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SYNTHESIS OF CONDENSED SYSTEMS ON THE BASIS OF THE REACTIONS OF HETEROCYCLIC COMPOUNDS CONTAINING AN AMIDINE FRAGMENT WITH BIFUNCTIONAL REAGENTS (REVIEW)

A. A. Kost

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The general principles of the creation of condensed heterocyclic systems with a bridged nitrogen atom on the basis of the reactions of α-amino nitrogen heterocycles with bifunctional compounds are examined. The mechanisms of the examined condensations, as well as the possibilities of the use of the examined reagents for the modification of the components of nucleic acids, are discussed.

The aim of the present review is to attempt to examine the general principles of the creation of condensed heterocyclic systems with a bridged nitrogen atom on the basis of the reactions of α-amino nitrogen heterocycles with bifunctional compounds for the search for new reagents that are potentially applicable for the modification of the heterocyclic bases of nucleic acids.

Despite the voluminous data on the synthesis of condensed systems, review works that examine the data from this point of view are not available. The data published up to 1959 is primarily summarized in the monograph by Mosby [1], which, however, classifies the literature with respect to the methods of synthesis of certain systems but not with respect to the reagents. This sort of attempt was made during an examination of the methods of synthesis of imidazopyrimidines [2]; however, the limited scope of the problem posed does not make it possible to formulate a general concept.

The overwhelming majority of reagents used for the solution of the formulated problem have been investigated in the case of the reaction with 2-aminopyridine. This makes it possible to restrict ourselves primarily to an examination of the reactions of 2-aminopyridine (I) with the aid of only individual examples to illustrate the generality of the method, possible complications in the process, and special details of the mechanism. Only α-amino nitrogen heterocycles constitute the subject of the examination, and in our subsequent use of the term heterocycle we will understand it to mean only such compounds.

For the creation of a new ring on the basis of an amidine fragment of a heteroring the reagent should have two electrophilic groupings, the distance between which determines the size of the resulting ring. Quite a few agents of this type can be conceived of in theory. In fact, however, the choice turns out to be considerably more limited, since not every pair of functional groups is compatible in the same molecule. Since very little is known regarding the mechanisms of cyclizations of the type under consideration, we were forced to construct our exposition of the material available on the character of the effect of agents with a clear understanding of the absolutely arbitrary character of the division introduced.

Dialkylating (Arylating) Reagents

2-Aminopyridine (I) reacts with alkyl halides primarily at the ring nitrogen atom [3] to give the N-alkyl derivative (II), which can either undergo intramolecular alkylation to give cyclization product III or react with a second molecule of the amine to give disub-

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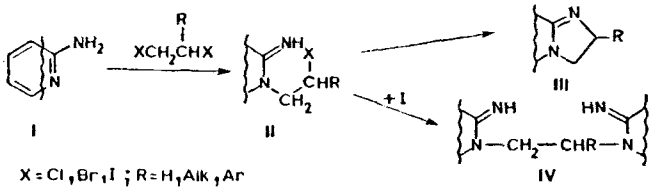
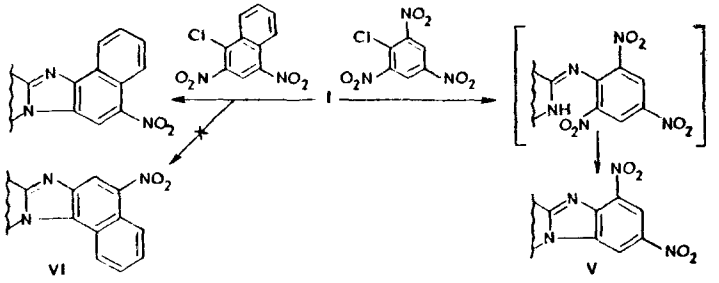
stituted derivatives of alkanes (IV). A second reaction pathway is usually realized for both amine I [3] and for other heterocycles [4]. However, examples of intramolecular alkylation are also known (for example, see [5, 6]).



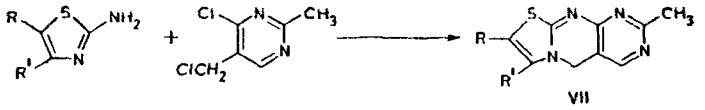
X = Cl, Br, I ; R = H, Alk, Ar

It is interesting that the reaction with 2,3-dibromopropionaldehyde [7] leads to the formation of an imidazole ring rather than to a pyrimidine ring. This should probably be explained by the lower electrophilicity of the carbonyl group of the agent as compared with the α-carbon atom bonded to the halogen.

Here, however, we are dealing with 1-chloro-2-nitro derivatives of benzene [8] and naphthalene [9], which react via an arylation scheme. It may be assumed that the reaction commences with attack by the carbon atom bearing the halogen on the sterically accessible amino group. The subsequent nucleophilic substitution of the nitro group is facilitated by the activating effect of a second nitro group and the advantageousness of the formation of an aromatic system [10]. The reaction proceeds under relatively severe conditions that are unsuitable for the components of nucleic acids.



As the hetarylating agent we need only note 2-methyl-4-chloro-5-chloromethylpyrimidine [11], the reaction of which with 2-aminothiazole leads to condensation product VII, the structure of which was confirmed by its identity with the product of oxidation of vitamin B_{12}.

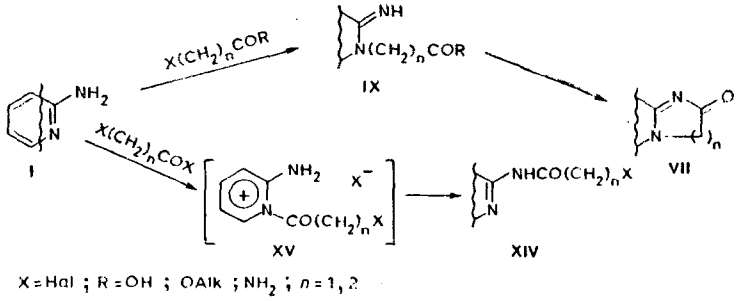


2,3-Dichloroquinoxaline reacts similarly [12].

