18.31
4-Methylpyridine	6.33	490	1.86	2.3	262	17.67
3,4-Dimethylpyridine	6.79	1160	9.67	1.5	120	17.33
4-Methoxypyridine	6.82	935	31.2	0.4	30	16.65
Imidazole	—	—	2950	—	—	14.05

The acetylation of anisidine and *p*-toluidine by acetic anhydride in the presence of pyridine in aqueous solution is pseudo-unimolecular, with a rate constant independent of the type or concentration of arylamine. Hence the migration of an acyl group passes through a limiting stage in which the acetylpyridinium ion is formed, followed by rapid reaction with the nucleophile[20,110]. Thus these amines at concentrations of $(5–10) \times 10^{-4}$ M compete successfully with water, which illustrates the high selectivity of acetylpyridinium ions for the type of nucleophilic agent[20,206–208]. Corresponding comparative data for water and acetate ions (Table) are well correlated by Brønsted's equation ($\beta = -0.5$ and 0.68 respectively).

Values of k_2 for the nucleophilic substitution of the four *N*-acetylpyridinium ions in the Table with thirteen *O*- and *N*-nucleophiles (alkoxide and phenoxide ions, aliphatic amines, cyclic amines, and hydrazines) reveal a decrease in sensitivity ("levelling") of the acetylpyridinium ions to the basicity of the attacking nucleophile as this quantity increases[205]. The Brønsted constants fall in a series of *O*-nucleophilic reagents, from 0.9 for the acetate ion to 0.2 in alkoxides. For amines of moderate strength $\beta = 0.9$, after which it drops sharply. "Levelling" is absent in the less reactive acetylimidazolium ion.

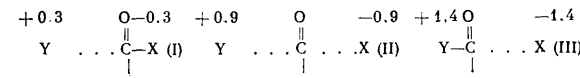
The scheme which has now been worked out for reactions at the carbonyl group in derivatives of carboxylic acids postulates the equilibrium formation of a tetrahedral addition product, which then breaks down:



(Nuc = neutral molecule or anion)

With strongly basic nucleophiles the intermediate adduct is rapidly converted into the final products, and when $k_2 \gg k_1$ the addition stage (k_1) is rate-determining. The dependence of the reactivity of the acid derivative RCOX on the basicity of the leaving group X will then be minimal. With weaker nucleophiles k_{-1} is relatively larger, and cleavage of the adduct begins to limit the overall rate of the process. Bender demonstrated that the second stage could rightly be chosen as determining the rates of reactions involving inactivated esters[137,138]. These concepts are often used also to explain the regular features of nucleophilic substitution at a quinquevalent phosphorus atom. However, isolated reactions may occur at the carbonyl group and at the phosphorus atom without necessarily involving intermediate formation of addition products.

Jencks[205,208] has proposed a new classification of acyl migrations, which depends on the strength of the nucleophile and on the values of β for the nucleophile and for the leaving group:



(the numbers denote the change in the charge on the attacking or leaving group of atoms compared with the change of 1.7 for the complete reaction). The first class comprises reactions of strongly basic nucleophilic reagents with acylating compounds having good leaving groups (i.e. with *N*-acetylpyridinium ions); they have an unsymmetrical transition state with relatively little formation of new bonds and destruction of old bonds (termed an early transition state). These reactions bear a definite resemblance to S_N2 substitutions at a saturated carbon atom.

The third class, on the other hand, includes reactions of feebly basic nucleophilic reagents and compounds with poor component groups. If the existence of an intermediate tetrahedral adduct is assumed, its cleavage determines the overall rate of the reaction. The second class covers many reactions where the transition state is more or less symmetrical with respect to the attacking and leaving groups ($\beta = 0.7–1.0$). It includes also reactions of acetylpyridinium ions with amines where the two groups have closely similar pK_a values. Formation of a tetrahedral intermediate structure is difficult to predict here.

The aminolysis of 4-substituted *N*-phosphorylpyridinium ions (XI) in aqueous solution by aliphatic and heterocyclic amines and imines having pK_a = 2.6–10.8 shows slight sensitivity to the basicity of the attacking group (Brønsted nucleophilic constant in the range 0.2–0.3)[86]. The value of k_2 for the nucleophilic reagent is strongly dependent on the nature of the leaving group in (XI).

Information has been published on the hydrolytic stability of several other solid *N*-phosphorylpyridinium salts and their *N*-acyl analogues[25,30,31,68,86,110]. In both series

the rate of hydrolysis decreases with increase in the basicity of the 4-substituent, as a consequence of delocalisation of the positive charge through the longer conjugated chain. The contribution of onium or immonium forms should, of course, increase in the sequence $\overset{+}{H}O=$, $\overset{+}{N}H_2=$, $R\overset{+}{N}H=$, $R_2\overset{+}{N}=$. In conformity with this the resonance-stabilised 1-acetyl-4-dimethylaminopyridinium chloride is hydrolysed more slowly than the unsubstituted *N*-acetylpyridinium chloride with a rate ratio of 1/2000.

Nucleophilic catalysis by pyridine bases has been proved for the hydrolysis of acetic anhydride (in water [113,209], an acetate buffer [206,210,211], and aqueous-organic mixtures [199,212,213]), several mixed anhydrides [113,214], various acid chlorides in 89% aqueous acetone [99], acetyl fluoride [207], and arenesulphonyl chlorides in water [215]. Another model in kinetic investigations of hydrolysis is provided by *p*-nitro- and 2,4-dinitro-phenyl acetates [216-218], and certain sulphonic esters [219-221]. Nucleophilic catalysis by various pyridine derivatives of the methanolysis of 2,4-dinitrophenyl acetate, picryl acetate, and picryl benzoate, certain enol acetates, and arenesulphonyl chlorides has been investigated [222-227]. In all cases the results agree satisfactorily with the general scheme of catalysis

$$RCOX + B \rightleftarrows \left[\begin{array}{c} O^- \\ | \\ RCX \\ | \\ B \end{array}\right] \rightleftarrows \left[\begin{array}{c} R\overset{+}{C}B \\ \| \\ O \end{array}\right] X^- \xrightarrow{Nuc} RCONuc$$

(Nuc = H_2O, CH_3OH, etc.)

