HETARYLATION OF ORGANIC COMPOUNDS (REVIEW)

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Reactions of the direct introduction of nitrogenous aromatic heterocycles into nucleophilic organic compounds with the use in situ of N-acyl salts of heterocyclic cations and also of heteroaromatic anion radicals are discussed.

The hetarylation reaction is the name which we give to the direct introduction of aromatic heterocycles into organic compounds [1]. This review considers only those arylation reactions in which heteroaromatic systems are used directly without the previous production of hetarylating agents (such as quaternary salts, N-oxides and their quaternary salts, etc.) from them. Such reactions include those of nitrogenous aromatic heterocycles with nucleophilic organic compounds in the presence of acylating agents or in the presence of active metals. In the first case, hetarylation is effected by the N-acyl salts of the heterocycles formed as intermediates in situ and is similar in many respects to the widely-used and thoroughly studied reactions of electrophilic substitution by tropylium, cyclopropenylium and arenediazonium salts, etc. Naturally, the mechanisms of hetarylation with salts of other heteroaromatic cations such as pyrylium salts (the so-called Treibs–Krohnke reaction [3, 4]) is similar.

Hetarylation with nitrogenous heterocycles in the presence of active metals is performed by anion radicals formed as intermediates in the one-electron reduction of the nitrogenous heteroaromatic systems [5].

Hetarylation of N-Acyl Salts of Aromatic Heterocycles

The hetarylation reaction with N-acyl salts of pyridine in situ was first performed, to their own surprise, by Claisen and Haase [6] at the beginning of the present century. On acylating acetophenone with benzoyl chloride in the presence of pyridine, in addition to the O-benzoyl derivative of the enolic form of acetophenone, they isolated a compound containing a pyridine nucleus the structure of which was established only in 1951 [7]. In 1905, Reissert [8] discovered that the reaction of quinoline or isoquinoline with KCN in the presence of benzoyl chloride formed N-benzoyl derivatives of α-cyano-1,2-dihydroquinoline or -isoquinoline. These compounds, subsequently called "Reissert's compounds," proved to be extremely reactive and have assumed an important place in preparative organic chemistry (see the reviews [9, 10]) and the reaction in which they are formed has entered chemical history as Reissert's reaction.

On considering from the usual points of view reactions of nitrogenous heteroaromatic compounds in the presence of acylating agents, it becomes clear that Reissert's reaction is a special case of the hetarylation of an inorganic compound.

In a study of the acylation of dimethylaniline [11] and of some ketones [12-14] by acyl halides in the presence of pyridine, it was found that in these circumstances pyridine residues entered the dimethylaniline nucleus and the ketone molecules. It was possible to introduce a quinoline residue similarly [15]. It was considered [7, 11, 15] that N-acylpyridinium salts are formed in the cases described. However, only in the last decade through the efforts of many workers, including the author of the present review, have the synthetic possibilities of this interesting reaction been established and its mechanism been studied. The author hopes that the publication of the present review and the unsolved questions connected with the hetarylation reaction that remain will stimulate in the reader an interest in this field of the chemistry of heteroaromatic compounds.

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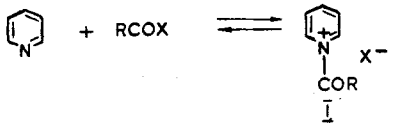
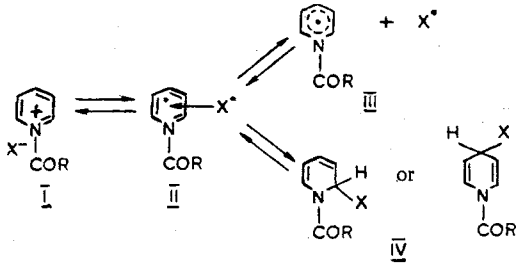
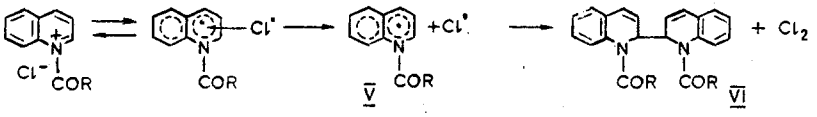
Mechanism of the Reaction. The first stage of the reaction of nitrogenous heteroaromatic systems containing a "pyridine" nitrogen atom in the ring with organic compounds in the presence of acylating agents is the formation of aromatic N-acylcyclammonium salts. Only in a few cases have such hetarylating agents been isolated [1, 16, 17], but their formation in solutions and their participation in reactions in situ has been strictly demonstrated [1, 22].



