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Advances in the Chemistry of Enamines

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The review surveys the results of studies on the physicochemical and chemical properties of enamines. Special attention has been devoted to the employment of enamines in the synthesis of various heterocyclic systems.
The bibliography includes 236 references.

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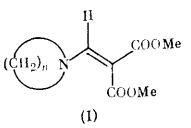
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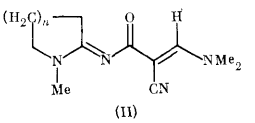
I. INTRODUCTION

The chemistry of enamines is at present one of the most vigorously developing fields of organic synthesis and the number of publications concerning the properties and reactions of these compounds continuously increases. Because of this and despite a whole series of reviews dealing with various aspects of the chemistry of enamines and related compounds[1-14], it is useful to survey the extensive data published in recent years (mainly in 1977–1982), obtained in the study of various types of enamine systems. The present review does not deal specially with publications describing the methods of synthesis of various enamines since fundamentally new data have not become available in this field and the known methods of synthesis of enamines have already been discussed in detail[1]. As a rule, studies on the chemistry of different classes of enamines which have been included in the reviews mentioned above are also not dealt with.

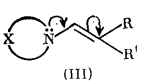
II. STRUCTURAL STUDIES, PROTONATION, AND HYDROLYSIS OF ENAMINES

The spectroscopic studies on enamines published in recent years were devoted mainly to stereochemical aspects of these compounds[15-24]. The study of the hindered rotation about the enamine C–C bond in enaminoesters of type (I) has shown that the main factors which determine the kinetic and thermodynamic parameters of this process are the degree of conjugation of the nitrogen atom with the double bond in the ground state and the extent of the non-bonding interaction between the amino-fragment and the *cis*-COOMe group which is non-planar in the ground state[15]:

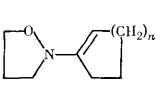

(I)

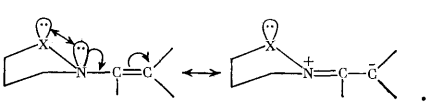

(II)

Another problem, that of hindered rotation about the single N–C bond, was also investigated in the above study[15]. An analogous process has been discovered and investigated for enaminoacylamidines (II)[16]. The study of the ^{13}C NMR spectra of a large group of enamines[17-19] established that the chemical shifts of the β-carbon atom in these compounds are extremely sensitive to the steric factor[17]. On the other hand, if this factor does not vary in various compounds, the chemical shift of the β-carbon atom serves as a characteristic of the electron density. In cyclic enamines the electron density and hence the degree of conjugation of the nitrogen atom with the C–C bond is highest for the pyrrolidine enamines[18]:


(III)

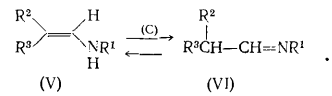
The study of the ^{15}N NMR spectra led to the conclusion that the nitrogen atom in enamines has the sp^2 configuration[19]. On the other hand, photoelectron spectroscopic data indicate a pyramidal configuration of the nitrogen in enamines, in contrast to the corresponding radical-cation where the configuration is planar[20]. It is extremely interesting that the ^{15}N NMR spectra are not correlated with ^{1}H NMR and ^{13}C NMR spectroscopic data in the sense that the chemical shifts in ^{15}N NMR are almost indistinguishable for pyrrolidine and piperidine enamines. The authors attribute this inconsistency to the fact that in their view a change in electron density at the nitrogen atom is not in this instance a decisive characteristic of the chemical shift of this atom[21]. One must agree with this view, since extensive chemical and physicochemical data leave no doubt at the present time that the degree of the "enamine" conjugation in the pyrrolidine enamines [III, X = $(CH_2)_4$] is greater than in the piperidine and morpholine analogues. This is also supported by the results of the X-ray diffraction analysis of enamines[22], which indicate a higher degree of planarity of the enamine fragment in the pyrrolidine enamines than in the piperidine and morpholine analogues. The literature concerned with the differences between the $p\pi$ conjugations in enamines of type (III) has been analysed in detail[23]; the authors attempted to increase the extent of this conjugation still further by replacing the pyrrolidine ring by the tetrahydroisoxazole ring:


(IV)


(A) (B)

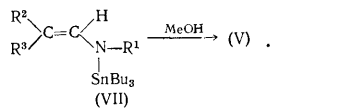
The idea was that the repulsion of the neighbouring free electron pairs leads to an increase of the extent of the enamine conjugations (A) ↔ (B). However, it has been established both spectroscopically (^{1}H and ^{13}C NMR) and chemically (reaction with acrylonitrile) that in enamines (IV) the

degree of $p\pi$ conjugation and hence the reactivity with respect to electrophiles are lower owing to the negative inductive effect of the oxygen atom. Among the studies devoted to the imine–enamine tautomerism[25–27], we shall note those dealing with the secondary enamines (V) lacking β-electron-accepting substituents[25]:



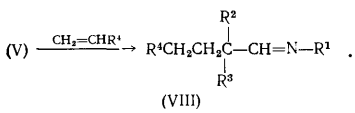
(V) (VI)

Such enamines are usually unstable and the equilibrium (C) is displaced towards the corresponding imines (VI). However, the authors[28] were able to isolate the kinetic product (V) by the methanolysis of the organometallic derivatives (VII) in the presence of a deficiency of methanol:



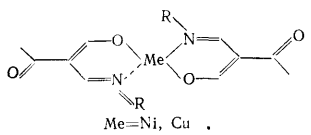
(VII)

It is known that the reactions of the imine (VI) with unsaturated compounds, which proceed via equilibrium (C), require prolonged heating (for 24 h at 80 °C) and in many cases do not occur at all. On the other hand, when the pure enamine (V) is used in such processes, a rapid exothermic reaction is observed even at 0 °C with formation of a substituted imine (VIII):



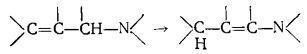
(VIII)

The formation of extremely stable copper(II) and nickel(II) complexes of enaminoketones and enaminoamides is accompanied by the conversion of the enaminocarbonyl compounds into the iminoenol form[28]:

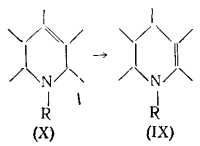


Me=Ni, Cu .

The communication of Martinez and Joule[29], which includes extensive literature and experimental data on the allylamine → enamine isomerisation, was devoted to the problem of the stability of the enamine structure:



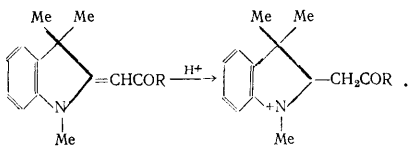
It was established that the enamines 2-piperideines (IX) are thermodynamically more stable than 3-piperideines (X) and that isomerisation takes place in the presence of bases:



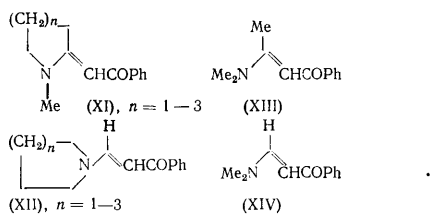
(X) (IX)

The energy gain is due to the $p\pi$ conjugation and has been estimated as 2.5 kcal mol^{-1}.

The problem of the protonation and hydrolysis of enamines occupies a notable place in their chemistry[1,11]. Investigations of the traditional type, dealing with the study of the insufficiently clear problems of the mechanism of the hydrolysis of enamines of various types and the factors determining the particular site of the protonation of these compounds, and studies in which the protonation of enamines is used as an intermediate stage for the attainment of synthetic aims have been published in recent years. Among the investigations of the first kind, we may point to those dealing with the protonation of enamines in the gas phase[20,31], where it was shown that in cases where there is no steric inhibition of the $p\pi$ conjugation in enamines the protonation proceeds via the β-carbon atom. A number of studies have been devoted to the problem of the protonation of enaminoketones, but, whereas Kozerski[32] established with the aid of ^{13}C NMR what is in general an unusual fact[1,11], namely the *O*-protonation of these compounds, Bailey et al.[33] indicate a rare instance† of the protonation of enaminoketones at a carbon atom:



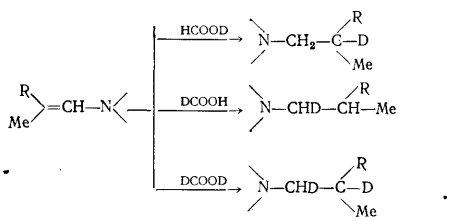
The study of the basicity and ^{1}H NMR spectra of the cyclic enaminoketones (XI) and (XII) and their acyclic analogues (XIII) and (XIV) showed that compounds (XI) and (XIII) are more basic approximately by 2–3 orders of magnitude than compounds (XII) and (XIV), which is caused by the different sites of protonation [compounds (XI) and (XIII) are protonated at the β-carbon atom, while compounds (XII) and (XIV) are protonated at the oxygen and nitrogen atoms[35]]:



(XI), $n = 1-3$ (XIII)

(XII), $n = 1-3$ (XIV)

The use of deuterated acids as protonating agents made it possible to obtain deuterated compounds from the enamines[36]:

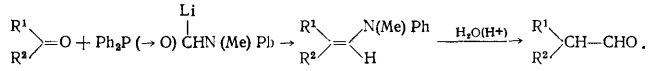


The mechanism of the hydrolysis of enaminoketones has been investigated at different pH of the solution[37] and the stages determining the rate of the overall process have been established. For the enamines RNHC(Me)=CHCOMe (R = alkyl) these stages involve the addition of water (at pH > 2) and the decomposition of the carbinolamine (at pH < 2). When R = aryl, hydration is the slow stage in all the media investigated. The kinetics of the hydrolysis of the enaminoketones (XI)–(XIV) have been investigated in a number of

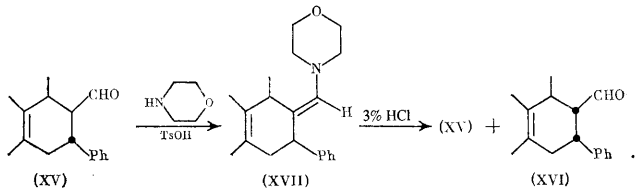
† Bailey et al.[33] state that this is the first instance of the *C*-protonation of enaminoketones. In fact this is not the case—the *C*-protonation of enaminoketones had been observed for the first time much earlier[34].

studies[38,39]. It has been shown that the rate of C-protonation limits the rate of hydrolysis at pH 3–6 and that the rate and direction of the process depend significantly on the ring size#.