The hydrolysis of acetic anhydride is highly sensitive to the acetate-ion concentration [206,210,211,213]: e.g. the catalytic effect of pyridine is completely inhibited in the presence of a buffer comprising 1.06 M acetate plus 0.54 M acetic acid in 40% dioxan [206]. On the other hand, the extraordinarily high isotope effect of $k_{H_2O}/k_{D_2O} = 5 \pm 1$ has been found for hydrolysis in acetate buffers [210,211]. This could be explained theoretically on the assumption of solvolysis of the acetylpyridinium ion as the rate-determining stage [201-203].

Transfer from water to methanol as solvent slows down the solvolysis of acetic anhydride by a factor of 10^5 [219], and in the latter solvent pyridine is only slightly more active than the acetate ion as a catalyst. Hydrolysis catalysed by pyridine is retarded with increase in the concentration of dioxan in mixtures with water [206,213]; it is supposed that decrease in the polarity of the solvent is accompanied by a significant fall in the equilibrium constant K_{eq} of the stage of formation of the *N*-acetylpyridinium ion (decrease in k_1 with simultaneous increase in k_{-1}).

Study of the hydrolysis of several chlorides of carboxylic acids in 89% acetone in the presence of butylamine, trimethylamine, triethylamine, pyridine, and trimethylpyridine distinguished [99] those reacting by an S_N2 mechanism (through formation of *N*-acyl salts) from those reacting by unimolecular ionisation (S_N1). The rates of hydrolysis of piperidinocarbonyl, *NN*-di-isopropylcarbamoyl, and 2,4,6-trimethylbenzoyl chlorides remained almost unchanged in the presence of any of the amines, but acetyl, pivaloyl, benzoyl, and 2,4,6-trimethyl-3,5-dinitrobenzoyl chlorides showed a 10^5–10^7-fold acceleration in the presence of pyridine. The sequence of catalytic activity obtained for the tertiary amines

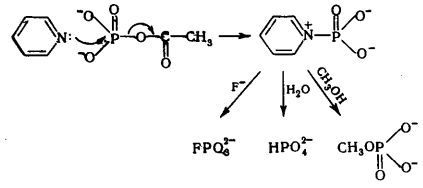
pyridine > trimethylamine > triethylamine > trimethylpyridine

is typical of nucleophilic catalysis.

The hydrolysis of benzenesulphonyl chloride in aqueous solution in the presence of ten pyridine derivatives having donor and acceptor substituents at positions 3 and 4 in the ring is well represented by the first-order equation $k_{obs} = k_w + k_b[B]$ [215,227]. The reaction is accelerated by the presence of donor substituents, and slowed down by acceptor substituents. Its sensitivity to the basicity of the nucleophiles is intermediate between the above cases of carbonyl compounds and phosphoric acids. It is postulated that, because of the greater polarisability of the sulphur atom, the bond may be formed in the transition state at a greater distance than for the carbon atom.

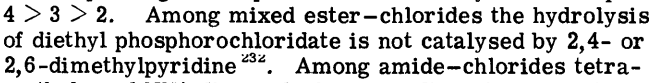
Various acid derivatives of phosphorus are of considerable interest in connection with the factors governing the possibility that hydrolysis may occur by mechanisms of general base and nucleophilic catalysis [197,228]. The relative reactivity of substrates may be affected not only by structural features but also by the pH of the solution (neutral molecule, mono- and di-anion).

In 1952 Koshland discovered that pyridine catalyses the hydrolysis of an acetyl phosphate in buffer solutions [19]. The list of nucleophilic catalysts was later extended when it was established that pyridine, 4-methylpyridine, triethylenediamine, and probably triethylamine attack the phosphorus atom preferentially, ensuring rupture of the phosphorus–oxygen bond, whereas trimethylamine, imidazole, and *N*-methylimidazole cause rupture of the carbon–oxygen bond [229,230]. The reactions were not catalysed by 2-methylpyridine, 2,6-dimethylpyridine, or 2,4,6-trimethylpyridine, which is consistent with the scheme



In the case of acetyl phenyl phosphate all the amines mentioned attack only the carbon atom, being catalysts of acyl migration.

Di-isopropyl and diethyl phosphorofluoridates are hydrolysed in a bicarbonate buffer 5–20 times as rapidly in the presence of 10 mole % of imidazole and pyridine derivatives [231]; with picolines the catalytic activity diminishes depending on the position of the methyl in the sequence 4 > 3 > 2. Among mixed ester–chlorides the hydrolysis of diethyl phosphorochloridate is not catalysed by 2,4- or 2,6-dimethylpyridine [232]. Among amide–chlorides tetramethyl- and *NN'*-dipropyl-phosphorodiamidic chlorides are hydrolysed at comparable rates in neutral or weakly acid aqueous solutions, the reactions being catalysed by 3,5-dimethylpyridine, pyridine, and 4-methylpyridine, but not by their 2-methyl analogues [200]. On the other hand, some catalysis by 2,6-dimethylpyridine has been found with *NN'*-diethylphosphorodiamidic chloride (XVII), obviously by the general base mechanism [232]:



Nucleophilic catalysis has been established for hydrolysis of the phosphorus-nitrogen bond in phosphoramidic [233-235] and *p*-chlorophenylphosphoramidic [236] acids. In neither case did 2-methylpyridine, 2,6-dimethylpyridine, or pyridine-2-carboxylic acid show appreciable activity. A test of six pyridine bases having $pK_a = 2.8$–6.0 gave satisfactory correlation of the Brønsted k_2 values ($\beta = 0.22$) [235]: i.e. the anions of these amides exhibit the same

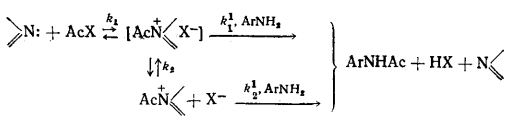
diminished sensitivity to the basicity of the nucleophile as does *N*-phosphorylpyridinium (XI)[86]. It was proved that intermediate *N*-phosphorylated pyridines may accumulate during the reaction.