Dialkylating agents have been used for the modification of nucleic acids, but the result is "crosslinking" of the two heterobases (structures of the IV type) but without the formation of a new ring [4].

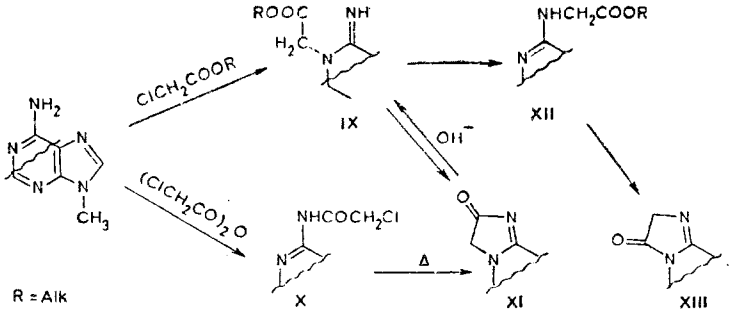
Reagents Capable of Alkylation and Acylation

Here we are primarily dealing with halo-substituted acids and their derivatives. The reaction of amine I with haloacetic acids was investigated by Chichibabin [13]. The condensation products are imidazo[1,2-a]pyrimidin-2-ones (VIII, n = 1). Chloroacetamide reacts



X = Hal ; R = OH ; OAlk ; NH_2 ; n = 1, 2

similarly [14]. The correctness of structure VIII was later confirmed [15, 16], and the isolation of intermediate IX made it possible to establish that the reaction usually commences with alkylation of the ring nitrogen atom. However, the primary reaction product in the case of strong acylating agents [17] is X, which undergoes cyclization of ketone XI. The process does not always take place unambiguously. Moreover, one cannot always draw correct conclusions regarding the scheme of the process on the basis of the structures of the final and intermediate products. Thus in the case of the reaction of N^9-methyladenine with α-halo acids [17] it was shown that opening of the imidazole ring of XI occurs under alkaline conditions. The resulting acid (IX) undergoes the Dimroth rearrangement [18] to give XII. It is only natural that cyclization of the latter leads to lactam

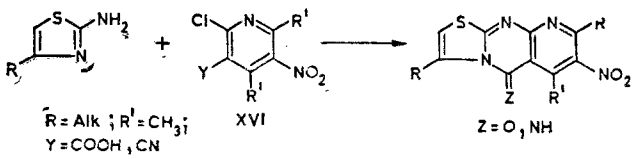


XIII rather than to ketone XI. The prior cyclization of acid IX to ketone XI is not a necessary condition for the occurrence of the Dimroth rearrangement. When one carries out the condensation under conditions that permit the rearrangement, one should therefore observe the formation of the most stable isomer; a mixture of both possible isomers is most often formed.

The reaction of amine I with derivatives of β-halopropionic acid [19] leads to 2-oxopyrido[1,2-a]pyrimidines (VIII, n = 2). In this case also, the ring nitrogen atom is alkylated, but it is not acylated. Examples of the use of activated derivatives of hydroxy acids such as β-propiolactone are known [19]. The presence of substituents in the heteroring may substantially change the relative nucleophilicity of the individual groupings of the molecule and, consequently, the direction of attack of the agent. Thus in the reaction of 2-amino-5-bromopyridine with β-propiolactone alkylation takes place at the amino group [19]. In this case also the reaction may be complicated by rearrangements. In the case of anhydrides and halides of halogenated acids, in which the electrophilicity of the carbonyl carbon atom is high, one can isolate a product of acylation of the amino group (XIV) as an intermediate; the latter is probably formed as a result of isomerization (presumably intermolecular) of the primary reaction product, viz., an acylium salt of the XV type. The fact that 1-acylpyridinium salts are formed exceptionally easily and, being strong acylating agents, readily transfer an acyl group to amines [20, 21] constitutes evidence in favor of this assumption.

Bis(β-chloroethyl)carbamoyl chloride reacts with 2-aminobenzimidazole as a γ-halo acid with the formation of a seven-membered ring; the ring nitrogen atom undergoes acylation in this case, while the amino group undergoes alkylation [22].

The condensations of amine I with o-chlorobenzoic acid [23] and 2-aminothiazole [24] with nicotinic acid derivatives (XVI) are examples of the use of aromatic halo acids. In contrast to aliphatic halo acids, the ring nitrogen atom is acylated in this case, while

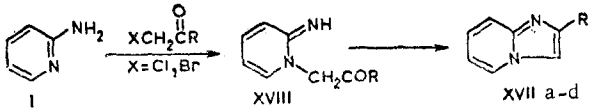


the amino group is arylated. Steric factors, which hinder attack on the ring nitrogen atom, probably determine the direction of attack. It might be assumed that the amino group is arylated initially, whereas cyclization is the result of subsequent acylation. However, no data on the structures of the intermediates are available for most such models.

Reagents of this type are of interest for the modification of nucleic acids and have already found some application, although it should be remembered that the reaction is frequently accompanied by side processes.