The protonation of enamines with formation of immonium cations followed by their hydrolysis made it possible to develop a series of interesting synthetic methods. Thus enamines are intermediates in a new synthesis of homologous aldehydes from ketones[41]:

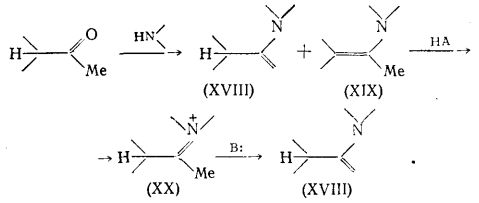


The formation of the *cis*-isomer (XVI) from the *trans*-compound (XV) was required[42]. The usual isomerisation procedures were unsuccessful but treatment of the intermediate enamine (XVII) with hydrochloric acid leads to a mixture of isomers containing 52–56% of the *cis*-compound (XVI):

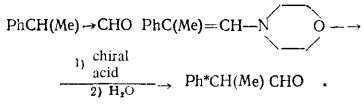


The required isomer (XVI) was isolated from this mixture by crystallisation[42].

The conversion of enamines into immonium salts has been used for the selective synthesis of enamines with a terminal double bond[43]. It has been shown[43] that, although treatment of ketones with amines gives rise to a mixture of the enamines (XVIII) and (XIX), the conversion of this mixture into the salt (XX) followed by treatment with t-butylamine or secondary amines leads to the selective formation of the enamine (XVIII):



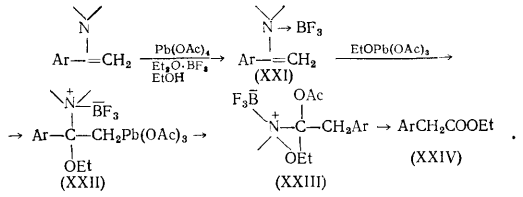
The intermediate synthesis of immonium salts also serves as a basis for the preparation of optically active carbonyl compounds[44–46]. For example, it has been established that, when enamines are protonated by chiral acids with subsequent hydrolysis, the initial carbonyl compounds undergo "deracemisation" and the degree of formation of optically active aldehyde and ketones depends on the configuration of the enamine and the structure of the optically active acid[45]:



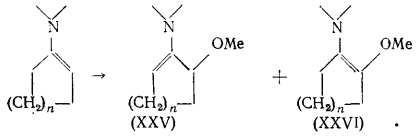
The dependence of various properties, including the protonation and hydrolysis, of enamines on ring size has been discussed in a review[40].

III. OXIDATION AND REDUCTION OF ENAMINES

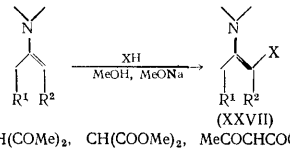
The number of studies devoted to the oxidation of enamines of different types is relatively small. It has been established that, when enamines are oxidised by lead tetra-acetate in the presence of boron trifluoride etherate[47], a rearrangement involving the formation of the adducts (XXI)–(XXIII) with BF_3 takes place and results in the formation of arylacetic acid esters (XXIV):



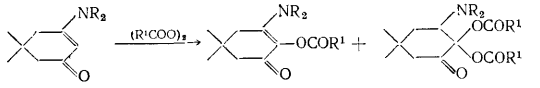
The anodic oxidation of enamines in methanol leads to the methoxyenamines (XXV) and (XXVI)[48]:



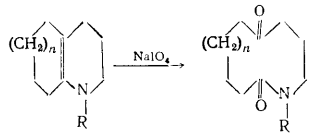
Substituted enamines of type (XXVII) have been obtained in the presence of organic anions[49]:



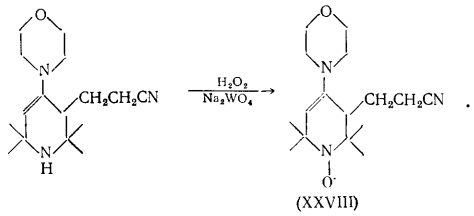
When alicyclic enaminoketones interact with diacyl peroxides, acyloxylation products are formed[50]:



The oxidation of bicyclic enamines is one of the ways of synthesising macrocyclic compounds[51]:

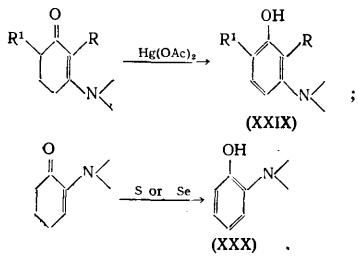


The nitroxy-radicals (XXVIII) have been obtained by the oxidation of certain heterocyclic enamines[52]:

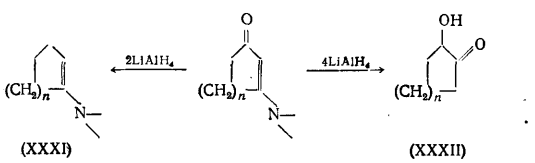


Enaminoketones can serve as the starting compounds in the synthesis of derivatives of *m*-aminophenol (XXIX) or *o*-aminophenol (XXX)—either the oxidation of enaminoketones[53] or

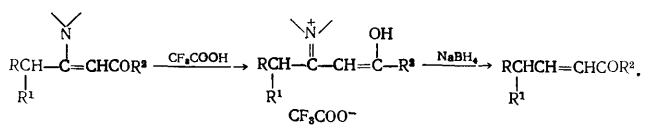
their dehydrogenation with sulphur or selenium[54] are used for such purposes:



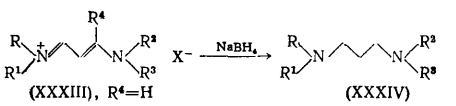
The reduction of enaminoketones with lithium tetrahydroaluminate was investigated in the same study[54] and it was established that, depending on the excess of the reductant, enamines or acyloins, (XXXI) and (XXXII) respectively, are formed:



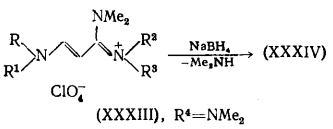
A successful method of the reduction of enaminoketones to the corresponding unsaturated ketones was used by Nilsson[55]:



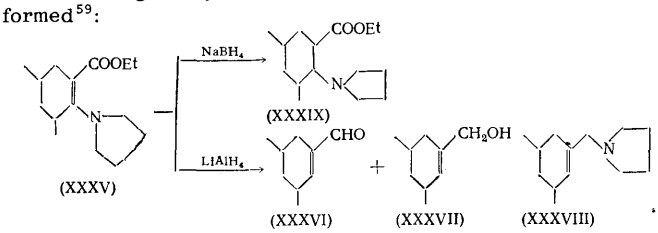
The reduction of enaminoketones by diborane to alkyl vinyl ketone derivatives[56] and the polarographic reduction of enaminoketones to the corresponding aminoalcohols[57] have also been described. Like enaminoketones, enaminoimines can be reduced in the form of the enaminoimmonium salts (XXXIII, $R^4 = H$) by $NaBH_4$ to diaminopropanes (XXXIV)[58]:



It is of interest that in the case of the salts of the enaminoamidines (XXXIII, $R^4 = NMe_2$) the reaction is accompanied by the elimination of dimethylamine[58]:



In the reduction of the enaminoesters (XXXV) with lithium tetrahydroaluminate, a mixture of derivatives of unsaturated aldehydes (XXXVI), hydroxymethylalkenes (XXXVII), and aminomethylalkanes (XXXVIII) is formed[59]. The reaction of compound (XXXV) with sodium tetrahydroborate proceeds more unambiguously and the aminoesters (XXXIX) are formed[59]:



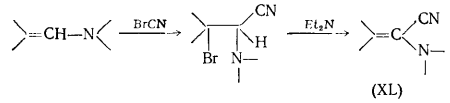
Orthophosphorous acid is an effective reagent for the reduction of enamines; saturated amines are formed in this case in high yields[60]. Finally, we may note a study[61] in which the asymmetric synthesis of β-aminoacids was achieved by the reduction of chiral enamines either catalytically over palladium or with $NaBH_3CN$:



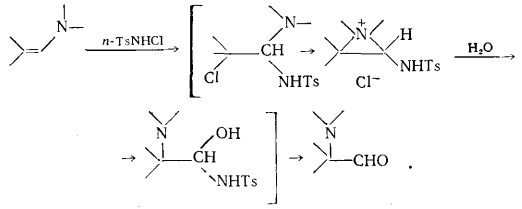
In the former case (catalytic reduction) the process proceeds with retention of the configuration, while in the latter case the configuration is inverted[61].