A similar pattern of nucleophilic catalysis is exhibited by the hydrolysis of the dianions of *o*- and *p*-nitrophenyl phosphates substituted in the ring by hydrogen, chlorine, acetyl, and nitro[237-239]. In the last case the reaction with pyridine is highly sensitive to the leaving group ($\rho = -1.03$), and almost completely insensitive to the basicity of the attacking group. This probably belongs to the first type of nucleophilic reactions in the Jencks classification[205], with almost complete absence of a phosphorus–nucleophile bond in the transition state. Pyridine bases and other nitrogen nucleophiles do not catalyse the hydrolysis of monoanions of phenyl, *p*-nitrophenyl, and *o*-nitrophenyl phosphates[236,238], but acceleration has been found with *para*-substituted *o*-nitrophenyl phosphates[238]. The reaction mechanism is assumed to approximate to the classical $S_N2(F)$, with formation of new bonds and rupture of old bonds in the transition state (type II in the Jencks classification).

Among neutral phosphoric esters appreciable catalysis by pyridine derivatives and imidazole has been found with ethylene methyl phosphate[240]. In buffer solutions ring-opening takes place preferentially, and to a less extent hydrolysis of the P–OCH_3 bond. The reaction is only slightly affected by steric hindrance in the catalyst molecule (4-methylpyridine > 3-methylpyridine > 2,4-dimethylpyridine > pyridine > 2,6-dimethylpyridine) and has $k_{H_2O}/k_{D_2O} \simeq 2$. Hence it is an example of general base catalysis. Tetrabenzyl pyrophosphate has also been investigated[241,242].

Litvinenko and his coworkers[243-253] have made a long series of kinetic investigations on the benzoylation of arylamines in the presence of tertiary amines in aprotic solvents. Various substituted pyridines exhibit high catalytic activity, considerably exceeding those of triethylamine and dimethylaniline[243,244]. The sequence of relative efficiencies follows the increase in basicity (pK_a in water) of the pyridine base: 3-NO_2 < 3-Cl < H < 3-CH_3 < < 4-CH_3 < 4-$(CH_3)_2N$. The Hammett correlation gives $\rho = -3.74$, indicating that the catalytic effect is highly sensitive to structural changes in the catalyst; 2-methylpyridine and 2,6-dimethylpyridine are relatively ineffective. A similar correlation was made of the constants of the non-catalytic reaction k_0 and of the catalytic reaction k_B with respect to the structure of the arylamine $RC_6H_4NH_2$ ($\rho = -2.67$, -1.35): this corresponds to an increase in the effective charge on the reaction centre in the transition state for catalysis by pyridines. The ratio k_B/k_0 increases as the amine to be acylated becomes less strongly basic, which is typical of nucleophilic reactions. The influence of *meta*- and *para*-substituents in the benzoyl chlorides is less marked, and *p*-chloro-, *p*-methoxy-, and *p*-dimethylamino-benzoyl chlorides are appreciably less reactive than would be expected from the σ-values. It has been explained by postulating the possibility of direct polar conjugation of the substituents with the reaction centre, which is more strongly developed than in Hammett's standard series (dissociation of carboxylic acids[248]).

Kinetic confirmation has recently been obtained of the formation of *N*-acyl salts during the acylation of *p*-anisidine by *m*-toluene- and *p*-nitrobenzene-sulphonyl chlorides in nitrobenzene in the presence of pyridine[252,253]. Values of $k_{eff} = k_0 + k_{Py}[Py]$ fell as the reaction proceeded. This is possible if the intermediate adduct of pyridine with the arenesulphonyl halide (acyl halide) dissociates into ions, either partly or completely, in the strongly ionising solvent, so that two catalytic paths—interaction of the arylamine with an ion-pair or with an acylpyridinium cation—are available for the reaction. Accumulation of the gegenion (Br^-, Cl^-) will displace the dissociation equilibrium and then formation of the primary adduct, similarly to the hydrolysis of acetic anhydride and phenyl acetates[206,208]:



(for cases of acylation by means of acid anhydrides see Refs. 245 and 250).

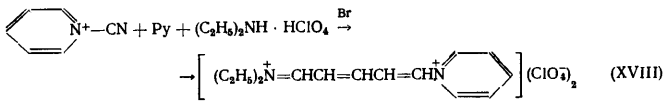
Bonner and his coworkers[116,254,255] have recently studied the kinetics of the trifluoroacetylation and the acetylation of several phenols and alcohols by trifluoroacetic, acetic, and trifluoroacetylacetic anhydrides in the presence of pyridine and its homologues in carbon-tetrachloride solution. The pyridines are assumed to have a dual function: they form hydrogen-bonded solvates with phenols, which makes the oxygen atom more strongly nucleophilic; and they solvate the leaving acetoxy-group in the transition state[116]. Calculation showed[254] that the hydrogen bonding of *p*-cresol and *p*-chlorophenol makes them more strongly nucleophilic by factors of 300 and 700 respectively. The degree of association of aliphatic alcohols with pyridines is small, which explains the slight catalytic effect (at 25°C). The isotope effects $k_H/k_D = 1.51$ and 1.40 obtained with deuterophenol and duetero-*p*-chlorophenol indicate that heterolysis of the oxygen–hydrogen bond is of some importance in acetylations[255].