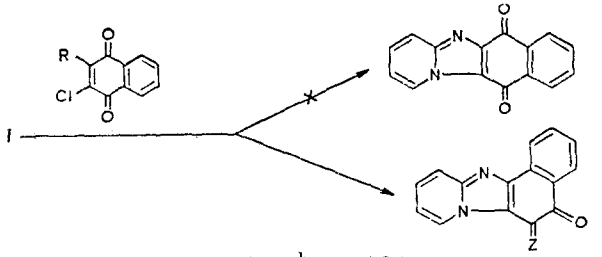
Alkylating Derivatives of Carbonyl Compounds

In 1925 Chichibabin [25] obtained imidazo[1,2-a]pyridine (XVIIa) by treatment of amine I with bromoacetaldehyde at 150-200°C. It was later shown [26] that XVIIa is readily obtained in aqueous alcohol solutions at room temperature. In this case the structure of the condensation product is unambiguous regardless of the direcion of addition of the agent. The reaction of amine I with chloroacetone [25] leads to the methyl homolog of XVIIa, to which the XVIIb structure was assigned, although one might have expected the formation of two isomers. It was later established [27, 3] that alkyl, benzyl, and phenacyl halides alkylate heterocycles virtually only at the ring nitrogen atom, i.e., with the formation of compounds of the XVIII type, which also determines the structure of the condensation product. The direction of addition of the agent was confirmed in a number of cases by alternative synthesis [28].



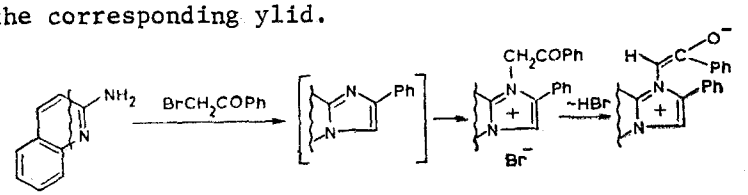
XVII a R=H; b R=CH_3, c R=Alk, d R=Ar

The use of aliphatic and aromatic α-halo carbonyl compounds is currently a popular method for the creation of condensed systems (for example, see [2]). The choice of agents is quite extensive. As examples one may mention 2-chlorocyclohexanone [29], 2-bromo-1-tetralone [30], ω-chloro-2-acetothiophene [31], tosyloxyacetone [32], and 2,3-dichloro- and 2-acetamido-3-chloro-1,4-naphthoquinone [33]. Halonaphthoquinones [33] react at α-halo carbonyl compounds to give condensation products XIX. In the case of the 2,3-dichloro derivative the reaction is accompanied by hydrolysis of the chlorine atom that does not participate in cyclization, and this leads to o-quinone derivative XIXa.



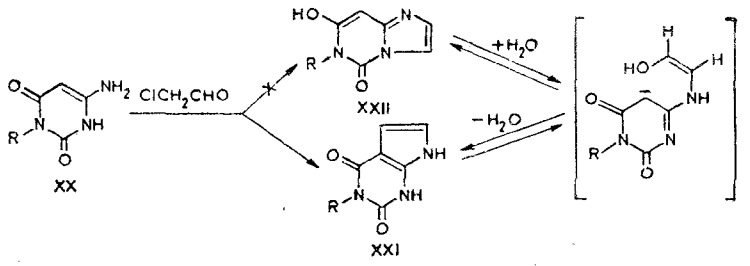
R=Cl, $NHCOCH_3$; XIX a Z=O, b Z=$NCOCH_3$ XIX a, b

Like the reagents of the types examined above, α-halo carbonyl compounds do not always react unambiguously. Thus the reaction of 2-aminoquinoline with phenacyl bromide [34] does not stop at the step involving the formation of the imidazoquinoline. The latter is alkylated by a second molecule of the agent, while the resulting quaternary salt is stabilized in the form of the corresponding ylid.



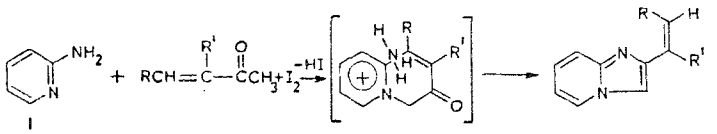
The expected condensation products are formed in the reaction of chloroacetaldehyde with adenine and cytosine derivatives [35]. At the same time, pyrrolo[2,3-d]pyrimidine derivatives (XXI) are formed in the reaction with pyrimidine XX [36], although one cannot exclude the initial formation of XXII, which undergoes rearrangement to the thermodynamically more stable isomer XXI.

The possibility of this recyclization with attack of the carbanion was demonstrated in the case of the conversion of pyrimidoindoles to α-carbolines [37, 38].



1,2-Dichloroethyl ether [5], which can be regarded as a reagent with a "latent" carbonyl group, should be classified with reagents of the same type. The use of such agents may prove to be more expedient in a number of cases, since the generation of an aldehyde function at the instant of cyclization makes it possible to avoid undesirable side processes. Nevertheless, it is possible that processes of this sort take place without the generation of an oxo compound by direct nucleophilic attack of the nitrogen atom of the amino group on the carbon atom of the agent, which is activated by the presence of an adjacent ethoxy group and a halogen atom.

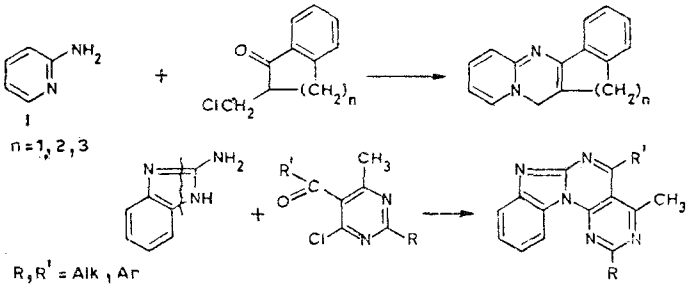
Giller and co-workers [39, 40] have proposed an interesting variant of a reaction of the type under consideration that consists in the reaction of vinyl ketones with amino-substituted heterocycles in the presence of iodine.



The first step in the process is the King reaction [41], which leads to a β-ketoalkylpyridinium iodide; under the reaction conditions the latter undergoes cyclization to a vinyl-substituted imidazo[1,2-a]pyridine.