IV. ADDITION TO THE ENAMINE DOUBLE BOND, CYCLOADDITION, AND REARRANGEMENTS

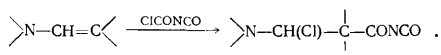
The addition of bromocyanogen to the double bond of enamines with subsequent elimination of hydrogen bromide has been a convenient method of synthesis of α-cyanoenamines (XL)[62]:



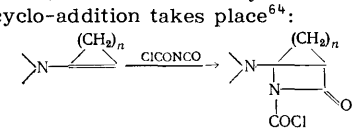
The reaction of enamines with chloramine-T is also accompanied by the initial addition of the latter to the C–C bond and ultimately leads to α-aminoaldehydes[63]:



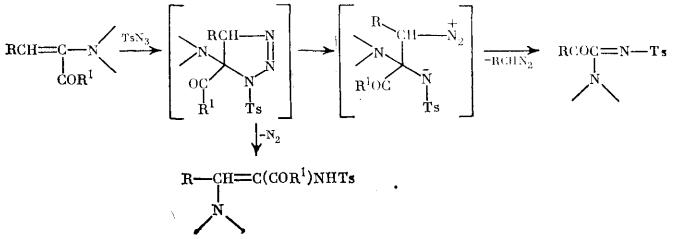
When chloroformyl isocyanate reacts with acyclic enamines, addition to the double bond is observed[54]:



On the other hand, on treatment of cyclic enamines with this reagent, 1,2-cyclo-addition takes place[64]:

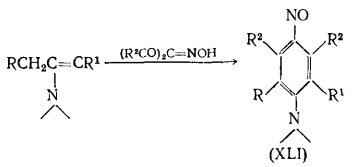


Cycloaddition reactions occur also in the interaction of enamines with aryl azides and arenesulphonyl azides[65–67]. For example, enamines having an α-keto-group react with sulphonyl azides in two ways[67]:



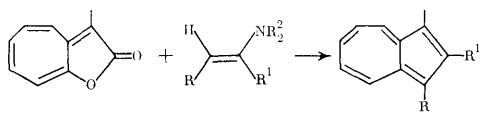
The interaction of enamines with diazoacetic ester, which also proceeds via a type of cycloaddition mechanism, leads to pyrazolines[68]. The reactions with enamines of α,α′-dibromoketones (with formation of cyclopentenones)[69], of unsaturated ketones (with formation of pyran derivatives)[70],

and of acetylenedicarboxylate ester (with formation of condensed cyclobutenes)[71] proceed via this same mechanism.
A new method of synthesis of nitrosoanilines (XLI) by the reaction of enamines with isonitroso-β-dicarbonyl compounds has been published recently[72]:



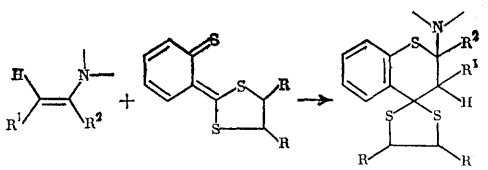
(XLI)

A number of studies have been devoted to the synthesis of azulenes (XLII) from bicyclic lactones (XLIII) and enamines[73–75]:

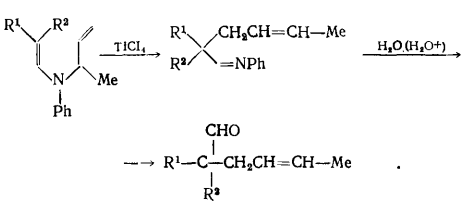


(XLIII) (XLII)

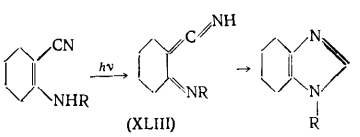
The reaction of enamines with *o*-thioquinone methide[76] results in the formation of [1:1]-adducts:



The reactions of enamines with thioacylketen thioacetals were described in the same communication[76]. In many instances the reactions of enamines are accompanied by rearrangements. It was mentioned above that, when enamines are oxidised in the presence of boron trifluoride etherate, a transformation of the type of the Favorskii rearrangement is observed[47]. In the presence of titanium tetrachloride enamines having substituents at the nitrogen atom with a terminal carbon–carbon double bond undergo the aza-Claisen arrangement[77]:

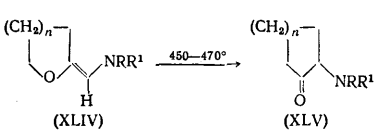


The photochemical rearrangement of enaminonitriles results in the formation of imidazole derivatives[78] with the aminoketimine (XLIII) as an intermediate[79]:



(XLIII)

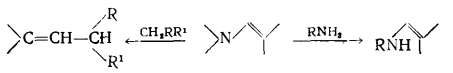
It has been established recently that enamines of type (XLIV) are converted at high temperature into the aminoketones (XLV) in high yields[80]:



(XLIV) (XLV)

V. THE REACTIONS OF ENAMINES WITH NUCLEOPHILES AND ELECTROPHILES

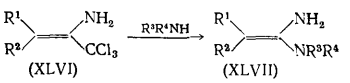
The reactions of enamines with nucleophiles which are most frequently used are those with various amines (transamination)[81–87] and with compounds having an active methylene unit[88]:



The kinetics of the transamination reactions of various enamines have been investigated[82,87]. In the study of the interaction of the enaminoketones MeCOCH=C(Me)NHR with phenylhydrazine, it was established[82] that the rate of the process depends on the character of the substituent (electron-donating groups accelerate the reaction) and the configuration of the initial enaminoketone (the *E* derivatives react more slowly than the *Z* derivatives). The rate-limiting stage of the reaction is *C*-protonation[82].

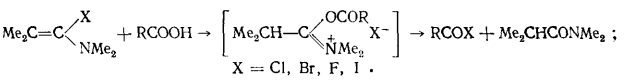
It has been shown[87] that the rate of transamination depends on the degree of delocalisation of the negative charge of the enamines by β-substituents and the possibility of the stabilisation of the transition state as a result of the formation of an intramolecular hydrogen bond. It was established that the rate of the process depends on the solvent—the rate of transamination in ethylene glycol is 40 times higher than in dimethylformamide.

In those cases where a readily removed group (for example a halogen) is attached to the β-carbon atom of the enamine, the reactions with nucleophiles are accompanied by the substitution of this group[89–91]. It is of interest that α-trichloromethyleneamines (XLVI) react with amines to form enediamines (XLVII), i.e. a reaction of the type of haloform cleavage takes place[90]:

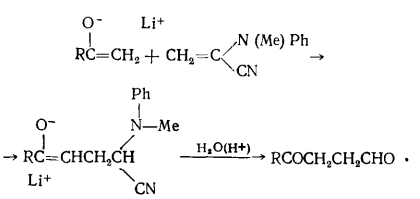


(XLVI) (XLVII)

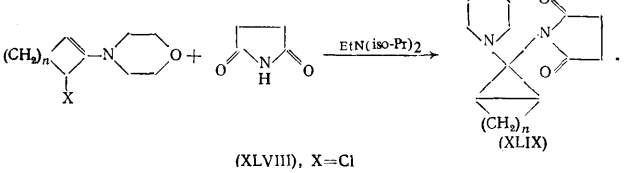
The reaction of α-halogenoamines with carboxylic acids constitutes a convenient method of synthesis of acid halides[91]:



The interaction of enamines with enolate anions is the basis of a new synthesis of 1,4-dicarbonyl compounds[92]:

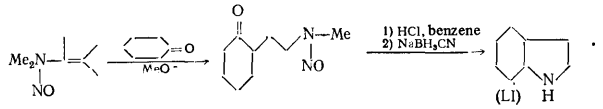


The succinimide anion reacts with chloroenamines (XLVIII) to form the bicyclic compounds (XLIX) having the *trans*-configuration. The corresponding *cis*-bicyclic compounds are formed when succinimide reacts with enaminosulphonium salts (L)[93]:

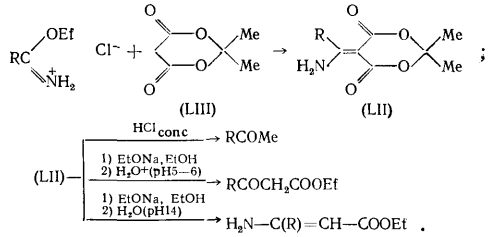


(XLVIII), X=Cl
(L), X=$Me_2\overset{+}{S}$ (anion—FSO_3^-)
(XLIX)

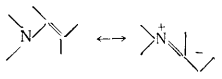
N-Nitrosoenamines are also capable of reacting with nucleophiles[94]. For example, perhydroindoles (LI) can be obtained as a result of such reactions:



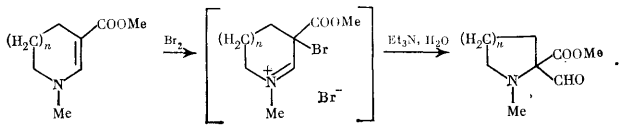
The enamines (LII), synthesised by the reaction of iminoesters or lactim-esters with Meldrum's acids (LIII), proved to be convenient intermediates for the preparation of β-monosubstituted enamines, β-dicarbonyl compounds, and substituted ketones[95–97]:



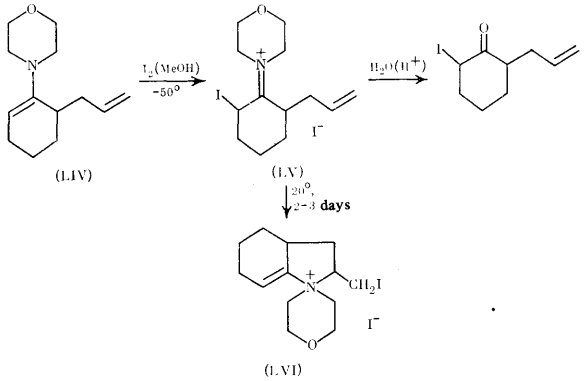
The interaction of enamines with electrophiles can proceed via two centres (in enaminoketones there is yet another centre—the oxygen atom): the nitrogen atom and the β-carbon atom:



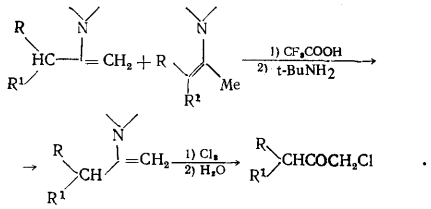
The halogenation of enamines has been studied in extremely great detail and usually proceeds via the β-carbon atom. Thus β-bromination is an intermediate stage in the synthesis of azacyclic aldehydes[98]:



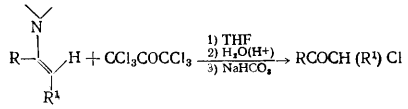
When the enamine (LIV) is iodinated at a low temperature, it is possible to isolate the intermediate immonium salt (LV), which is converted into the corresponding iodoketone on treatment with water and, on being kept at 20 °C, cyclises to an indolinium derivative (LVI)[99]:



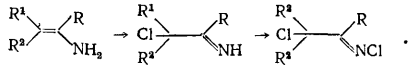
A new simple synthesis of halogenomethyl ketones[100] is based on the phenomenon already discussed (see above), according to which the treatment of immonium salts with bases leads to the selective formation of enamines with a terminal double bond:



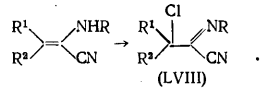
It has been established recently[101] that hexachloroacetone can be used as a chlorinating agent in the reaction with enamines at −78–0 °C in tetrahydrofuran (THF):



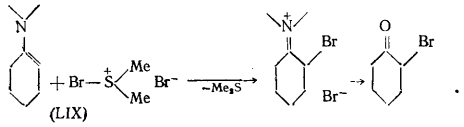
When β,β-disubstituted primary enamines are chlorinated, the reaction involves initially the β-carbon atom and then the nitrogen atom with formation of *N*, β-dichloro-derivatives (LVII)[102]:



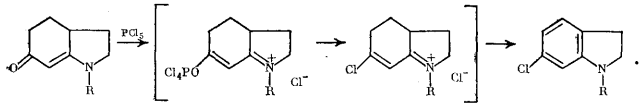
The C-chlorination of cyanoenamines by *N*-chlorosuccinimide[103] leads to α-halogenoimidoyl cyanides (LVIII):



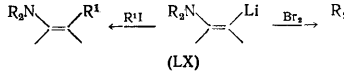
α-Bromoketones have been synthesised recently by the reaction of bromodimethylsulphonium bromide (LIX) with enamines and subsequent hydrolysis of the intermediate immonium bromides[104]:



The reactions of enaminoketones with reagents such as phosphoryl chloride or phosphorus pentachloride[105] proceed in accordance with the same principle as the reactions of amides with these compounds—there is initial electrophilic attack on the oxygen atom. In many instances the process is accompanied by aromatisation:

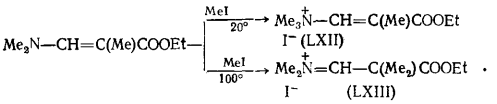


Finally, the introduction of the halogen atom into the "enamine" β-position can be achieved also via the lithioenamines (LX). In the study by Duhamel and Poirier[106] and others by the same workers[13,107,108], lithioenamines were introduced into reactions not only with the halogens but also with other electrophiles such as alkyl halides and aldehydes:

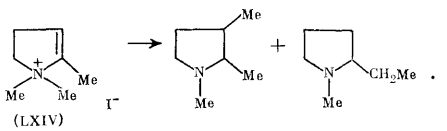


Studies of the alkylation reactions of enamines occupy a very notable place in their chemistry[107–124], much attention being devoted to factors which determine the site of attack by the

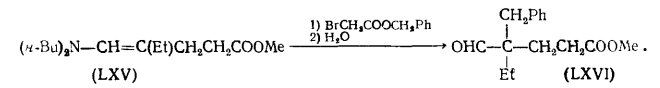
alkylating agent (*N*- or *C*-alkylation). The study of the alkylation of α-methyl-β-(*N*,*N*-dimethylamino)acrylic acid ester (LXI) by methyl iodide established[109] that the pathway followed in the process depends on the temperature—the enammonium salt (LXII) is formed at a low temperature, while the product at a high temperature is the immonium salt (LXIII):



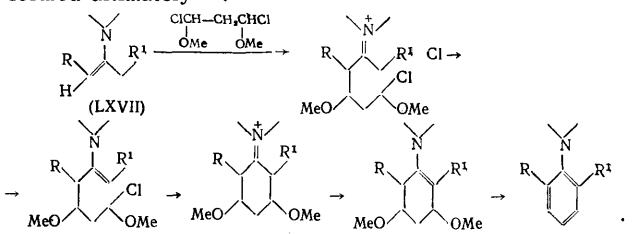
The question whether the β-*C*-alkylation of enamines is an independent process or whether the *N*-alkyl derivatives formed initially rearrange to the *C*-alkyl derivatives has been considered[112]. The enammonium salt (LXIV) was heated to 240 °C and the mixture reduced with formic acid was analysed by gas–liquid chromatography. It was established that, on heating, the *N*-methyl group migrates to the enamine carbon atoms:



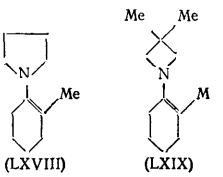
The authors[112] also showed that, when a mixture of enammonium salts is heated, the migrating *N*-alkyl substituents are distributed in both enamines formed, which indicates the intermolecular character of the N→C transfer of the alkyl substituent. An unusual β-*C*-alkylation has been described[113]. It was established that the interaction of the enamine (LXV) with benzyl α-bromoacetate leads to the β-benzylaldehyde (LXVI) (after hydrolysis) and not to the expected alkoxycarbonylmethyl derivative:



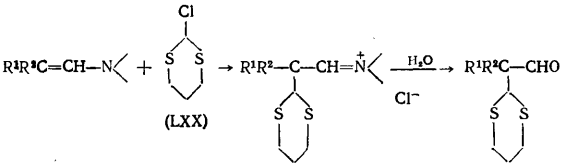
Regardless of the nature of the alkylating agent, the alkylation of *N*-monosubstituted-cyanoenamines proceeds at the N atom and the best results are obtained when triethyloxonium fluoroborate is used[114]. The same reagent has been employed successfully for the *O*-alkylation of enaminoamides[86] The reaction of the enamines (LXVII) with 1,3-dichloro-1,3-dimethoxypropane proceeds in an interesting manner—in this case double *C*-alkylation takes place and aniline derivatives are formed ultimately[115]:



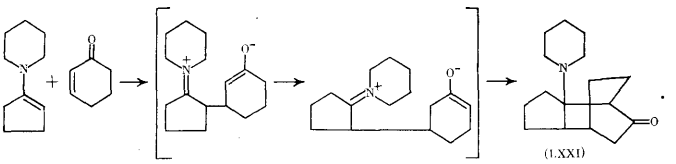
Comparison of pyrrolidine and azetidine enamines (LXVIII) and (LXIX) in reactions involving alkylation by methyl iodide[116] showed that the iodide is involved in *N*-alkylation to a greater extent:



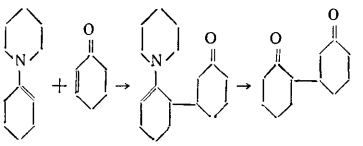
The alkylation of enamines by 2-chloro-1,3-dithian (LXX) has served as the basis of a new method of synthesis of malonodialdehyde with one protected aldehyde group[117]:



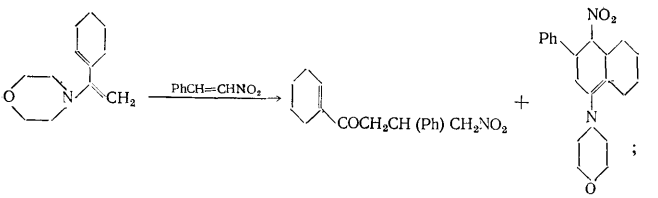
Compounds with an active double bond also readily alkylate enamines[118–122]. Thus the reaction of an enamine derived from cyclopentanone with cyclohexen-2-one results in the formation of compound (LXXI)[120]:

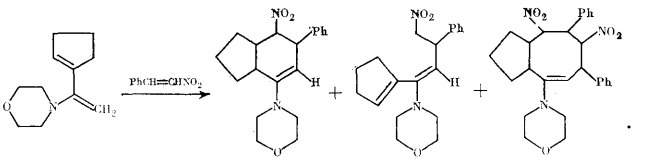


It is of interest that the reaction of the enamine derived from cyclohexanone proceeds differently[120]:



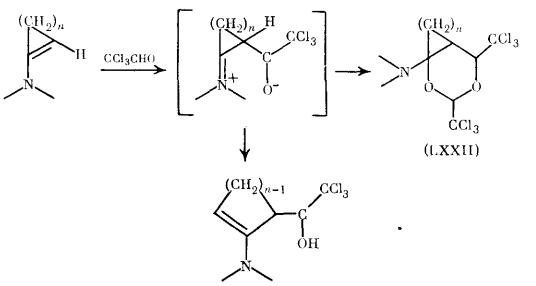
The influence of ring size on the alkylation reaction also follows from an examination of the reactions of β-nitrostyrene with cyclohexynylenamines[121] and cyclopentynylenamines[122]:



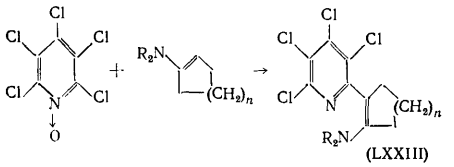


It is noteworthy that such differences are observed also in acylation reactions—in the interaction with methanesulphonyl chloride[121,122].