There are grounds for believing, in spite of established opinion, that the simple equilibrium shown above exists only in reactions of tertiary amines. In the reaction of acylating agents with nitrogenous heteroaromatic systems not only are the N-acyl salts of type (I) then capable of decomposing into the initial reactants but, as a result of reaction with anions, they can also apparently be converted into other electroneutral particles [22]; for example:



In actual fact, the possibility of the existence of the N-acyl salts (I) in the form of charge-transfer complexes (CTCs) (II) is not a matter of doubt in view of the increased electrophilicity of the N-acyl heteroaromatic cations as compared with the N-alkyl and N-aryl* cations, where the existence of CTCs has been demonstrated [25, 26]. The decomposition of the complexes (II) into free radicals has been shown by means of ESR and chemically [22]. In particular, in an investigation of mixtures of isoquinoline and of phenanthridine with benzoyl chloride (but not the fluoride) a signal was found by the ESR method corresponding to an unpaired electron. The heating of mixtures of quinoline, isoquinoline, or benzoquinolines with acyl chlorides led to the dimers (VI), the formation of which can be explained only by the recombination of the N-acyl heteroaromatic radicals (V) [22, 27].



Compounds of type (VI) have also been obtained by the reaction of quinoline or isoquinoline with acid anhydrides in the presence of zinc dust [22, 28].

In general, the possibility of the formation of N-alkyl and N-aryl heteroaromatic radicals in the one-electron reduction of the corresponding cations by several anions has been discussed repeatedly in the literature [29-31] and is apparently inherent in all heteroaromatic cations under certain conditions which depend on the electrophilicity of the cation, the nucleophilicity of the anion, and the ionizing capacity of the solvent.

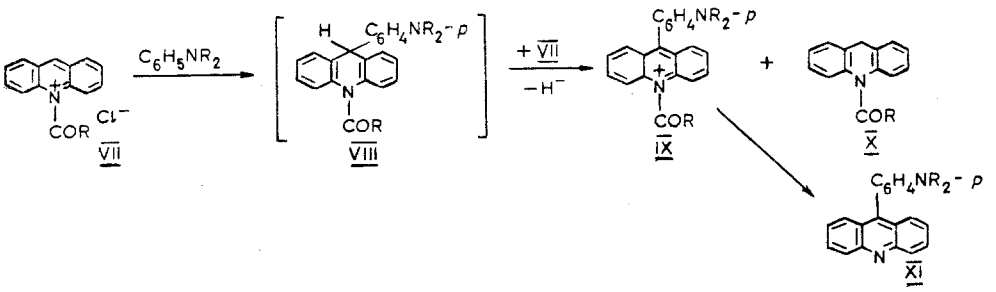
The reaction of anions and heteroaromatic cations with the formation of a σ bond between them (compounds of type (IV), called "Kryptosalze" ["Crypto-salts" or pseudo-salts"] [32] or "pseudo-bases" [33], or "Reissert compounds" [9, 10] depending on the nature of the anion) is also well known and is determined by the nature of the cation and of the anion. An analysis of much literature information (see, for example, the reviews [26]) shows that anions of low nucleophilicity (ClO_4^-, BF_4^-, $AlCl_4^-$, etc.) form only ionic bonds with

*Concerning the influence of substituents attached to the heteroatom on the electrophilicity of pyridinium cations, see [23-25].

heteroaromatic cations. Similar quaternary salts are present in solution in the form of ion pairs or of solvated free ions and exhibit the greatest reactivity with respect to nucleophilic agents. More highly nucleophilic anions (I^-, OH^-, CN^-, etc.) react with cations to form, depending on the electrophilicity of the cation, CTCs or new compounds with a σ bond between the anion and a carbon atom of a ring. The compounds (IV) formed may also take part in reactions with nucleophilic agents with the replacement of the X groups by other residues, but the activation energy of such substitution reactions is apparently higher than the activation energies of reactions involving the direct addition of nucleophiles to cations. Additional proofs of the conversion of the N-acyl salts (I) initially formed into electroneutral products have been obtained in a study of the electrical conductivity of crystalline 2-(N,N-diphenylcarbamoyl)isoquinolinium chloride [22].

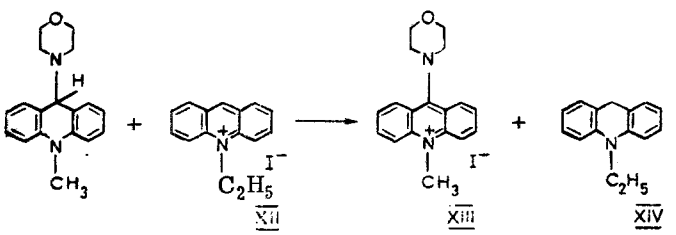
Thus, the formation of the dimers (VI) and also a study of the electrical conductivity and ESR spectra of solutions of nitrogenous heteroaromatic compounds and acyl halides in neutral solvents shows the simultaneous presence of both N-acyl heteroaromatic cations (I) and N-acyl heteroaromatic radicals (III) and (V).