Reagents of this type make it possible to incorporate various functional substituents in the newly formed system. Thus bromopyruvic ester reacts with derivatives of I with retention of the carbethoxy group [42]. Similarly, chloro(bromo)malondialdehyde forms an imidazole ring with amino-substituted heterocycles with retention of one of the carbonyl groups [7]. One must note ω-chloro-ω-acylaminoacetophenone [43] and amides of monochloroacetic acid [44], the use of which makes it possible to incorporate an amide group with an extensive set of substituents in the newly formed imidazole ring. The mild conditions under which the condensation is carried out, which makes it possible to use them for a large number of heterocycles, constitute a substantial advantage of reagents of this type.

The use of β-halo carbonyl compounds leads to condensed systems with a pyrimidine ring. Everything that we stated above regarding the scheme of addition of the agent and the advantages and disadvantages of the method is equally valid for β-halo carbonyl compounds [45]. As examples, let us cite the reaction of cyclic β-halo ketones [46] and the use of β-halo carbonyl agents based on pyrimidine derivatives [47].



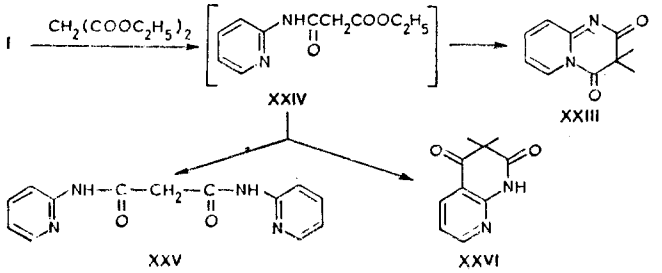
Thus α- and β-halo carbonyl compounds have found wide application for the synthesis of condensed systems and, in particular, for the modification of the heterocyclic bases of nucleic acids [35].

Diacylating Reagents

Reactions of free dicarboxylic acids with heterocycles that lead to the creation of a new ring are unknown. Although guanidine derivatives can form 4,5-dioxoimidazoles with

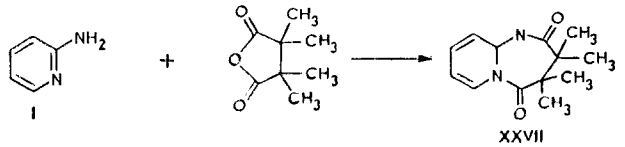
oxalyl chloride [48], oxalyl chloride usually reacts with two molecules of the amine to give the corresponding oxamides. Attempts to obtain 2,3-dioxoimidazo[1,2-a]pyridines from amine I and oxalic acid derivatives have been unsuccessful [49].

However, dicarboxylic acid derivatives are used for the creation of six- and seven-membered rings. Thus the condensation of amine I with diethyl malonate [50] leads to pyrido[1,2-a]pyrimidine XXIII.

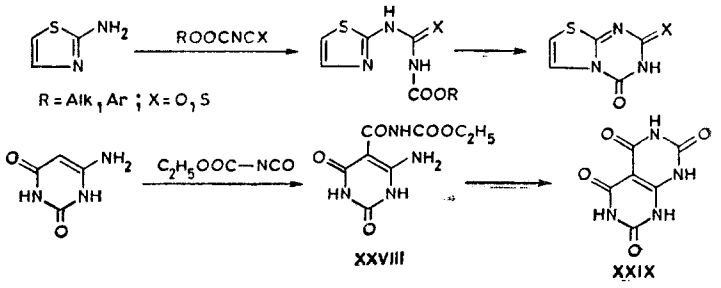


In the case of the reaction with 2-aminoimidazole it was shown [51] that the process commences with acylation of the amino group. In a number of cases [52] the reaction is complicated by reaction of amino acyl derivative XXIV with a second molecule of the amine (as observed for dialkylating reagents), and the corresponding diamide XXV is formed in addition to the expected condensation product (XXIII). The process involving the formation of the diamide frequently becomes the dominant process. In addition, it has been shown [53] that in the reaction of 6-substituted 2-aminopyridines with malonic acid esters cyclization of intermediate XXIV takes place at the C_3 atom of the pyridine ring to give naphthyridines XXVI. The authors explain this by the steric effects of the substituent, which make attack by the carbethoxy group on the carbon atom preferable. Reactions of this type require relatively severe conditions and have not been widely used.

Compounds of the XXVII type, which have a seven-membered ring, are formed quite readily in, for example, the reaction with succinic anhydride or substituted derivatives of the latter [54].

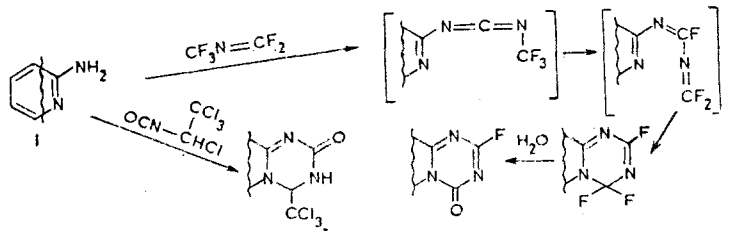


Here one may cite ethoxy- and phenoxycarbonyl isocyanates [55], as well as ethoxycarbonyl isothiocyanate [56, 57], the action of which leads to the formation of a triazine

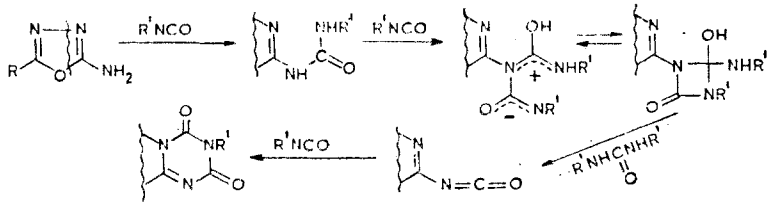


ring. However, ethoxycarbonyl isocyanate reacts with 6-aminouracil [58] at the most nucleophilic C_5 atom to give XXVIII, which is readily converted to condensation product XXIX.