It has been shown recently that cyclic enamines readily enter into the Mannich reaction in the β-position[123]. The reaction of enamines with chloral also proceeds extremely smoothly[124] and, when the interaction involves two molecules of chloral, bicyclic compounds of type (LXXII) are formed:

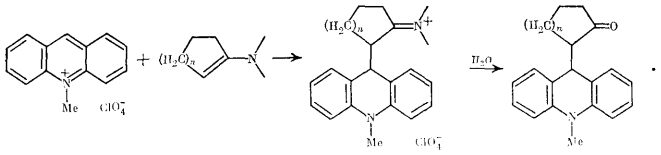


In the presence of a sufficiently mobile halogen atom, aromatic halogeno-compounds can react with enamines. Thus polyhalogenopyridines or their *N*-oxides react with enamines[125] to form β-pyridyl derivatives (LXXIII):

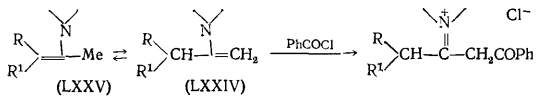


(LXXIII)

Another pathway leading to the β-arylation of enamines has been demonstrated by Chupakhin and co-workers[126,127]— heteroaromatic systems with a marked π-electron deficit were introduced into the reaction. For example:

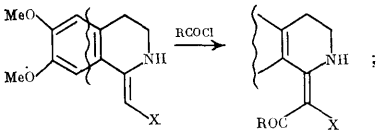


Like alkylation, the enamine acylation reaction can proceed via the nitrogen and/or β-carbon atoms. It has been established[128,129] that, when an isomeric mixture of the tertiary enamines (LXXIV) and (LXXV) is acylated, only the less substituted isomer (LXXIV) reacts:



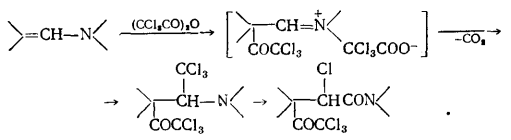
(LXXV) (LXXIV)

Secondary enamines of the isoquinoline series (LXXVI) are *C*-acylated on interaction with acid chlorides[130]:

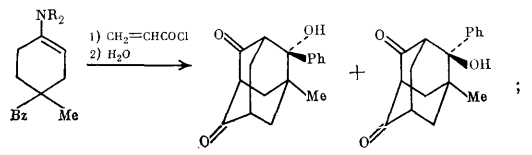


(LXXVI), X = CN, $CONH_2$.

The β-*C*-acylation of enamines by trichloroacetic anhydride is a convenient method of synthesis of amines with α-trichloromethyl and β-trichloroacetyl groups[131]. The subsequent hydrolysis of the compounds obtained is also unusual and leads to α-chloroamides[131]:

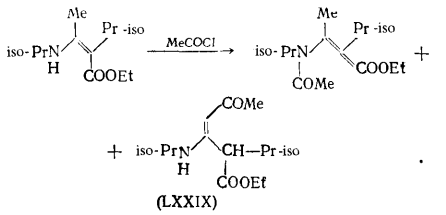


A new interesting method of synthesis of the adamantanediones (LXXVII) and (LXXVIII) is based on the acylation of enamines by unsaturated acid chlorides[132]:



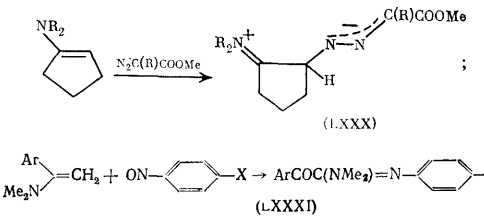
Bz = COPh . (LXXVII) (LXXVIII)

When β-aminocrotonic ester is acylated by acid halides, two (*Z* and *E*) *N*-acylated and *C*-acylated isomers are formed in each case[133]. The reaction of aminocrotonic ester with trifluoroacetic anhydride leads analogously to a mixture of *N*- and *C*-acylenamines[134]. However, if α-alkyl-β-aminocrotonic ester is introduced into the reaction with $(CF_3CO)_2O$, the acylation process proceeds selectively via the amino-group[134]. Similarly, the *N*-alkyl-β-aminocrotonic ester is acylated by acetyl chloride only at the carbon atom and its α-alkyl derivative only at the nitrogen atom[135]. However, in one instance it has been possible to isolate also the *C*-acylation product (LXXIX)[136]:



(LXXIX)

It is also noteworthy that β-amino-β-methylvinyl methyl ketone and its *N*-aryl derivative are acylated exclusively at the nitrogen atom[137,138]. In conclusion of this section, we shall mention the reaction of enamines via the β-carbon atom with arenesulphonyl isocyanates (the corresponding *N*-arenesulphonylcarbamido-derivative is formed)[139], the interaction of certain enamines with diazoacetic ester[140] which resulted in the isolation of zwitter-ion of type (LXXX), and the unusual reaction of α-arylenamines with *p*-substituted nitrobenzenes[141], which proceeds with formation of amidines (LXXXI):



(LXXX)

(LXXXI)

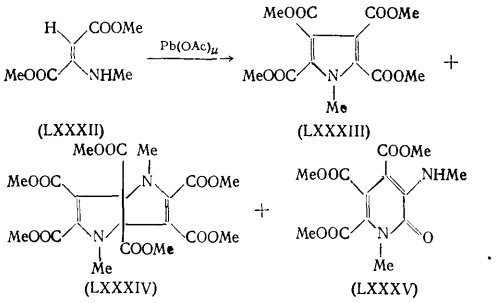
VI. ENAMINES IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

The most promising aspect of the development of the chemistry of enamines at the present time is their employment for the synthesis of various heterocycles. The greatest number of publications concerning the properties and reactions of enamines have been devoted to the problem of such synthesis and this field of study of the class of compounds under consideration is developing most vigorously. As a consequence of this, the syntheses of heterocyclic compounds on the basis of enamines can be usefully surveyed in a single Section of the review, although many of the reactions examined below could naturally be classified also as reactions with nucleophiles or electrophiles, oxidation reactions, reduction reactions, etc. As already mentioned above, many of the heterocyclisation reactions of enamines, which have already been described in recently published reviews[2,5,6], will not be considered in this Section.

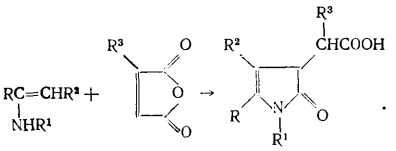
1. Synthesis of Five-Membered Heterocycles

Perhaps the greatest number of publications concerning the synthesis of five-membered heterocycles have been devoted to the preparation of various derivatives of pyrrole.

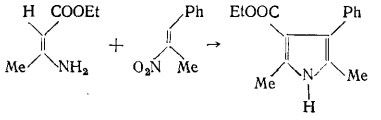
When β-methoxycarbonyl-β-methylaminoacrylic ester (LXXXII) is oxidised with lead tetra-acetate[142], a mixture of 2,3,4,5-tetramethoxycarbonyl-1-methylpyrrole (LXXXIII), pyrrolopyrrole derivatives (LXXXIV), and 2-pyridone (LXXXV) is formed:



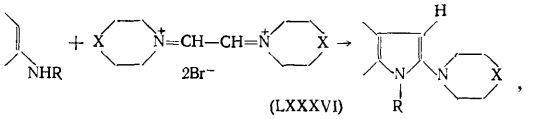
The condensation of secondary enamines with maleic anhydride derivatives leads to 2-pyrrolinone derivatives[143,144]:



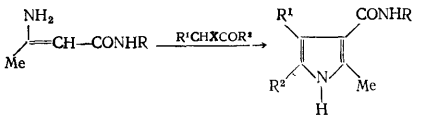
An interesting reaction of primary and secondary enamines with nitroalkenes, which results in the formation of substituted pyrroles, has been described recently[145]:



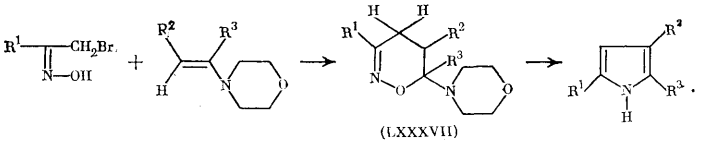
If cyclic enamines or enaminoketones are introduced into this reaction, the products are indole derivatives[145]. Substituted pyrroles have also been obtained by the reaction of enamines with di-immonium dibromide (LXXXVI)[146], i.e.



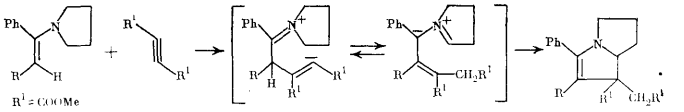
and of enaminoamides with carbonyl compounds[147]:



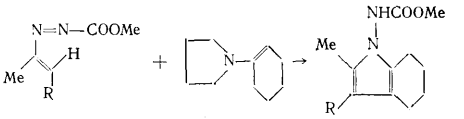
The reaction of enamines with α-bromoximes followed by the decomposition of the intermediate oxazine derivative (LXXXVII) by iron carbonyls also leads to pyrroles[148]:



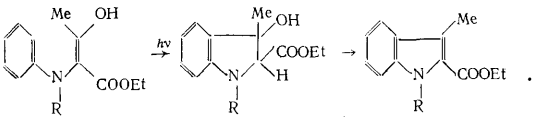
The acetylenedicarboxylic ester attacks β-monosubstituted enamines at the β-carbon atom with subsequent cyclisation to pyrrolizidine derivatives[149]:



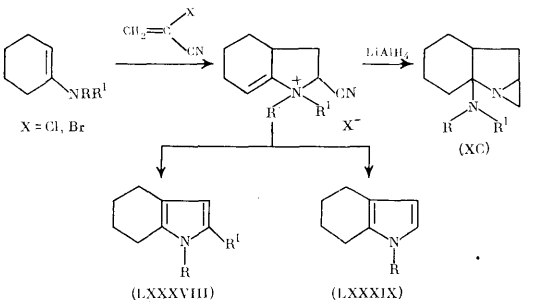
In many instances the employment of enamines ensures a simple and convenient approach to indole derivatives. Thus the condensation of enamines with aza-alkenes leads to hydrogenated indoles[150]:



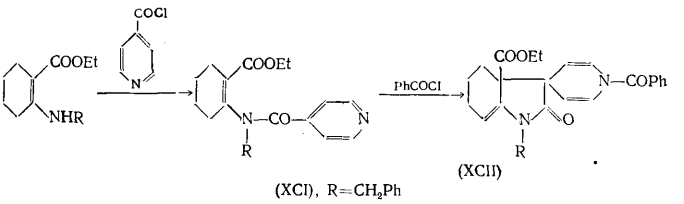
Indoles have also been obtained by the photochemical cyclisation of *N*-arylenamines[151]:



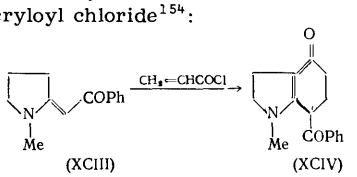
The interaction of enamines with α-halogenoacrylonitriles leads to hydrogenated 2-cyanoindolinium derivatives, which, on treatment with potassium t-butoxide, undergo the Stevens rearrangement and Hofmann elimination with formation of 4,5,6,7-tetrahydroindoles (LXXXVIII) and (LXXXIX), while on reduction with lithium tetrahydroaluminate they are converted into tricyclic hydrogenated indoles of type (XC)[152]:



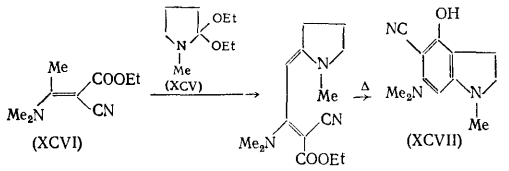
The reaction of the cyclic enamine (XCI) with isonicotinoyl chloride leads to the formation of an *N*-acyl derivative, which cyclises to the spiro-compounds (XCII) on treatment with benzoyl chloride[153]:



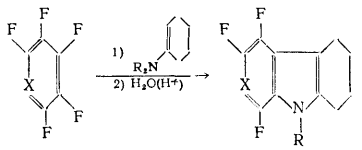
Another method of synthesis of indole derivatives is based on the use of cyclic enamines incorporating in their structure the pyrrolidin-2-ylidene ring[154,155], the functional groups of the side chain of which make possible the growth of an additional benzene ring. Thus hexahydro-4-indolone (XCIV) has been synthesised by the reaction of the enaminoketone (XCIII) with acryloyl chloride[154]:



The reaction of *N*-methylpyrrolidinone acetal (XCV) with the enaminoester (XCVI) followed by thermal cyclisation led to the synthesis of the indoline (XCVII)[155]:

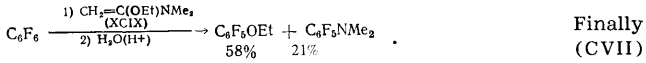


The corresponding benzene, quinoline, and benzazepine derivatives were synthesised in the same investigations[154,155] in accordance with analogous schemes. A number of carbazole derivatives have been obtained by the reaction of hexafluorobenzene with enamines derived from cyclohexanone[156,157]. Pentafluoropyridine reacts analogously[157]:

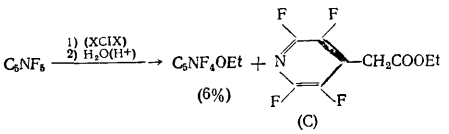


(XCVIII), X=C—F or N

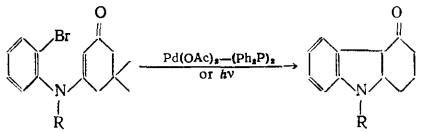
It is of interest that the reaction of compound (XCVIII, X = C—F) with keten *O,N*-acetals (XCIX) leads only to *O*- and *N*-arylation products[157]:



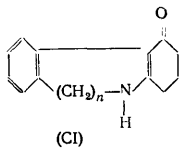
On the other hand, compound (XCVIII, X = N) is capable of β-*C*-arylation of compound (XCIX) with formation of the pyridylacetic ester (C)[157]:



N-Arylenaminoketones having a bromine atom in the *o*-position in the benzene ring cyclise to carbazoles in the presence of a palladium catalyst[158] or on ultraviolet irradiation[159]:

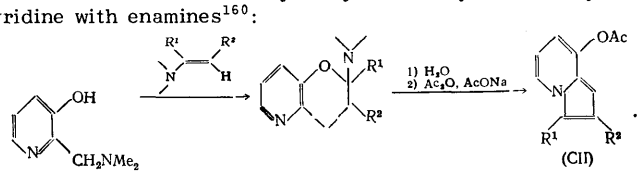


Derivatives of phenanthridine, benzazepine, and benzazocine (CI) have been obtained analogously on irradiation of the corresponding enaminoketones[159]:



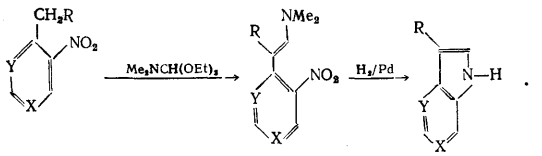
(CI)

An interesting synthesis of pyrrolo[1,2-*a*]pyridine (CII) is based on the reaction of 3-hydroxy-2-dimethylaminomethylpyridine with enamines[160]:



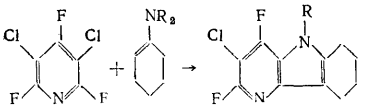
(CII)

Pyrrolo[1,2-*c*]- and pyrrolo[2,1-*b*]-pyridines (CIII) and (CIV) have been synthesised by the reduction of the corresponding nitroenamines (CV) and (CVI)[161–163]:

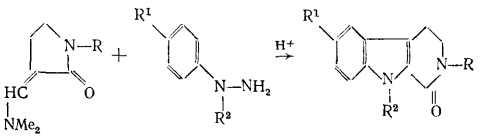


(CV), X = N, Y = CH
(CVI), X = CH, Y = N

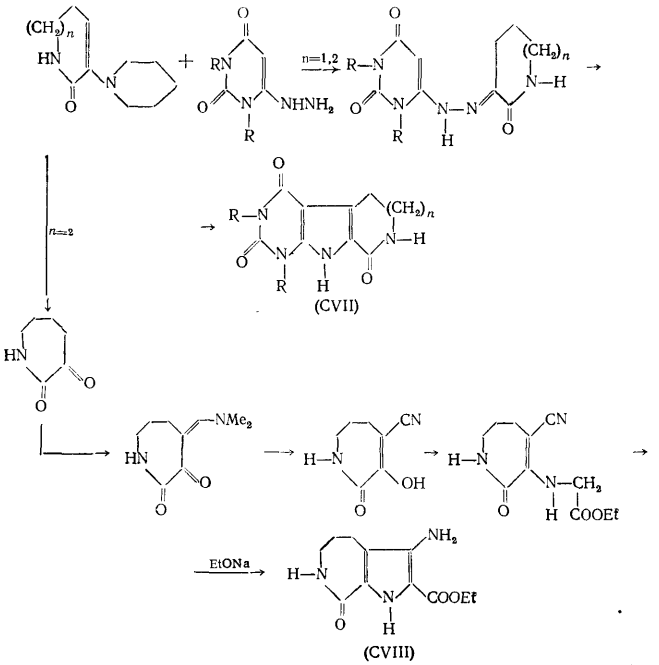
The arylation of enamines by polyhalogenopyridines[125] leads to carbolines:



Another pathway leading to carbolines has been found recently[164] in the study of the reaction of enamines derived from 3-formylpyrrolidinones with arylhydrazines:



Finally we may mention the syntheses of diazacarbolines (CVII)[165] and pyrrolo[2,3-*c*]azepines (CVIII)[166], based on the use of enamines derived from α-oxolactams:

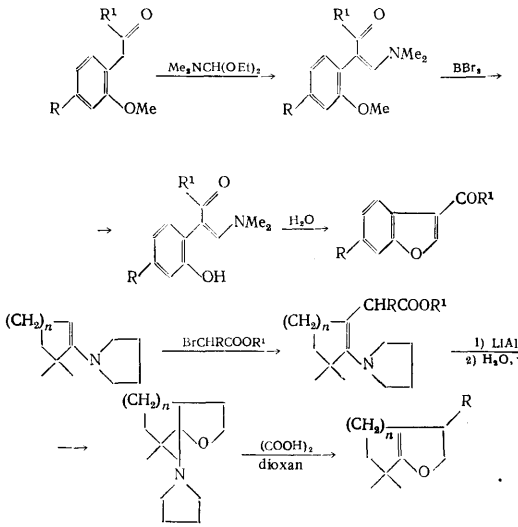


(CVII)

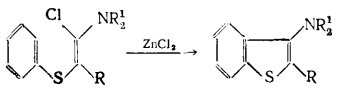
(CVIII)

Comparatively few studies devoted to the synthesis of furan and thiophen derivatives from enamines have been published recently. Furans have been obtained by the cyclisation of the enamine and phenolic groups in the *ortho*-positions relative to one another[167] and by the reaction of cyclic enamines with bromoacetic ester followed by the reduction of the

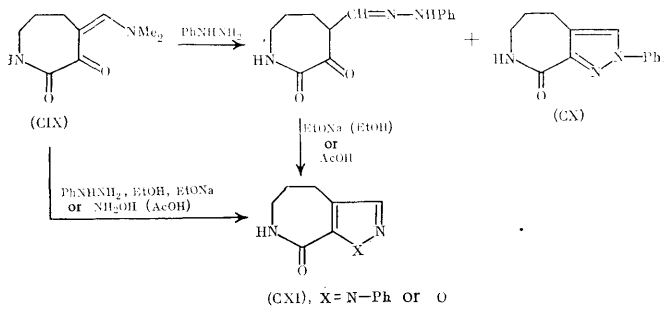
resulting β-*C*-substitution product with lithium tetrahydroaluminate[168]:



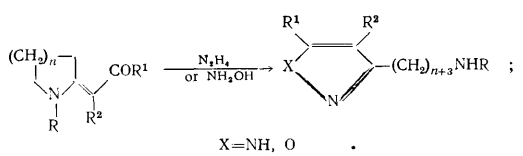
The synthesis of benzothiophens is based on the Friedel–Crafts reaction[169]:



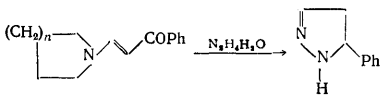
A number of studies have been devoted to the synthesis of azoles, in the first place pyrazoles. Pyrazoles are most often obtained by the reaction of enaminoketones with hydrazine derivatives[84,170-173]. The reaction of enaminoketolactam (CIX) with phenylhydrazine makes it possible to obtain the isomeric pyrazoles (CX) and (CXI) in which X = NPh[84]:



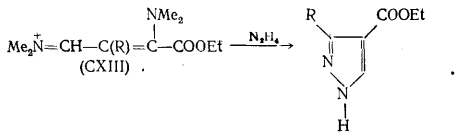
On treatment wth hydroxylamine, compound (CIX) is readily converted into a derivative of isoxazolo[5,4-*c*]azepine (CXI, X = 0).[84] The synthesis of pyrazole (and isoxazole) derivatives by the reaction of cyclic enaminoketones with hydrazine hydrate or hydroxylamine is of interest[173]:



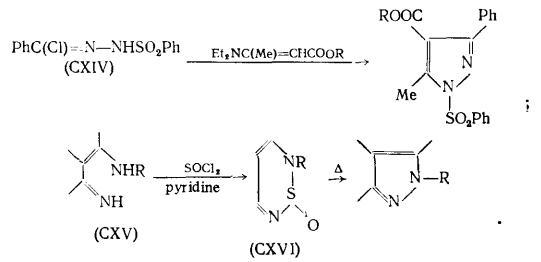
We may also point out that acid catalysis has proved extremely effective in the reactions enaminoketones (CXII) with hydrazine hydrate[171]:



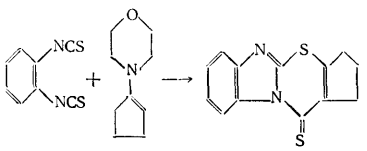
In addition it has been established that the rate of this reaction depends on the ring size and is a maximum for the six-membered cyclic enamine (CXII, $n = 2$) and a minimum for the seven-membered enamine (CXII, $n = 3$)[171]. The interaction of hydrazine with the enaminoimmonium salt (CXIII) is closely related to the above syntheses[174]:



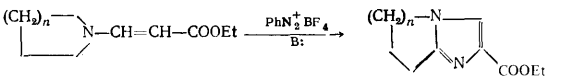
Pyrazoles have also been obtained by the condensation of enamines with diazo-compounds[175] and *N*-(benzenesulphonyl)-benzohydrazonoyl chloride (CXIV)[176] and by the reaction of enaminoimines (CXV) with thionyl chloride and subsequent thermal decomposition of the intermediate 1,2,6-thiadiazine *S*-oxide (CXVI)[177]:



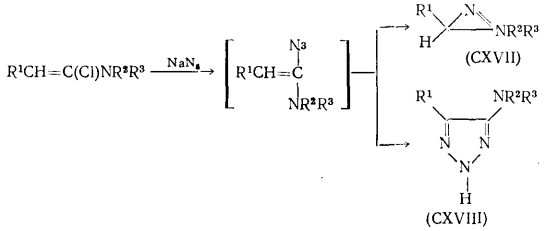
The reactions of cyclic enamines with *o*-phenylene di-isothiocyanate lead to the closure of the imidazole and thiazine rings[178]:



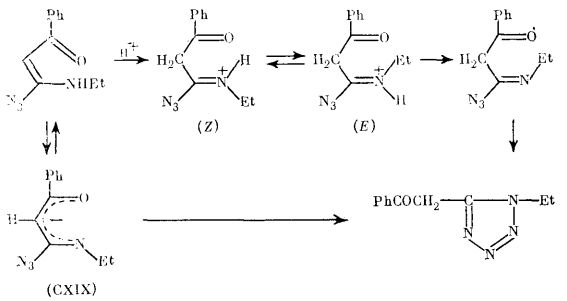
Imidazole derivatives can also be obtained from enaminoesters and arenediazonium salts in the presence of bases[179]:



The interaction of α-chloroenamines with sodium azide[180] leads to various products depending on the substituent at the enamine nitrogen: the azirines (CXVII) are formed from *N*-arylenamines, while the more basic *N*-alkylene-enamines give rise to the triazoles (CXVIII):



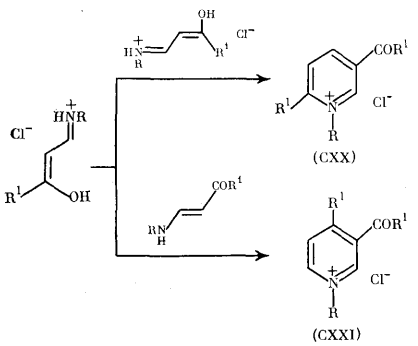
α-Azidoenamines containing the benzoyl group in the β-position (azidoenaminoketones) readily cyclise to tetrazoles[181] and in an alkaline medium the rate-limiting stage of the process is the formation of the anion (CXIX), while in an acid medium the rate-limiting stage is *Z*–*E* isomerisation:



(CXIX)

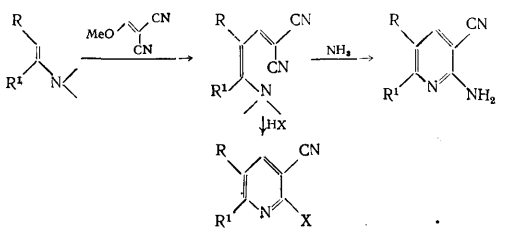
2. Synthesis of Six-Membered Heterocycles

Most of the studies concerning the synthesis of six-membered heterocycles from enamines have been devoted to the synthesis of various pyridine systems and it has been possible to synthesise both monocyclic pyridines and pyridines condensed with various carbocyclic and heterocyclic compounds. Substituted pyridinium salts are formed extremely readily when enaminoketones are treated with acids[182]. However, in this case there is a possibility of both the condensation of two molecules of the *O*-protonated forms and of the interaction of the *O*-protonated form with a neutral molecule. Accordingly, the isomeric pyridinium salts (CXX) and (CXXI) are produced:

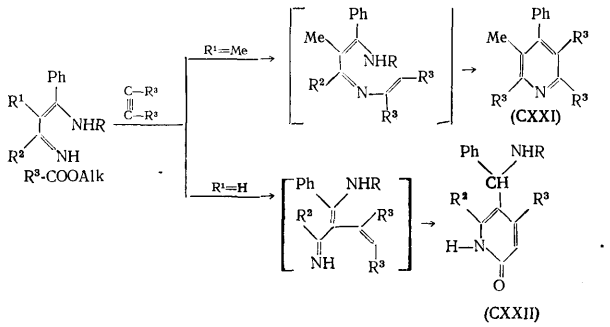


(CXXI)

The interaction of enamines with methoxymethylenemalononitrile followed by treatment with ammonia or acids leads to 3-cyanopyridines[183]:

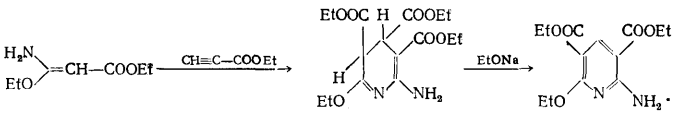


Acetylenedicarboxylic ester can react with enaminoimines[184] in two ways—alkylation of the enamine nitrogen atom results in the formation of derivatives of esters of nicotinic acids (CXXI), while alkylation at the β-carbon atom leads to derivatives of 2-pyridone (CXXII):

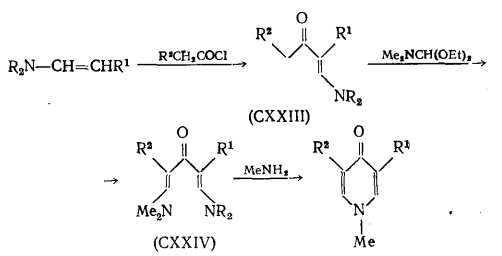


(CXXII)

The interaction of propiolic ester with α-alkoxyenaminoesters leads to derivatives of 2-aminopyridine[185]:

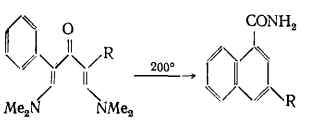


The reaction of two molecules of β-aminocrotonic ester with formaldehyde leads to the formation of 3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine[186]. A convenient synthesis of 4-pyridone derivatives has been developed[187,188] on the basis of the ability of enamines to undergo β-acylation and transamination with primary amines:

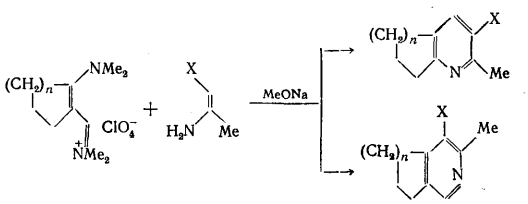


(CXXIV)