Korshak et al.[105,256-259], in an investigation of low-temperature polyesterification in the presence of tertiary amines, also conclude that two mechanisms of catalysis—nucleophilic and general base—operate in the acylation of monohydric and dihydric phenols by acid chlorides. The latter mechanism is especially important with highly basic aliphatic amines (e.g. triethylamine) and highly acidic phenols[256]. Nucleophilic catalysis evidently predominates with sterically unhindered pyridine bases[257]. Thus the degree of conversion of phenol in the competitive benzoylation of phenol and methanol fell rapidly as pK_a decreased in the series of bases—tributylamine, triethylamine, ethyldimethylamine, 2,4,6-trimethylpyridine, 2-methylquinoline, 2-methylpyridine, isoquinoline, 3-methylpyridine, pyridine, and quinoline[258]. The solvent—its tendency to solvate the reactants physically and chemically—has an appreciable effect on the relative contributions of nucleophilic and general base catalysis. The quantity $q = (1 - x)/x$, where x is the conversion of phenol, has maximum values in dioxan, acetone, and nitrobenzene, and minimum values in benzene and dichloroethane.

3. Reactions of *N*-Acylpyridinium Cations with Opening of the Ring

Cleavage of the pyridine ring (the Zincke–König reaction[3,119-141]) with the formation of glutaconaldehyde or its anils or enamines is characteristic of quaternary pyridinium and benzopyridinium salts containing an electron-accepting substituent attached to the nitrogen atom. *N*-(2,4-Dinitrophenyl)- and *N*-cyano-pyridinium salts are cleaved in this way in the presence of alkali and various

aromatic amines and *N*-alkylanilines[260–265]. 4-Methylpyridine and 4,4′-bipyridyl have also been used successfully (but not 2-methylpyridine). Besides the use of cyanogen chloride and bromide, the König reaction has been accomplished by the action of sulphur trioxide and ethyl chlorosulphate[226], carbonyl chloride, phosphoryl chloride, phosphorus pentachloride, thiocarbonyl chloride, and other thio-acid chlorides[262,267]. The combined action of cyanogen bromide and triethylamine perchlorate on pyridine yields the simplest polymethine dye (XVIII)[268]:

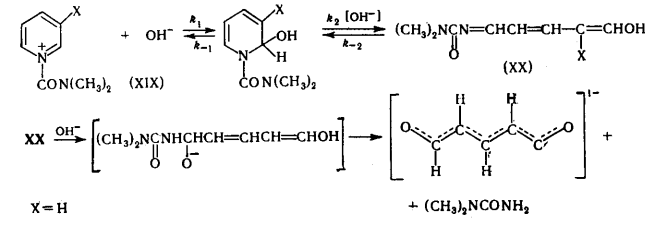


(XVIII)

The view arose (probably because of the predominance of acylation processes) that acyl chlorides were incapable of initiating cleavage of the pyridine ring[262,269]. However, such a process was observed on the interaction of diphenylcarbamoyl chloride with pyridine in the presence of alkali[40] and when adducts of pyridine with di-*o*-tolyloxalimidoyl chloride and with *N*-phenylbenzimidoyl chloride were treated with various aromatic amines in alcoholic solution[45]. A case in which alkaline benzoyl chloride was used was also reported[270], but the yield of glutaconaldehyde was not indicated. Derivatives of this aldehyde are obtained in almost theoretical yield when *N*-nitro- and *N*-nitroso-pyridinium ions are cleaved under alkaline conditions[119,270]. This reaction is a sensitive test for pyridine[74,271]. Other analytical applications of the König reaction will be found in Refs. 272–276.

The cleavage of *N*-acylpyridinium salts is facilitated by the presence of compounds containing active methyl or methylene groups. They condense with the cleavage product to give polymethine dyes. Thus aroyl chlorides and pyridine react comparatively readily with 2,3-dihydro-2-oxobenzofuran, oxindole, or 3-hydroxy-1-methylindole[63,277]. With cyanoacetic esters initial nucleophilic addition to acylpyridinium salts is followed by opening of the pyridine ring at $C_{(2)}$[278].

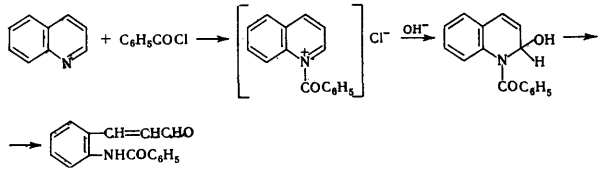
Kinetic investigation of the cleavage of *N*-dimethylcarbamoylpyridinium cations (XIX: X = H, $CONH_2$) under alkaline conditions[44,279,280] shows that the equilibrium formation of pseudobases when the hydroxide ion attacks the ring at $C_{(2)}$ is more rapid than opening of the ring. The rate of the latter is proportional to $[OH^-]^2$ or $[B][OH^-]$, where B is a base (e.g. CO_3^{2-}). The resulting 5-dimethylureidopenta-2,4-dienals (XX)



X = H

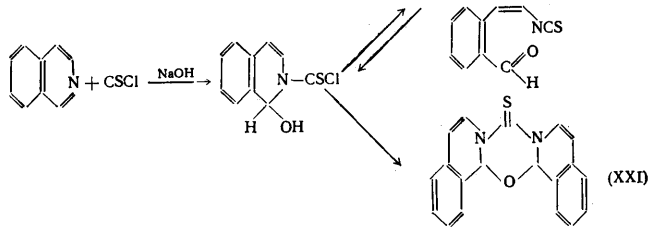
are relatively stable, and can be isolated from the solution. The strong "acidifying" action of the 3-carbamoyl group in (XIX) on the relative ease of formation of the pseudobase is significant: the pH of equilibrium between cyclic and open-chain forms is shifted to 8.6 from 10.64 for X = H; the constants $k_2(CONH_2)$ and $k_2(H)$ differ by factors of 10^5, although for reactions involving migration of the acyl group (Section III, 2) they increase only 3 to 14 times[44].