1,2,2,2-Tetrachloroethyl isocyanate [59] and perfluoroazapropylene [60], the action of which also leads to the formation of a triazine ring, have also been recently used for similar purposes.



It must be mentioned here that alkyl and aryl isocyanates, being monofunctional agents, can nevertheless react with amino-substituted heterocycles to give a new triazine ring [61-63]. The mechanism of the reaction is unclear and gives rise to some discussion. Let us cite one of the most convincing (in our opinion) variants [62].

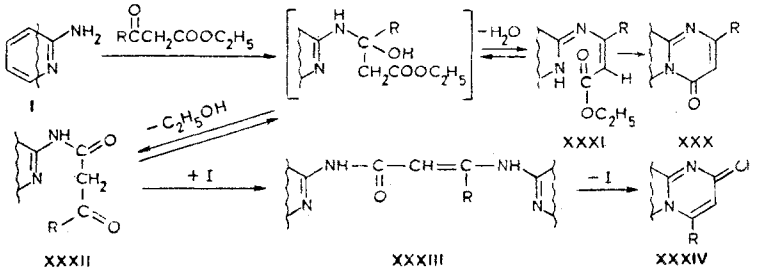


It must be noted that condensations of this sort are markedly complicated by numerous side processes [63] and can hardly be of preparative value.

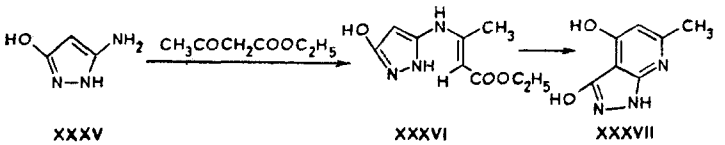
Upon the whole, of the reagents of the examined group the greatest interest is elicited by bifunctional derivatives of isocyanates and isothiocyanates, the reactions of which with amino-substituted heterocycles proceed under rather mild conditions to give the products in good yields and can be carried out in aqueous media, which is important for the problem of the modification of nucleic acids that is of interest to us.

Acylating Derivatives of Carbonyl Compounds

Pyruvic and glyoxylic acids have not been investigated with respect to their behavior in condensations of the type under consideration. On the other hand, β-oxocarboxylic acids are quite widely used; their reactions with amine I lead to pyrido[1,2-a]pyrimidines XXX



[64]. It is assumed that the reaction commences with attack by the carbonyl carbon atom on the nitrogen atom of the amino group to give aminocrotonate XXXI. Subsequent ring closing leads to the formation of a pyrimidine ring with a keto group in the α position relative to the bridged nitrogen atom. Most of the agents of this group react via the scheme presented above, although there are, of course, exceptions [65]. Reactions of this type depend substantially on the conditions under which they are carried out and do not always proceed unambiguously. Thus Khitrik [66] has shown that the expected condensation product (XXX) is formed when amine I is heated rapidly with acetoacetic ester. However, during an attempt to carry out this reaction stepwise under mild conditions it was found that the primary product is acyl derivative XXXII, which upon heating adds a second molecule of I to give XXXIII. A further increase in the temperature leads to cyclization of the latter to pyridopyrimidone XXXIV with splitting out of a molecule of I. In the light of modern concepts it might be assumed that the initial product in this case also is an aminocrotonate of the XXXI type, which upon gradual heating is converted to XXXII. It is evident that the direction of cyclization of aminocrotonate XXXI will be determined by both steric factors and the relative nucleophilicities of the possible centers of attack. Thus the condensation of aminopyrazolone XXXV with acetoacetic ester [67] evidently also commences with the formation of aminocrotonate XXXVI, but in this case the most nucleophilic center is probably the C_4 atom, and cyclization leads to the formation of structure XXXVII.



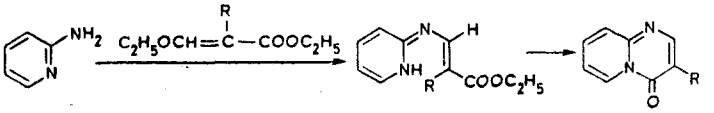
XXXV XXXVI XXXVII

Various keto esters, including the cyclic type, have been subjected to this reaction. By varying the size of the ring and its nature one can obtain diverse condensed systems that include a pyrimidine ring [68]. The use of the corresponding aliphatic [69] or cycloaliphatic nitriles [70] in place of esters makes it possible to introduce an amino group in the resulting pyrimidine ring.

Reagents of this group are widely used in the chemistry of heterocycles but have not found application in the modification of the components of nucleic acids. This is probably associated with the necessity for the use of high temperatures (100-200°C) and aprotic solvents.

Unsaturated Acylating Reagents

With respect to the character of their effect, the reagents of this group are most intimately related to those examined in the preceding section. Thus the reaction of amine I with ethoxymethylenemalonic ester [7] leads to condensation products of the XXX type. The direction of addition of the agent was demonstrated [72] by the isolation of an intermediate aminocrotonate (XXXIa) and its cyclization to lactam XXXa. Replacement of one of the ethoxy

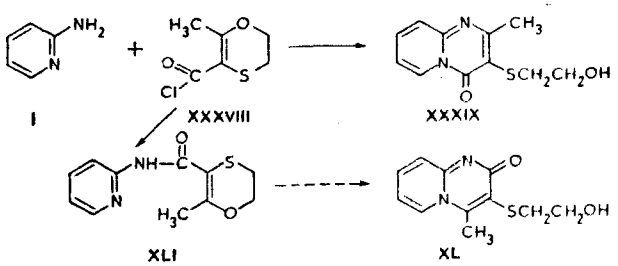


I XXXIa XXXa

groups of the reagent by a nitrile group naturally does not affect the overall scheme of the reaction. However, in this case cyclization may proceed with the participation of both the carbethoxy and nitrile groups, and this leads to the formation of two reaction products [71-73].