Accordingly, the hetarylation reaction can take place by two mechanisms — cationic and radical mechanisms [22] — the realization of one of which apparently depends on many factors affecting the stabilization of the cations (I) formed initially: the nature of the counter-ion, the possibility of the delocalization of the positive charge in the cation, the ionizing capacity of the solvent, etc. As a rule, N-acylacridinium salts react in situ by the cationic mechanism, N-acylquinolinium, -isoquinolinium, and -benzoquinolinium salts by a radical mechanism, and pyridinium salts by both mechanisms, but this can be changed by varying the solvent or by using catalysts and UV irradiation. With the cationic reaction mechanism, fully aromatized substituted heterocycles are obtained as the result of migration of a hydride ion from the N-acyl dihydro derivatives formed as intermediates to the N-acyl heteroaromatic cations (I). In the case of hetarylation by the radicals (V) such hydride migration does not take place because of the reduced electrophilicity of the N-acyl heteroaromatic radicals and the reaction stops at the stage of the formation of the dihydro derivatives [22]. For example, in the reaction of acridine with dialkylanilines [34-37], indoles [38, 39], pyrroles [40], furan [41], and other nucleophilic aromatic heterocycles and with aliphatic compounds [42-45], 9-substituted acridines and 10-acyldihydroacridines are formed:



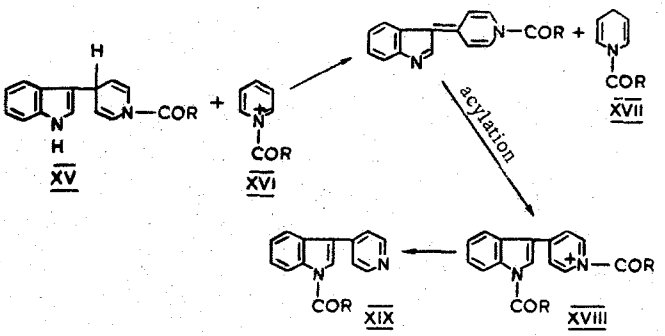
Apparently, the N-acylacridinium cation (VII), on attacking the activated aromatic nucleus of a dialkylaniline, forms a 10-acyl-9-aryl-9,10-dihydroacridine (VIII). Then, under the action of an excess of the compound (VII), hydride migration takes place with the formation of the N-acyldihydroacridane (X), which can be isolated in almost theoretical yield [35], and the unstable N-acyl salt (IX), which is readily converted in the presence of an excess of acridine into the final reaction product (XI). Hydride migration is possible in this reaction because of the greater electrophilicity of the N-acylacridinium cation (VII) than of the cation (IX), which has an electron-donating dialkylaminophenyl substituent.

To confirm the proposed scheme of cationic hetarylation, a model reaction of hydride migration analogous to that described above has been performed [35]:



In this case, hydride transfer also takes place because of the greater electrophilicity of the N-ethylacridinium cation (XII) than of the ion (XIII) in view of the presence of an electron-donating substituent in the latter. The salt (XIII) formed in this process is stable and has been isolated together with N-ethyldihydroacridine [22, 35]. The hydride reduction of acridine methiodide to N-methyldihydroacridine by reaction with various N-methyldihydroacridines having electron-donating substituents in position 9 takes place similarly [35].

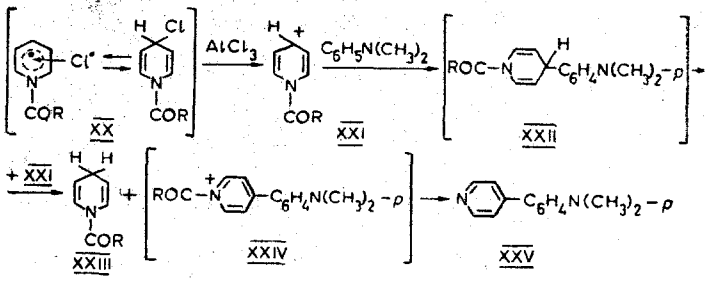
Hetarylation by pyridine in the presence of acylating agents may take place both by a radical mechanism with the formation of 4-substituted 1-acyl-1,4-dihydropyridines and by a cationic mechanism with the formation of 4-substituted pyridines. In particular, when the reaction of pyridine with indoles and acyl halides is performed in absolute benzene, 1-acyl-4-(indol-3-yl)-1,4-dihydropyridines are formed [46]. In more highly polar solvents, the reaction takes place with the formation of 1-acyl-3-(pyridin-4-yl)indoles [47]. The authors concerned do not discuss the reasons for the formation of the 1,4-dihydropyridine (XV) in some cases and the completely aromatic compound (XIX) in others. Bergman [47] has given a reaction scheme analogous to that shown above for the acridinylation of dialkylanilines [35] including the stage of the reduction of N-acylpyridinium salts to 1-acyl-1,4-dihydropyridines (XVII), for formation of which was demonstrated [47]. However, instead of a simple hydride-transfer scheme, Bergman suggested the following less probable process:



It remains unclear through what reagents the transfer of the acyl group is effected, while according to the scheme given above transacylation could take place after the loss by compound (XV) of a hydride ion through the resulting cation, since the acylating capacity of N-acylpyridinium cations is extremely high [1]. In actual fact, under analogous conditions in the reaction of pyridine with indole in the presence of trichloroacetyl chloride, the acylation and not the pyridinylation of indole was observed [47].