N-Alkyl-quinolinium and -isoquinolinium pseudobases are very stable and exist only in the cyclic form[4]. For this reason Reissert assigned a pseudobase structure to the product of the reaction of quinoline with benzoyl chloride in the presence of 10% alkali[34], but later he suggested the "open" benzamidocinnamaldehyde structure[281]:



The open structure (with the *trans*-configuration) has now been proved by various spectral methods[282,283].

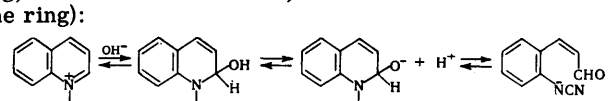
Reissert's method is of applied significance for the preparation of various polyfunctional compounds[282]. Pseudobases can be prepared by means of cyanogen bromide[284–287]. Reaction of isoquinoline with thiocarbonyl chloride in alkaline medium yields a ring-cleavage product together with a compound (XXI) formed by dehydration of the pseudobase[288]:



(XXI)

A stable pseudobase has been obtained from an *N*-benzoyl salt of 5-nitroquinoline; in this case its cyclic structure and the absence of tautomeric conversion to an acyclic form have been proved[283].

A series of studies by Johnson and his coworkers[106,123,126,283,287–290] on *N*-cyano-quinolinium and -isoquinolinium ions have revealed the great importance of pseudobases in the occurrence of most reactions of such compounds (acid–base equilibria of two types, hydrolysis, ring-opening, formation of *O*-ethers, bromination and nitration in the ring):



The formation of pseudobases and opening of the pyridine ring are two stages of a general process of attack by the nucleophilic reagent (hydroxide ions, arylamines) at the α-carbon atom of the heterocyclic ring. This process frequently competes with reactions involving migration of the acyl group to other nucleophiles.

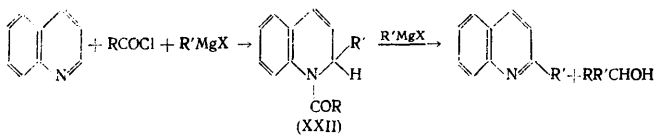
4. Hetarylation

The reaction of *N*-acyl-quinolinium and -isoquinolinium salts with the cyanide ion is of great importance for synthetic organic chemistry. In contrast to the hydroxide ion, the cyanide ion does not cleave the heterocyclic ring and, with few exceptions, does not detach the acyl group. Attack at $C_{(2)}$ leads in this case to the formation of extremely stable 1-acyl-2-cyano-1,2-dihydroquinolines or 2-acyl-1-cyano-1,2-dihydroisoquinolines (so called

Reissert compounds). *N*-Acyl-pyridinium and -acridinium salts do not undergo this reaction[34,281]—see, however, Ref. 291. In view of the appearance of two reviews on the Reissert reaction[292,293], we shall merely give references to the most important papers published during the past three years on the subject of the present paper[294-310]. The interaction of *N*-cyanoquinolinium with anhydrous hydrogen cyanide has been discussed[283,284].

Pyridine undergoes the Grignard reaction with difficulty, while its *N*-alkyl salts are sparingly soluble in most of the solvents used in this synthesis[1]. When pyridine interacts with a Grignard reagent in the presence of acylating agents, the corresponding 1,4-dihydropyridines are formed[292], and easily pass into 4-substituted pyridines. With 4-substituted pyridines, however, Grignard reagents attack position 2, not 4, in the *N*-acylpyridinium ions[311].

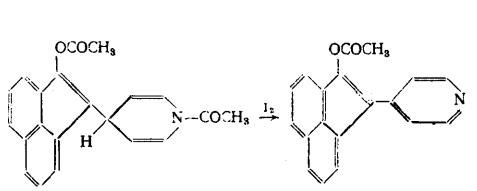
The addition of Grignard reagents to a mixture of quinoline and an acyl halide gives compounds of type (XXII), but with the reactants mixed in the opposite sequence, i.e. in excess of the organomagnesium compound, the 1,2-dihydro-derivative loses a proton, and is converted into a 2-substituted quinoline[312,313], the acyl group giving the corresponding tertiary alcohol:



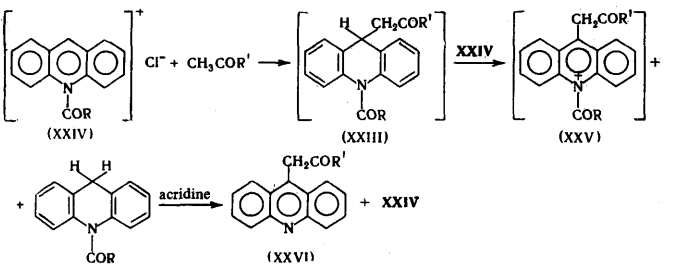
(XXII)

Similarly, *N*-acylpyridinium salts react *in situ* with silver acetylides at position 2[314].

In the early work Claisen and Haase[315], in a study of the reaction of acetophenone with benzoyl chloride in the presence of pyridine, isolated a compound $C_{20}H_{17}NO_2$ as well as the expected *O*-benzoyl derivative of the enol. Much later a compound containing a pyridine group was also obtained by the acylation of acenaphthenone with acetic anhydride in pyridine[316]. McEwen[98] showed that 4-substituted 1-acyl-1,4-dihydropyridines had been obtained in both cases: e.g. Ghigi's product[316] was 2-(1-acetyl-1,4-dihydropyrid-4-yl)acenaphthylen-1-yl acetate. Oxidation by iodine gives the 4-substituted pyridine:

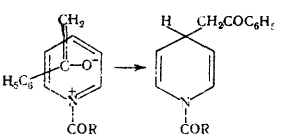


Under similar conditions *N*-acylquinolinium salts usually "quinolinate" both monocarbonyl and β-dicarbonyl compounds to form 2-substituted 1-acyl-1,2-dihydroquinolines[192,278]. Hetarylation—not acylation—products also constitute the main yield of the reactions of *N*-acylated isoquinolinium, phenanthridinium, and acridinium salts with various keto-compounds[317,318]. In this way preparative yields of ketones of the acridine series have been obtained directly from acridine and acyl halides with acetophenone. The probable mechanism of the latter reaction is that the initially formed 10-acyl-9,10-dihydro-9-phenacylacridine (XXIII) is converted, by detachment of a hydride ion on attack by an *N*-acylacridinium cation, into an unstable *N*-acyl salt (XXV), which is decomposed by excess of acridine with regeneration of the salt (XXIV) and formation of the product (XXVI)[319]:



The distribution of electron density can be used to explain preferential attack by a nucleophile at position 2 or 4 in the pyridine ring[320]. Other approaches have tried to take into account both the electronic nature of the two reactants and the character of the transition state (Kosower–Klopman theory[321,322] and Pearson's general acid–base principle[323]).

Kosower[324] suggested that substitution occurs at the $C_{(4)}$ atom of the pyridine ring if the reagents (electron donors) form charge-transfer complexes with pyridinium cations; if, however, the formation of such complexes is hindered, position 2 is substituted. For example[321], the benzoylpyridinium cation reacts with the enolate anion of acetophenone to form initially an adduct (XXVII), in which the nucleophilic atom of the ambident group is situated near position 4, and the anionic centre near the positively charged nitrogen atom:

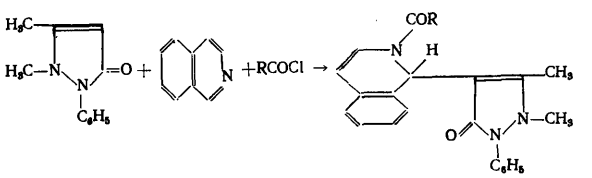


(XXVII)

Nevertheless, Kosower himself stresses that his ideas do not apply to the behaviour of the cyanide ion, which attacks *N*-alkylpyridinium salts solely at $C_{(4)}$, although no absorption band corresponding to charge transfer has yet been detected.

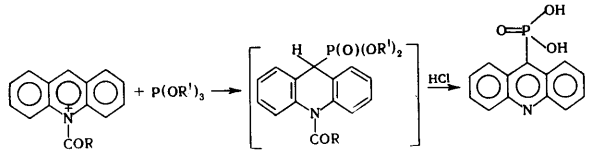
In terms of Pearson's generalised acid–base principle[323] the character of the attack by the nucleophilic agent (a generalised Lewis base) on *N*-acylated heteroaromatic cations, which are ambident ions, will be determined by the relative "hardness" or "softness" of individual positions in the ring. Hence position 4 is attacked in pyridinium salts, but the orientation in quinoline and isoquinoline remains obscure as before. The thermodynamic factor is probably decisive[122,325]. Comparison of the 1,2- and 1,4-dihydroquinoline structures shows the former to be thermodynamically preferred, with the $C_{(3)}=C_{(4)}$ double bond conjugated with the benzene ring, and the necessary conditions established for production of a homoaromatic structure (in terms of Winstein's ideas[326]).

The reactions of *N*-acylated heterocyclic cations *in situ* with pyrazolones, thiazolidine-2,4-diones, rhodanine, thio- and iso-rhodanines, azalactones, and other azolidones are of the same type (interaction with ambident methine anions)[327-331]:

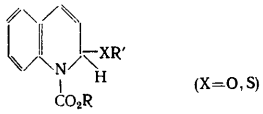


It has recently been established that the Dakin–West synthesis involves the intermediate pyridylation of oxazolones by *N*-acetylpyridinium cations [332,333] (for greater detail see Ref. 180). The cyclopentadienyl ring has also been hetarylated (by the reaction of *N*-acylated pyridinium and benzopyridinium salts with azulenes) [334]. The reaction of *N*-acylpyridinium salts with nitroalkanes [335] yields anomalous products not containing a pyridine ring, but quinolinium salts form hetarylation products containing two quinoline ring systems.

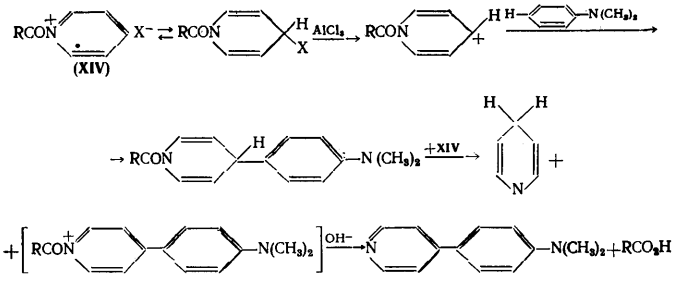
Interaction between *N*-acylated heteroaromatic cations and compounds having a heteroatom with a lone pair of electrons mostly involves attack on the carbonyl carbon atom, as stated above, with elimination of the heterocycle and migration of the acyl (acylation of amines, alcohols, thiols, etc.). However, there are several examples of reactions occurring by a mechanism of hetarylation. Thus the well known synthesis of *N*-pyrid-4′-ylpyridinium chloride by chlorinating pyridine with thionyl chloride [336–338] probably involves attack by pyridine as a nucleophile on $C_{(4)}$ in the *N*-acyl salt. Among the very few cases of intramolecular hetarylation is the formation of dyes by interaction between quinoline-2-carboxylic acid and acetic anhydride or between quinoline-2-carbonyl chloride and quinoline [339–341]. Another example is the successful accomplishment of the Arbuzov rearrangement for trialkyl phosphites by the action of *N*-acyl-pyridinium, -quinolinium, and -acridinium salts [342,343]:



It has recently been shown [344] that, in the presence of acylating agents (ethyl chlorocarbonate, acetyl and benzoyl chlorides), quinoline readily adds alkoxide and thiolate ions at position 2. This method has been used to prepare high yields of 1,2-dihydro-derivatives of general formula