β-Chloro- [74] and β-aminocrotonic esters [75] react similarly. In the latter case the initial step of the reaction, viz., transamination, should be reversible, but the liberation of ammonia shifts the equilibrium to favor the formation of the condensation product.

An interesting example of reactions of the type under consideration is the reaction of amine I with chloro anhydride XXXVIII, which leads to the formation of pyridopyrimidine XXXIX, the structure of which was established on the basis of the UV spectra [76]. However, one cannot exclude alternative structure XL without clear evidence, especially since



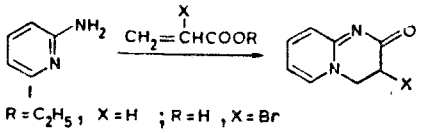
I XXXVIII XXXIX XLI XL

XLI, the cyclization of which will lead to XL but not to XXXIX, was isolated from the reaction mixture (in 4% yield).

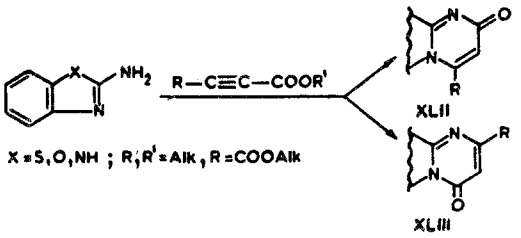
The conditions under which the reaction is carried out have a substantial effect on the scheme of the process and, consequently, on the structure of the condensation products. The reaction frequently proceeds ambiguously and, as a rule, at high temperatures in nonpolar solvents. All of this limits the applicability of reagents of this type for the purposes of interest to us.

Derivatives of acrylic and propiolic acids, which react quite well in polar media, are agents of the same type. Acrylic acid itself reacts readily with amine I to give N-carboxyethylation products; the formation of cyclic compounds was not noted [77]. Activation of

the carboxy carbon atom of acrylic acid by conversion to the ester or by the introduction of an electron-acceptor substituent in the α position makes this carbon atom sufficiently electrophilic for reaction with the amino group of the heterocycle [78].



Acrylonitrile reacts similarly [79]. However, it may additionally cyanoethylate the functional groupings of the heterocycle.

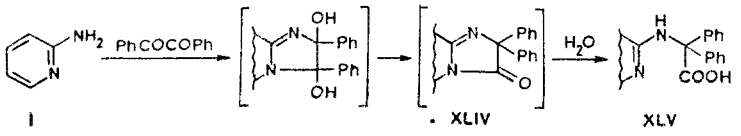


Compounds with a triple bond undergo condensation to give compounds of the XLII type but not of the XLIII type [80], although exceptions are known [81]. Thus the condensation of 1-methyl-2-aminoimidazole with dimethyl acetylenedicarboxylate [82] leads to the formation exclusively of XLIII.

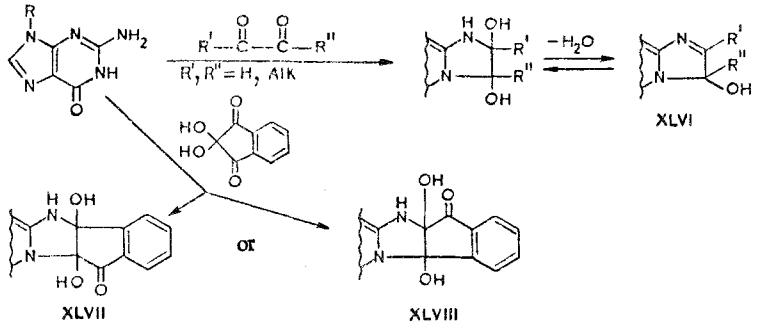
The condensation of cytosine and adenine derivatives with cyanoacetylene [83] also leads to the formation of a new pyrimidine ring.

Dicarbonyl Reagents

α-Dicarbonyl compounds react with amino-substituted heterocycles to give unstable condensation products. A reaction with benzil [84] that leads to a very unstable substance (probably XLIV), which reacts with water to give amino acid XLV, is known for amine I.

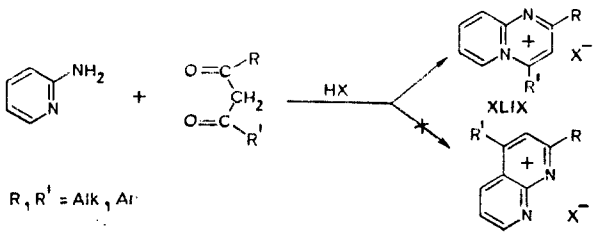


The reactions of the simplest α-dicarbonyl compounds [85] with guanine derivatives lead to unstable three-ring structures XLVI.

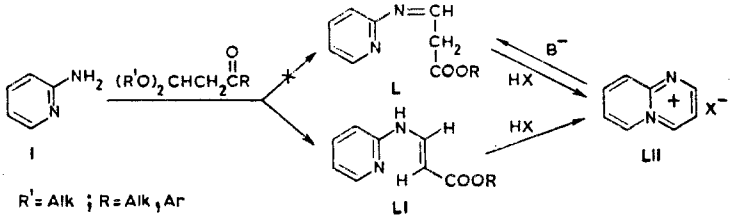


Guanine derivatives also react with ninhydrin. It is assumed [86] that the process takes place via a similar scheme; the structure of the cyclization product has not been rigorously proved (structures XLVII and XLVIII are alternatively possible). However, the center of electrophilic attack in the reaction of ninhydrin with cytosine derivatives [87] is the 5-C atom, and a pyrrole ring rather than an imidazole ring is formed.

Methods for the creation of a new ring with the aid of β-dicarbonyl compounds have been developed most extensively. Reactions with them usually lead to the formation of a pyrimidine (structure XLIX) rather than a pyridine ring [88, 89].