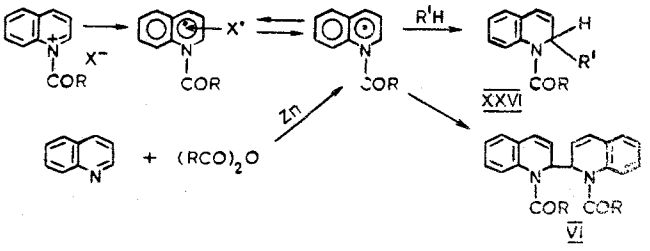
The change in the mechanism of the hetarylation reaction may apparently be explained by the assumption that in feebly ionizing solvents the N-acylpyridinium salts formed are in the state of a close ion pair, which facilitates the transfer of an electron of the anion to the lowest vacant π orbital of the cation with the formation of N-acylpyridinium radicals. In polar solvents, however, nitrogenous heteroaromatic cations and anions in the dissociated salt are solvated, the formation of radicals is more difficult and, probably, in this case cationic hetarylation takes place with subsequent hydride migration as was shown above.

To increase the activity of the N-acylpyridinium salts in cationic hetarylation reactions it has been proposed to use Lewis acids as catalysts [48-51]. In these circumstances, the yields increase sharply and it is possible to use various N-acylpyridinium salts in the reaction and to determine the influence of the acyl residues on the reactivity of the salts. The action of the catalysts is apparently explained by a change in the nature of the counter-ion and the resulting change of the cationic interaction in the N-acylpyridinium salts. In the presence of $AlCl_3$ or other Lewis acids, the complex counter-ions $AlCl_4^-$ or others with the same elevated nucleophilicity are formed, the reaction of which with the pyridinium cation is limited only by electrostatic forces. The following mechanism of the hetarylation of dimethylaniline can be imagined:

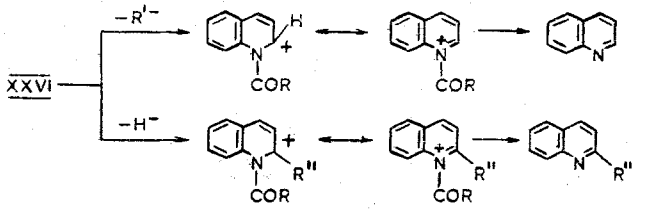


On reaction with nucleophilic aromatic [52-55], heteroaromatic [41-43], and aliphatic [56] compounds, N-acylquinolinium and N-acylisoquinolinium salts form high yields of stable N-acyl derivatives of 1,2-dihydroquinoline and 1,2-dihydroisoquinoline. In these cases, the reactions take place, even though slowly, at room temperature in the absence of catalysts. They can be accelerated by heating or by irradiation with UV light [57]. In contrast to acylpyridinium salts, in reactions of acylquinolinium salts the yields are practically independent of the electronic nature of the acyl residue (which again confirms the radical mechanism of the reactions). Also in harmony with a radical mechanism of the reactions is the fact that the yields are substantially affected by the nature of the anions of the 1-acylquinolinium salts. Thus, in the reactions of quinoline and benzoyl fluoride, benzoyl chloride, benzoyl bromide, and benzoyl iodide with dimethylaniline under standard conditions the yields rise regularly with an increase in the nucleophilicity of the anion, which permits the assumption of the participation in the reactions not of the 1-acylquinolinium cation but of a charge-transfer complex which subsequently decomposes into a 1-acylquinolinium radical and halogen [53, 57]. The presence of radicals in the reaction mixture has been confirmed by ESR spectroscopy.

A characteristic feature of radical hetarylation reactions is the formation of dimers in the hetarylation of compounds possessing weak nucleophilicity (benzene, anisole, thiophene, cyclopentadiene, etc.):

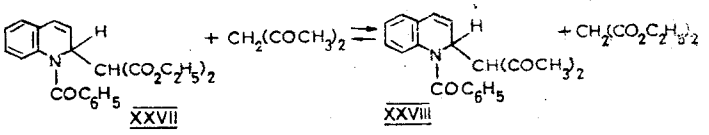


Derivatives of types (XXVI) and (VI) are also formed in the definite radical hetarylation of nucleophilic organic compounds with N-acyl heteroaromatic radicals under the conditions of the Dimroth reaction [58-62]. N-Substituted heteroaromatic radicals possess electrophilic properties [22, 63] and therefore with any hetarylation mechanism there is an electrophilic reaction. In all cases, the addition of the heterocyclic residues to the position with the highest electron density is observed [1] although the electrophilicity of heteroaromatic radicals has nevertheless proved insufficient for the detachment of a hydride ion from the dihydro derivatives (XXVI). Partially hydrogenated compounds of type (XXVI) are converted fairly readily into aromatic systems either by the detachment of a hydride ion or as the result of the loss of carbanions, particularly in those cases where the carbanions split off are stabilized by neighboring carbonyl groups [64, 65]:



$R' = CH(CO_2R)_2$; $CH(COCH_3)_2$; $CH(CN)CO_2C_2H_5$; $R'' = C_6H_4NR_2\text{-}p$

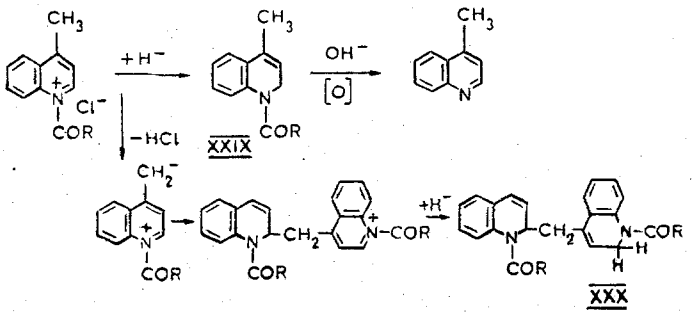
The ease of cleavage of a carbon–carbon bond in compounds of type (XXVI) with electron-accepting substituents in the side chain is responsible for the possibility of the occurrence of transhetarylation reactions as a result of which the heterocyclic residue migrates to other compounds with labile hydrogen atoms [64, 65], as is the case in cyclopentatriene compounds [66], for example [64]:



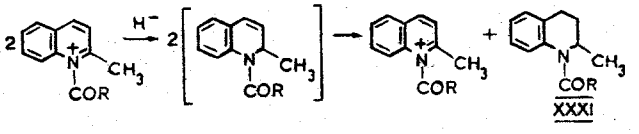
There are similar examples of such easy cleavage of a C—C bond in the literature [66-68] and, as it appears to us, the mechanism of this process is similar in many cases to Grob fragmentation [69] and,

apparently, has a general nature. Thus, the reversibility of radical hetarylation reactions and the possibility of the occurrence of transhetarylation reactions in some cases have been established [64, 65].

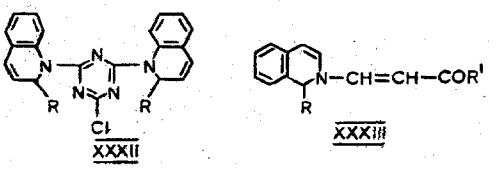
Hetarylating Agents. The following have been used successfully in situ as hetarylating agents in the direct hetarylation of organic compounds: N-acylpyridinium salts [1, 6, 11, 14, 46-51], N-acylquinolinium salts [40-46, 52, 53, 70-75], N-acylisoquinolium salts [54, 56, 76-79], N-acylacridinium salts [34-39, 80-82], N-acylphenanthridinium and other N-acylbenzoquinolinium salts [22, 55, 78], and also N-acyl salts of some azines [10, 22] and azoles [83, 84]. Thus, the hetarylation reaction apparently has a general nature and can be extended to any heteroaromatic systems having a nitrogen atom of the pyridinium type in the ring. The electronic effects of substituents in the benzene rings of benzopyridines have practically no influence on the yields of hetarylation products [57, 70]. This has also proved to be valid, in particular, for 8-methylquinoline [70], although it has been shown previously [72] that the Reissert reaction does not take place with 8-substituted quinolines because (in the opinion of Popp et al. [72]) of the screening of the nitrogen atom and the difficulty of formation of 1-acyl salts. The Reissert reaction could not be extended to many substituted quinolines, to pyridine, and to acridine [9, 10], while the hetarylation of organic nucleophiles by all these compounds takes place fairly readily. Exceptions are formed by 2- and 4-substituted pyridines and quinolines. 1-Acyl salts of 2- and 4-methylquinolines do not take part in the hetarylation reaction but are converted (with the capture of a hydride ion) into 1-acyl-1,2-dihydroquinoline derivatives [85]. 1-Acyllepidinium and 1-acylquinaldinium salts behave differently. Depending on the conditions of performing the reactions, acyllepidinium cations are converted either into 1-acyl-1,2-dihydroquinolines (XXIX) (at 50°C) or into the "dimers" (XXX) (at 100°C):



The reaction of acyl halides with quinaldine forms 1-acyl-1,2,3,4-tetrahydroquinaldines (XXXI), apparently as the result of the disproportionation (with hydride transfer) of the intermediate 1-acyl-2-methyl-1,2-dihydroquinolines [85]:



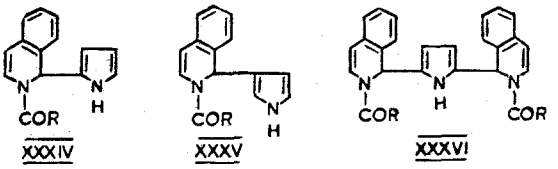
Halides of aliphatic, aromatic, and heterocyclic carboxylic acids [1] and sulfonic acids [1, 9, 10, 46] and chlorides of some acids of phosphorus [86-88] have proved suitable for the formation of N-acyl salts of heteroaromatic cations and subsequent hetarylation with them. Hetarylation takes place in the presence of some analogs and vinylogs of acyl halides such as cyanuryl chloride [74, 89, 90] and β-chlorovinyl ketones [91], with the formation of compounds of types (XXXII) and (XXXIII):



Hetarylation of Activated Aromatic and Heteroaromatic Nuclei. A necessary condition for the successful occurrence of the hetarylation reaction, as for the similar azo coupling reaction, is a sufficiently high nucleophilicity of the compounds undergoing hetarylation. Such compounds include aromatic amines, phenols, and other activated aromatic nuclei, and also π-excess heterocycles (pyrrole, indole, furan, etc.).

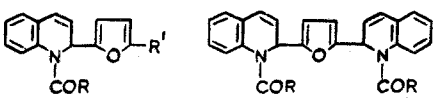
In the reaction of six-membered aromatic nitrogenous heterocycles in the presence of acyl halides with such compounds, various heterocyclic derivatives of dialkylanilines and their analogs have been obtained: N-phenylmorpholine, N-phenylpyrrolidine, and N,N'-diphenylpiperazine, and also 1-alkyl-2,3-dihydroindoles and 1-alkyl-1,2,3,4-tetrahydroquinolines [6, 11, 15, 35, 48-55, 76, 92]. The most active hetarylating agents have proved to be N-acylisoquinolinium salts [76] and acylacridinium salts [35-37]. Apart from the dialkylanilines and their analogs, it has been possible to introduce an isoquinoline residue in this way only into the nucleus of resorcinol dimethyl ether and of 2,6-di-tert-butylphenol, where the hydroxy group is screened and is not acylated; other activated aromatic compounds were either acylated under the reaction conditions (phenols, anilines) or were insufficiently nucleophilic (anisole).

The pyrrole ring hetarylates more readily. Attention was first drawn to the possibility of the hetarylation of pyrrole by Fischer and Ernst [93], who, by the reaction of pyridine and cyanogen bromide on 3-ethoxycarbonyl-2,3-dimethylpyrrole, isolated a colorless substance containing a pyridine residue the structure of which they were unable to determine. Later [94, 95] pyridinylpyrrole residues of undetermined structure were obtained in attempts at the acylation of pyrroles with acyl chlorides in pyridine. In the reaction of 2-ethoxy-3,4-dimethylpyrrole with pyridine in the presence of ethyl chloroformate, 3,4-dimethyl-2,5-di(pyridin-4-yl)pyrrole was unexpectedly obtained [96]. As a result of a detailed study [97, 98] of the conditions for the hetarylation of pyrrole it has been established that, contrary to other information in the literature [99], it is possible with any N-acyl salts of nitrogenous heteroaromatic cations. The most active proved to be N-acylisoquinolinium salts, the reaction of which with unsubstituted pyrrole at room temperature gave mono(2-acyl-1,2-dihydroisoquinolin-1-yl)pyrroles (XXXIV, XXXV) and bis(2-acyl-1,2-dihydroisoquinolin-1-yl)pyrroles (XXXVI). The ratio of the compounds formed depends to a considerable degree both on the nucleophilicity of the pyrrole ring and on the electrophilicity of the N-acylcyclammonium salts, which is connected, under otherwise the same conditions, with the nature of the acyl residue: with active salts the bis derivative (XXXVI) is formed, in the main; with less active compounds a mixture of all three compounds, and with the still less reactive N,N-diphenylcarbamoylisoquinolinium salt only the mono derivative (XXXIV).



It is possible to introduce only one heterocyclic residue into an α position of the pyrrole nucleus of N-phenylpyrrole, the nucleophilicity of which is lowered because of the electron-accepting influence of the phenyl substituent. The monohetaryl derivatives (XXXIV) may also take part in a hetarylation reaction with the formation of (XXXVI) or of 2,5-dihetarylpyrroles with various heterocyclic residues or with the same heterocycles but with different acyl substituents in them [98].

By a similar method, it has proved possible to obtain various heterocyclic furan derivatives, as well, in one stage [41, 100, 101]. In particular, the reaction of furan, sylvane, or 2,5-dimethylfuran with quinoline, isoquinoline, or phenanthridine in the presence of acyl halides gave mono- and diheterocyclic derivatives of furan:

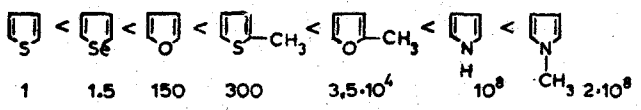


In this reaction, the formation of β-hetarylfurans with a free α position, as has been observed in the hetarylation of pyrroles, was not found.

Under similar conditions, N-acyl salts of acridine react with the formation of N-acyldihydroacridines and of 9-furylacridine.