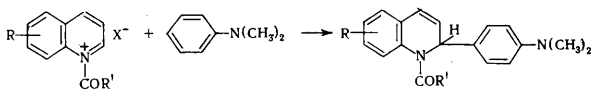


During recent years the chemistry of *N*-acylpyridinium salts has been developed most widely in the hetarylation of the aromatic ring. Like the usual inorganic cations and the widely studied carbonium ions, acylpyridinium ions and their benzo-analogues have proved convenient reagents for the introduction of a heteroaromatic substituent into an aromatic ring§. *N*-Benzoylpyridinium chloride is mostly used in the presence of aluminium chloride or copper powder [112,345,347], when there is no need to isolate the *N*-acylpyridinium salt. The mechanism of the reaction is apparently that the positive charge on the pyridine cation, as a result of the action of the aluminium chloride, becomes concentrated on the 4-carbon atom to form a carbonium ion:



It may also be supposed that *N*-acylpyridinium halides are present in solution either as charge-transfer complexes or as ion-pairs, in which donor–acceptor interaction occurs between the pyridinium cation and the anion [324]. Such systems are less strongly electrophilic than the "purer" cations present in salts with weakly nucleophilic anions like perchlorate, tetrachloroaluminate, etc. This is another explanation of the action of Lewis acids. In a comparative series of experiments on the pyridylation of dimethylaniline with various aliphatic acid chlorides the yield of 4-*p*-dimethylaminophenylpyridine increased as the alkyl chain became longer, which is evidently connected with the strengthening of the electron-accepting effect of the *N*-substituent in the intermediate *N*-acyl salt [37].

N-Acylquinolinium salts, which are most strongly electrophilic, react with dialkylanilines and their analogues in the absence of catalysts [351,352]:

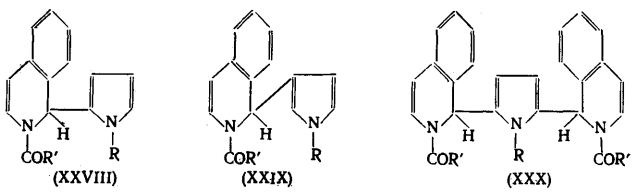


The nature of the anion in *N*-acylquinolinium salts has a significant effect on the yield of quinolination products. Thus the yield of 1-benzoyl-2-*p*-dimethylaminophenyl-1,2-dihydroquinoline increased regularly in the reactions of dimethylaniline with quinoline and a benzoyl halide (fluoride, chloride, bromide, iodide), which may be attributed simply to the increasing reactivity of the benzoyl halides in this sequence. On the other hand, this effect can also be explained by the formation of charge-transfer complexes (with transfer of the electron of the anion to a non-bonding orbital of the heterocycle), which facilitates occurrence of the reaction by a radical mechanism. The possibility of a radical scheme is seen still more clearly in the hetarylation of dialkylanilines by *N*-acylisoquinolinium salts [353,354], since the yields of reaction products were increased by exposure to ultraviolet radiation. The reaction between dialkylanilines and phenanthridinium salts proceeds similarly, but with smaller yields [355].

Acridine reacts more vigorously than other benzopyridines with dialkylanilines in the presence of acylating agents, but it forms 9-arylacridines and *N*-acylacridans [356], not 10-acyl-9-aryl-9,10-dihydroacridines. Hetarylation by acylpyridinium or acylbenzopyridinium salts has been described also with 1-alkyl-2,3-dihydroindoles, *N*-alkyltetrahydroquinolines, *N*-phenylmorpholine, *N*-phenylpyrrolidine, etc. [354,355,357–364]. Similarly to the benzene ring, acylpyridinium cations readily attack the electron-excess rings of such heterocycles as pyrrole, furan, and indole.

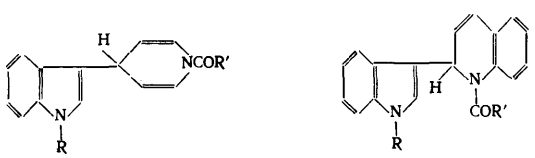
§Some 10–15 years ago there were only isolated publications on this topic [17,345,346]. After pyridylation had been developed [112,347], however, many papers appeared on hetarylation by quinolinium [348], pyrylium [348–350], etc. salts.

Fischer [365] long ago isolated a pyridine-containing substance from the action of pyridine and cyanogen bromide on ethyl 2,4-dimethylpyrrole-3-carboxylate. Much later pyrrolylpyridine derivatives of undetermined structure were obtained.[366,367] by the acylation of pyrroles with acyl chlorides in pyridine solution. However, a more detailed study of the reactions of *N*-acylpyridinium salts and the corresponding benzo-analogues with pyrroles has been made only comparatively recently[368-377], and has shown the formation of both monoadducts (of types XXVIII and XXIX) and bisadducts (XXX).



(XXVIII) (XXIX) (XXX)

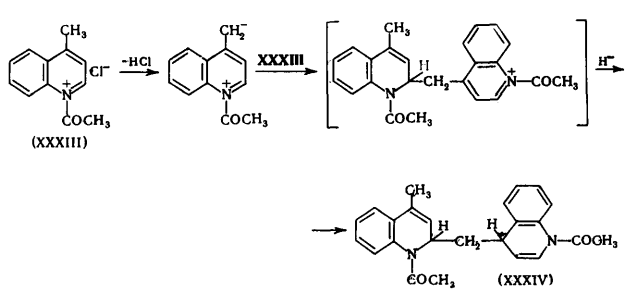
The hetarylation of indoles by *N*-acyl salts of six-membered nitrogen heterocycles [21,278,372,378-384] produces compounds of types



(XXXI) (XXXII)