As assumed in [90], Schiff base L is formed initially in the reaction of amine I with a β-ketoacetal. It was later established [91] that the structure of the intermediate corresponds to LI; however, this naturally does not affect the structure of cyclization product LII. The cyclization step is reversible; the pyrimidine ring of LII is opened during nucleophilic attack.



The establishment of the structures of the products of condensation with unsymmetrical β-dicarbonyl compounds is fraught with difficulties [92]. The following empirical principle was formulated on the basis of numerous experimental data [93]: if the reagent has alkyl and aryl substituents, the alkyl substituent is usually in the 2 position in the condensation product, whereas the aryl substituent is usually in the 4 position.

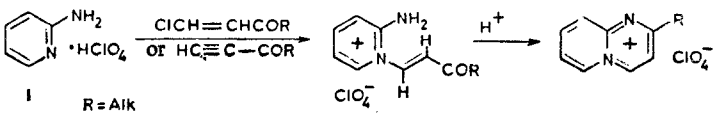
Malondialdehyde bis(diethylacetal) reacts similarly with amino-substituted heterocycles [94, 95]. Various cyclic β-dicarbonyl compounds such as 2-formylcyclohexanone have been successfully used in the condensations [96].

It is expedient in this section to regard β-chlorovinyl ketones as active agents that have a "latent" carbonyl group. Both alkyl [97] and aryl β-chlorovinyl ketones [98] react with amine I via the scheme examined above for β-diketones to give the corresponding condensation products of the XLIX type. The reaction is generally carried out in the presence of strong acids, and intermediate structures were not established. Aliphatic and cycloaliphatic β-chlorovinyl aldehydes undergo the condensation most readily [99].

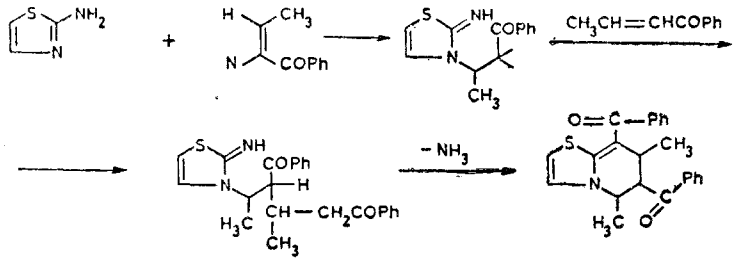
Thus α-dicarbonyl compounds have found application in the chemistry of nucleic acids, despite the high labilities of the condensation products. As regards β-dicarbonyl compounds, as we have seen, severe acid catalysis is required for successful reaction at the amidine fragment of the heteroring, and this is unsuitable for the components of nucleic acids.

Unsaturated Carbonyl Reagents

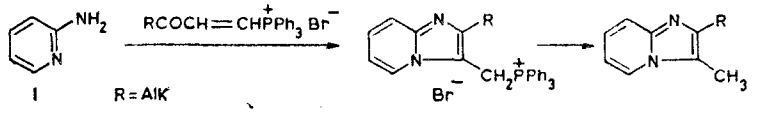
Like the derivatives of unsaturated acids examined above, α,β-unsaturated aldehydes and ketones primarily attack the endocyclic nitrogen atom by means of the β-carbon atom. It is known that the perchlorate of amine I reacts with acetylenic ketones to give compounds with the same structures as in the reaction with the corresponding β-chlorovinyl ketones [100].



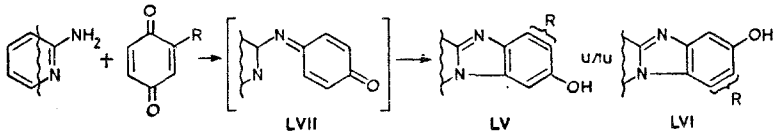
The reaction has a number of limitations and exceptions in the case of unsaturated ketones. As a result of a rather high reaction temperature, of the alternative possibilities, cyclization takes place at the carbon atom rather than at the ring nitrogen atom. Thus 2-aminoindoles react preferably with the formation of α-carbolines rather than pyrimidoindoles [101]. 2-Aminothiazole reacts with phenyl propylene ketone [102] to give LIII, which adds a second molecule of the reagent and undergoes cyclization to pyridothiazole LIV with the loss of a molecule of ammonia:



In the reaction of amine I [103] and adenine, guanine, and cytosine derivatives [104] with β-acylvinylphosphonium salts attack of the ring nitrogen atom occurs by means of the more electrophilic α-carbon atom of the agent, and a pyrimidine ring rather than an imidazole ring is formed as a result of cyclization.



The condensation with halonaphthoquinones has been discussed earlier. Functionally unsubstituted quinones react with amine I like unsaturated carbonyl compounds to give pyridobenzimidazole derivatives [105]. As is frequently observed in the reactions of quinones with amines, the process is usually accompanied by polymerization [16].

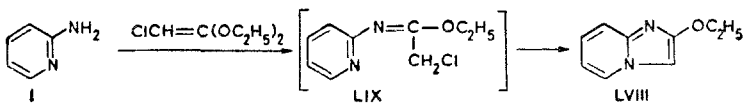


It is assumed that compounds with the LV structure are formed in this case, although structure LVI is not excluded. The formation of two substances, probably the 6- and 7-methyl-8-hydroxy derivatives, was noted when R = CH_3. The reaction with naphthoquinonediimine proceeds similarly [106]. It was demonstrated relatively recently in the case of the reaction of quinone with 2-amino-1,3,4-thiadiazole [107] that the first act in the reaction is the reaction of the amino group of the heterocycle with the carbonyl carbon atom of the quinone (structure LVII) and that the structure of the condensation product corresponds to LV.