Attempts have been made to extend the hetarylation reaction to thiophene, benzo[b]thiophene, 2-methylthiophene, selenophene, and 2-methylselenophene [22, 27]. It is known [102-105] that in electrophilic substitution reactions the relative reactivities of π-excess heterocyclic systems change in the following way*:

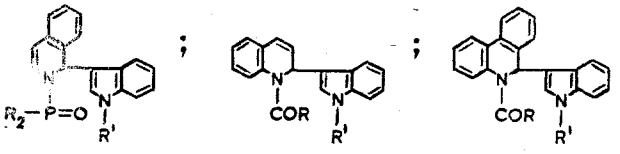
*The figures characterize the reactivities of these heterocycles in electrophilic substitution reactions [102-105].



In agreement with this, all attempts to perform the hetarylation of thiophene and of benzo[b]thiophene have proved unsuccessful. In the reactions of N-acylpyridinium and N-acylacridinium cations, only the initial reactants were isolated, but the reaction of N-acylisoquinolinium salts with thiophene and benzo[b]thiophene gave dimers of the N-acyl radicals formed as intermediates.

It has been possible to extend the arylation reaction to the more nucleophilic selenophene, 2-methylselenophene, and 2-methylthiophene where, as in the case of the furans, mono- and dihetaryl derivatives are formed [27].

In contrast to the hetarylation of pyrroles and other five-membered heterocycles, in the indole series this reaction has recently attracted great attention [39, 46, 47, 58, 91]. The reactions of indoles with pyridine, quinoline, isoquinoline, and some benzoquinolines in the presence of chlorides of carboxylic and sulfonic acids and also of acids of phosphorus and β-halogenovinyl ketones form the corresponding indole derivatives [22]:

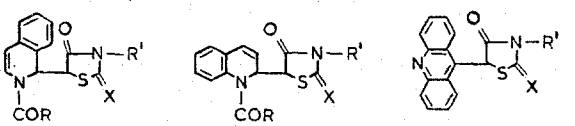


In the reaction of acridine with indoles under similar conditions, however, 9-(indolin-3-yl)acridines and N-acyldihydroacridines were obtained [39]. It must be mentioned that it has not previously been possible to introduce an acridine residue into the indole molecule in this way. Acridinylindoles can also be obtained by the reaction of acridine hydrochloride with indoles [39].

Hetarylation of Some CH-Acids

The most active N-acylisoquinolinium salts hetarylate organic CH-acids with pK_a values of about 20-21 (for example, acetone, with pK_a 20), while less active salts either are acylating agents under these conditions, or form dimers, or hetarylate the CH-acids. In particular, N-acylammonium salts are acylating agents only when tertiary aliphatic amines are used, and in these circumstances O-acylation and C-acylation of the carbonyl compounds take place to equal extents [6, 106, 107]. In the presence of pyridine, depending on the nature of the carbonyl component, either O-acylation (in reactions with β-dicarbonyl compounds) or pyridinylation (in reactions with ketones) takes place predominantly [12-15, 46]. As a rule, N-acylquinolinium, N-acylisoquinolinium, and N-acylphenanthridinium salts hetarylate both monocarbonyl and β-dicarbonyl compounds [7, 46, 78, 107]. Similarly, the reaction of acridine with acetophenones in the presence of acyl halides has led to 9-phenacylacridines and other ketones of the acridine series [56], although there is information in the literature that such reactions do not take place with acridine [46]. It has also been possible to synthesize heterocyclic derivatives of oxosteroids in the same way [79, 108, 109].

Making use of the activation of the heterocyclic nucleus in the molecules of thiazolidinones and pyrazolinones, like ketones, it has been possible to extend the method of hetarylation by N-acyl salts to these heterocycles, as well [42, 43].



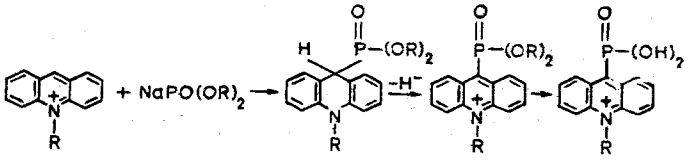
X = O, S, NC_6H_5; R = CH_3; C_6H_5; $N(C_6H_5)_2$; furyl; thienyl; OC_2H_5
R' = H; C_2H_5; C_6H_5

The alkaline hydrolysis of the compounds synthesized forms the corresponding thioglycolic acids of the heterocyclic series, and this can be regarded as a convenient preparative method for obtaining them [42, 43].

It has also been possible to extend the hetarylation reaction to such CH-acids as cyclopentadiene, phenylacetylene, indene, azulene, and guaiazulene (pK_a values 18, 15.5, 20, and 21, respectively) and others, while fluorene (pK_a 22.9) and ferrocene do not take part in this reaction [22, 110].