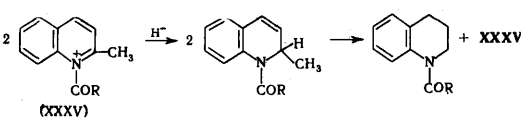
Thus 1-benzoyl-1,4-dihydro-4-indol-3′-ylpyridine has been obtained from pyridine, benzoyl chloride, and indole [178,378,380]. The yield is considerably lower when acetyl chloride is used, and with toluene-*p*-sulphonyl chloride the corresponding compound, formed in small quantities passed very readily into indolylpyridine. Under analogous conditions the reaction with *N*-acylacridinium salts gives only 3-acridin-9′-ylindoles [383,384]. The reaction of pyridine with indole in the presence of trichloroacetyl chloride involves the acylation (not the pyridylation) of indole, but in the presence of cyanogen bromide the pyridine ring is cleaved with formation of a pentadienal derivative of indole [379]. Isoindoles, in contrast to indoles, form 1,3-dipyridylisoindoles on interaction with pyridine and benzoyl chloride [385].

Many authors have pointed out that 1-acyl-2(and 4)-methylquinolinium salts cannot be used in hetarylations. Depending on the reaction conditions 1-acyl-4-methylquinolinium cations (XXXIII) are converted [386] either into 1-acyl-1,2-dihydro-4-methylquinolines or into "dimers" (at 50° and 100°C respectively). Detailed analysis of the mass spectrum of the "dimer" obtained with acetyl chloride indicates the structure (XXXIV). Its formation can be represented by the scheme (based on the dimerisation of 1-alkyl-4-methylquinolinium salts) [387]



(XXXIII) (XXXIV)

Formation of dimers has not been observed with 2-methylquinoline, probably because the methyl group is less strongly activated than in the 1-acyl-4-methylquinolinium ion [120]. 1-Acyl-1,2,3,4-tetrahydro-2-methylquinolines were always obtained when the reaction was conducted under various conditions, probably as a result of the disproportionation (with migration of hydrogen) of intermediate 1-acyl-1,2-dihydro-2-methylquinolines [380]:

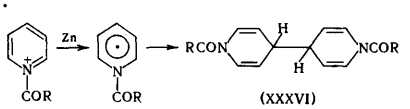


(XXXV)

5. One-electron Reduction of *N*-Acylated Heteroaromatic Cations

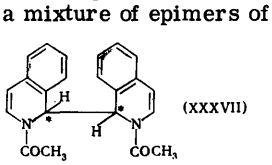
The strongly electrophilic character of *N*-acylated heteroaromatic cations is shown not only by their addition to reaction centres of high electron density or by their formation of charge-transfer complexes: reactions involving electron transfer and formation of the corresponding radicals are also facilitated in this series, since the one-electron reduction potentials of pyridinium cations fall when the electron-accepting properties of substituents attached to the heteroatom become stronger [388], and should be especially low with *N*-acylpyridinium salts and their benzologues. In fact, whereas *N*-alkylpyridinium salts are reduced only by sodium amalgam [389], zinc dust at room temperature or slightly above (30°C) is sufficient to reduce *N*-acylpyridinium salts; furthermore [74], a vigorous reaction with liberation of iodine is observed when potassium iodide is added to pyridine–arenesulphonyl chloride systems.

The formation of radicals by the action of benzoyl chloride and zinc dust on pyridine was first observed by Weitz et al. [390] Almost simultaneously Dimroth [391,392] observed the formation of a compound of type (XXXVI) in the reaction of acetic anhydride, pyridine, and zinc dust (more detailed information on its structure will be found in Ref. 393):



(XXXVI)

This reaction is characteristic of various *N*-acylpyridinium salts and their benzologues [394-400]. For example, isoquinoline forms a mixture of epimers of

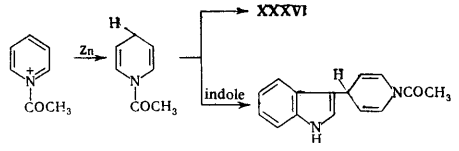


(XXXVII)

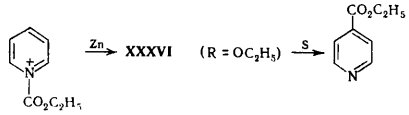
in equal proportions [397]. Acridine, however, does not yield a dimer but *N*-acetylacridan [401], which is probably explained by the greater stability of the *N*-acetylacridinyl radical: the latter does not recombine, but is reduced to the anion and then adds a proton.

For a long time the reaction could not be conducted with 2- and 4-methylpyridines [402,403], but the use of chloroformic esters as acylating agents enabled dimers of *N*-acylmethylpyridines and even of *N*-acyl-trimethylpyridine to be obtained [398-400]. With 4-substituted pyridines, however, 1,4-diacyl-1,4-dihydropyridine derivatives were isolated [399].

The N-acylpyridyl radicals formed in Dimroth's reaction are able not only to recombine but also to hetarylate nucleophilic aromatic or heteroaromatic compounds added to the reaction medium [28,404,405]:



4-Ethylpyridine has been prepared by the further reduction of pyridine with zinc in acetic acid (by Wibaut's method) [338,396,406-410], and the process has been exploited on an industrial scale [411-417]. The mechanism of the reaction has been discussed [338,408]. In spite of many unsuccessful attempts initially, it proved possible to obtain in this way 4-ethyl-2(and 3)-methylpyridines from 2- and 3-methylpyridines [418]. The use of chloroformic ester in this reaction yielded isonicotinic ester [419]:



---o0o---

Thus the chemistry of N-acylpyridinium salts and their benzo-analogues has already developed far enough to solve major theoretical and practical problems. From the point of view of synthetic organic chemistry several analogous compounds can be obtained by a different process, via the corresponding N-oxides. This line of attack, which has been especially broadly developed by Japanese chemists, is substantially different in its theoretical aspects, and therefore we have not dealt with it in the present paper.

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