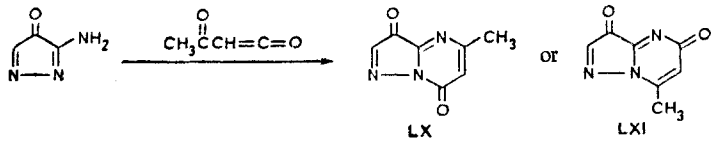
Thus processes that involve the participation of reagents of this group take place ambiguously and are frequently markedly complicated by side reactions. In the case of unsaturated ketones condensation at the amidine fragment of the heteroring is generally uncharacteristic, and proton catalysis and high reaction temperatures make these reagents unpromising for the modification of the heterocyclic bases of nucleic acids.

Ketenes and Their Derivatives

The most thoroughly investigated representative of this group of reagents is chloroketene diethylacetal. Its condensation with amine I leads to 2-ethoxyimidazo[1,2-a]pyridine (LVIII) as the principal reaction product [108]. However, the reaction proceeds ambiguously and generally leads to the formation of a mixture of substances [109]. This reaction evidently proceeds through the formation of imido ester LIX (the formation of such imido esters has been demonstrated for aromatic amines in reactions with substituted acetals [109]). In contrast to β-chlorovinyl ketones, the chlorine atom attached to the double bond that is unconjugated with the carbonyl group turns out to be inactive.

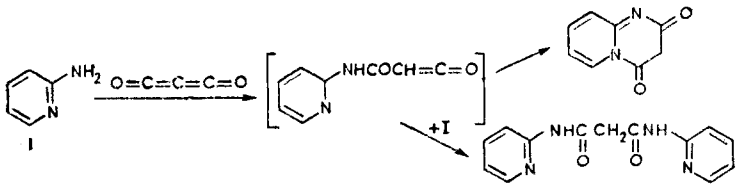


Under very mild conditions diketene forms cyclization products that are identical to those obtained in reactions with acetoacetic ester [110, 111]; the endocyclic nitrogen atom is primarily acylated in this case. In the example presented below, the structure of the pyrazolopyrimidine is postulated as LX, although one also cannot exclude the LXI structure.



LX LXI

Here, however, one may make reference to carbon suboxide, which reacts readily to give a dioxopyrimidine ring [112]. In the case of amine I, 2-aminobenzoxazole, and 2-amino-5-



I

phenyloxazole the yields of condensation products are close to quantitative [112]. However, in the case of aminopyrazoles it was noted that, in addition to the expected condensation product, the intermediately formed amide reacts with a second molecule of the amine to give the corresponding malonylbisamide [113].

Upon the whole, relatively little study has been devoted to reagents of this group. They are distinguished by high reactivities, as a result of which selectivity is virtually completely absent.

Summarizing the data examined above on bifunctional reagents used for the creation of condensed systems it may be stated that the majority of the agents that are being used successfully for the solution of purely synthetic problems in the chemistry of nitrogen heterocycles are evidently unpromising for the solution of the problem of interest to us. This is due primarily to the specificity of the requirements imposed on the agent for the chemical modification of nucleic acids (the necessity for carrying out the reactions in aqueous media at pH values close to neutral and at temperatures that do not exceed the physiological temperature substantially); compounds that are potentially applicable for the solution of our problem can be noted in virtually each of the groups of agents that we examined.

Upon the whole, we hope that our attempt to examine the basic principles of the creation of condensed heteroaromatic systems, despite its certain tendentiousness with respect to the presentation of the material, which was dictated by the problem posed at the outset, may prove to be useful in the selection of the strategy and tactics in the synthesis of condensed systems on the basis of the examined principle and may serve as an impetus in the search for new reagents and methods.

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SYNTHESIS AND AUTOOXIDATION OF 2-AMINO-1,3-DIALKYLINDOLES

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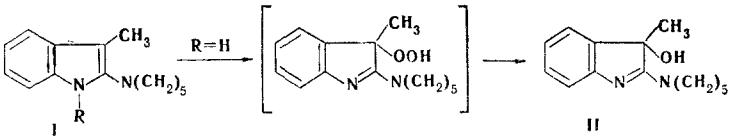
Autooxidation occurs during the liberation of the bases from the salts of 1,3-dialkyl-2-aminoindoles, and stable 3-hydroperoxides are formed. The same compounds can also be obtained without prior isolation of the salts via heterocyclization of 1-acyl-2-arylhydrazines. If one of the nitrogen atoms is not alkylated, the corresponding 3-hydroxy compounds are obtained.

Indole compounds readily undergo autooxidation to give 3-hydroxy and 3-peroxyindolenines or products of their subsequent transformation, viz., substituted oxindoles, 2-acylindoles, dimeric structures, or compounds with an opened pyrrole ring (see the previous reviews [1, 2]). The electron-donor amino group of 2-aminoindoles facilitates autooxidation substantially [3], since only the corresponding 2-imino-3-hydroxy-3-alkyl(phenyl)-indolenines can often be obtained in the isolation of these amines from salts [4-6].

It has been established [4, 7] that imine I (R = CH_3) is resistant to air oxidation, while the nitrogen-unmethylated analog of I (R = H) cannot be isolated from its hydrobromide, since during the reaction it is converted to hydroxy compound II.



I II

Nakagawa and co-workers [8] assume that the formation of hydroxy compound II proceeds through a step involving a hydroperoxide, since 3-hydroperoxides have been previously isolated in the autooxidation of 2,3-dialkylindoles [9]. The hydroperoxide itself was not isolated, but its intermediate formation is confirmed indirectly by the fact that in the presence of dihydrocollidinedicarboxylic acid ester (the Hantzsch ester), which is stable with respect to autooxidation under these conditions, it undergoes aromatization in almost quantitative yield.

We used our previously described method of heterocyclization of 1-acyl-2-arylhydrazines (III) [10] for the synthesis of the hydrochlorides of some 2-amino-1,3-dialkylindoles (IV) and unexpectedly observed [11] that the bases of these amines, which exist in the form of 2-iminoindolines (V), form stable 3-hydroperoxides (VI) upon brief standing in air and sometimes even during isolation from the salts; attempts to isolate 3-hydroperoxides VI from the

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