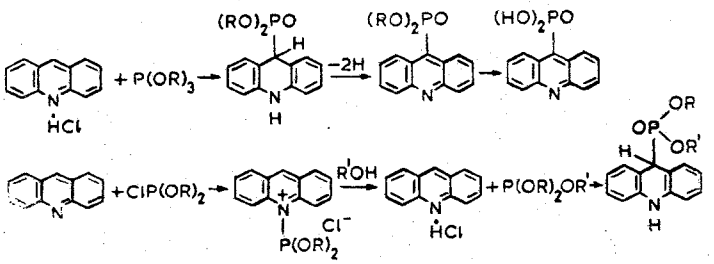
The Arbuzov Rearrangement under the Action of N-Acyl Heteroaromatic Cations

Recently it has been proposed to synthesize phosphonic acids of the acridine series by the reaction of acridinium salts with sodium diethyl phosphate [111].



Simultaneously [112], a general and more convenient method for synthesizing heterocyclic phosphonic acids on the basis of the reaction of heteroaromatic cations with trialkyl phosphites was developed. The performance of this reaction is particularly convenient with protonic salts of six-membered nitrogenous heterocycles or with their N-acyl salts, since in these circumstances the end-products of the reaction are heteroocyclic phosphonic acids, and not their quaternary salts [113-115].

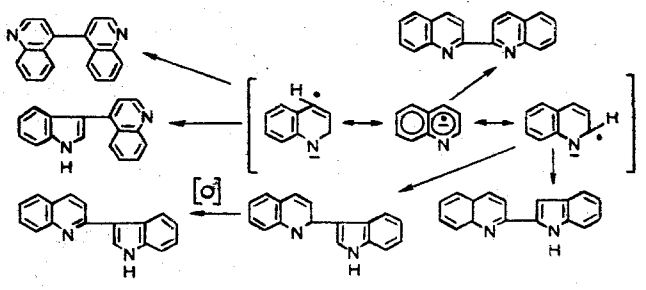
It has proved possible to simplify this method by combining the stages of obtaining the acridine hydrochloride and the trialkyl phosphites. For this purpose, the reaction of acridine with phosphorochloridites is performed in any alcohol, and the N-phosphoryl acridine salts so formed react with the alcohol to form trialkyl phosphites and acridine hydrochloride, which then takes part in the Arbuzov rearrangement [116]:



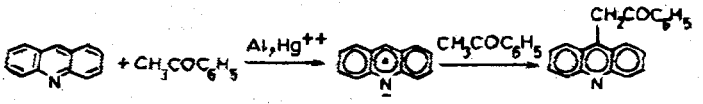
In this way it has also been possible to obtain mixed esters of 9,10-dihydroacridin-9-ylphosphonic acid.

Hetarylation of Organic Compounds with Nitrogenous Heteroaromatic Anion Radicals

It is not possible by using N-acyl salts to introduce heterocyclic residues into compounds containing NH, OH, and SH groups, since in these cases acylation, and not hetarylation, takes place. In view of this, a more universal method for the direct hetarylation of organic compounds used in heteroaromatic anion radicals formed in the one-electron reduction of nitrogenous bases with active metals has been developed [117-119]. In particular, when a mixture of any six-membered nitrogenous heterocycle and indole is heated with metals in an anhydrous aprotic solvent in an atmosphere of carefully dried nitrogen, a mixture of heterocyclic derivatives of indole and of biheterocycles is formed. The total yield of reaction products and the ratio of the isomeric hetarylindoles and biheterocycles formed is determined by the redox potential and by the coordinating capacity of the catalyst. Thus, in the reaction of quinoline with indole, depending on the catalyst, 2,2'-, 2,3'-, and 4,4'-biquinolinyls and 2- and 4-(indol-3-yl)quinolines, and also partially hydrogenated biquinolinyls, are obtained [117-119]:



Various hetarylindoles and also heterocyclic derivatives of other π-excess heterocycles, phenols, and aromatic amines have been obtained similarly. The hetarylation of ketones is possible in the same way provided that the heterocycle used in the reaction is reduced more readily than the ketone [120]. Otherwise, as the result of one-electron reduction of the ketones by the active metal, anion radicals are formed which attack the heterocyclic nucleus with the formation of tertiary alcohols or which dimerize with the formation of pinacones (Emmert reaction [121, 122]). On comparing the reduction potentials of various N-heterocycles and ketones, it was found that almost all pyridines, with the exception of acridine, are reduced with greater difficulty than acetophenone [123]. Because of this, on performing the Emmert reaction with pyridine, quinoline, and isoquinoline the corresponding tertiary alcohols are formed, while with acridine in all cases it was not carbinols but ketones of the acridine series that were obtained [120]:



In the absence of a nucleophilic organic compound, the reaction of six-membered nitrogenous heterocycles with active metals gave bihetaryls as a result of the recombination of the heteroaromatic anion radicals formed as intermediates. Preparative methods for obtaining pyridines, biacridinyls, biquinolinyls, and other biheterocycles have been based on this [119, 124].

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