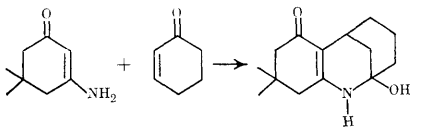
It is of interest that enamines of types (CXXIII) and (CXXIV) are capable of being converted into naphthalene, biphenyl, or diphenyl ether derivatives on heating[189], for example:



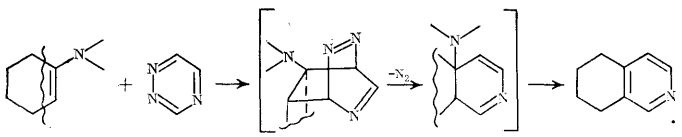
Hydrogenated quinoline derivatives have been synthesised in various ways—by the [4 × 2] cycloaddition of enamines to benzylideneanilines[190], by the reaction of enamines with acrylamide[191], and by the reaction of imines in the form of enamine tautomers with acrylic acid derivatives and propiolactone[192]. The reactions of enamines with enaminoammonium salts proceed via two pathways with formation of isomeric condensed pyridines[193]:



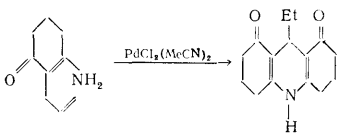
The first stage of the reaction of the enamine derived from dimedone with cyclohexene is *C*-alkylation of the enamine[194]:



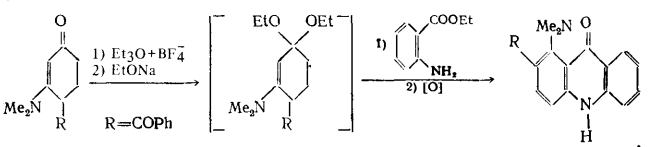
The Diels–Alder reaction, in which enamines behave as dienophiles, is also extremely interesting[195]:



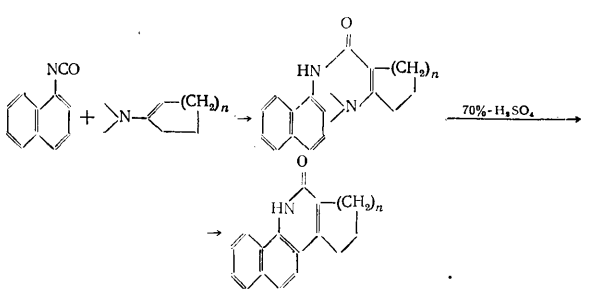
New syntheses of acridines have been developed as a result of the study of the reactions of primary enaminoketones having an unsaturated group in the β-position with the complex $PdCl_2(MeCN)_2$,[196] i.e.



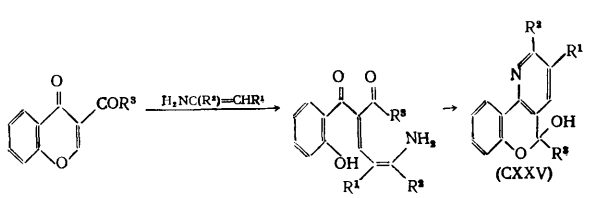
and of the reaction of tertiary enaminoketones with an alkylating agent and then anthranilic ester in accordance with the scheme[197]:



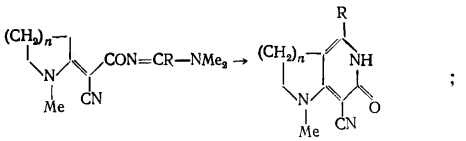
Complex tetracyclic systems containing the pyridone ring have been obtained in the reactions of cyclic enamines with α-naphthyl isocyanates[198,199]:



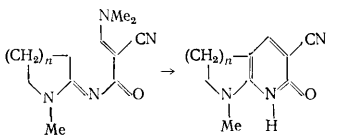
It has been possible to use enamines in a number of syntheses of pyridines condensed with oxygen-containing heterocycles–benzopyranopyridines (CXXV)[200], as well as derivatives of pyrano[4,3-c]pyridines[201], pyrano[2,3-*b*]pyridine[202], and pyrido[4,3-*b*]benzofuran[203]:



A number of studies have been devoted to the synthesis of condensed pyridines from enaminoamides[204–208]. The synthesis is based on the preparation and intramolecular cyclisation of enaminoacylamidines of the type (CXXVI, R = H) and (CXXVII)[204,207]. Condensed 2-pyridones can also be obtained from enaminoacylguanidines (CXXVI, R = Me_2N)[209]:

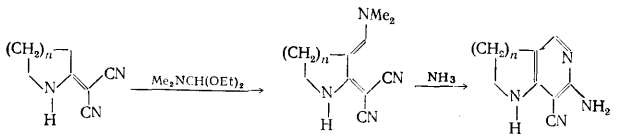


(CXXVI), n=1–3

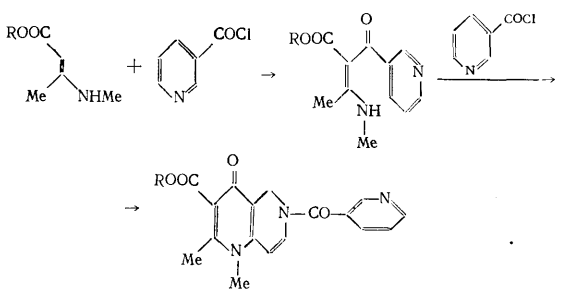


(CXXVII), n = 1–3

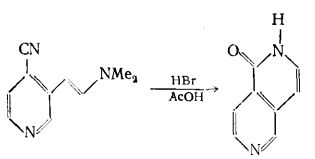
The study of the kinetics of these reactions showed that the cyclisation of compounds (CXXVI) is much faster than that of compounds (CXXVII)[205]. It has been established recently that enaminodinitriles are also convenient compounds for the synthesis of condensed pyridines[210]:



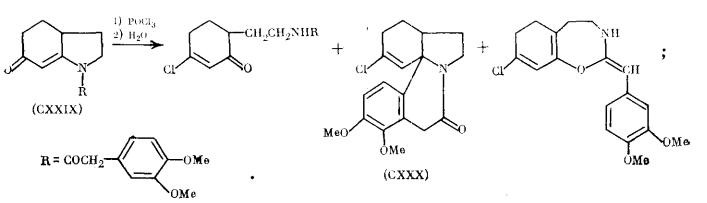
β-*C*-acylation of secondary amines by nicotinoyl chloride with subsequent cyclisation by means of the same reagent leads to 1,5-naphthyridines[153]:



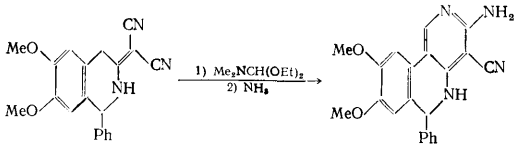
2,6-Naphthyridines have been obtained by the cyclisation of 4-cyano-3-(β-dimethylaminovinyl)pyridines[211]:



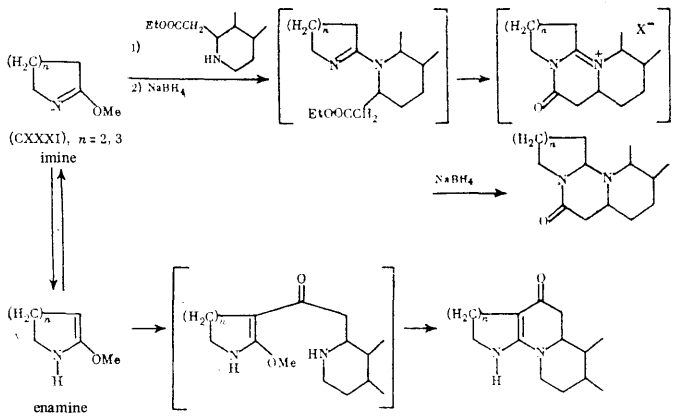
The reactions of certain enaminoketones with phosphoryl chloride and phosphorus pentachloride were discussed above[105]. When this reaction is carried out in acetonitrile, several compounds, including benzoxazepine and indoloquinolone (CXXX), are formed from the enaminoketone (CXXIX)[105]:



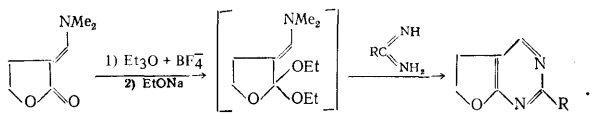
Pyrido[2,1-*a*]isoquinolines have been obtained by the reactions of enamines with 3,4-dihydroisoquinolines[212], while derivatives of the isomeric pyrido[4,3-*c*]isoquinoline system have been synthesised from enamines of the isoquinoline series[212] in accordance with a scheme analogous to that for the synthesis of condensed 2-aminopyridines:



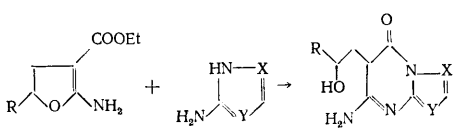
It is of extremely great interest to employ for synthetic purposes[26] the phenomenon of the imine–enamine tautomerism discovered previously[213] in the series of lactim esters. It has been shown[26] that *O*-methylvalerolactim and *O*-methylcaprolactim (CXXXI) react with derivatives of 2-ethoxycarbonylmethylpiperidine as both imines and enamines, giving rise to a mixture of condensed pyridines and pyrimidines:



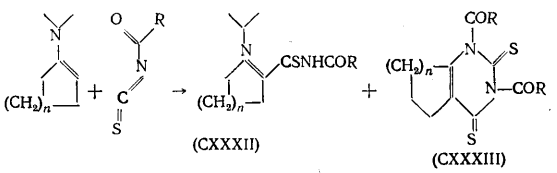
Enaminocarbonyl compounds react fairly readily with guanidine and amidines to form pyrimidine derivatives[197,214]. In a number of instances the carbonyl group must be activated, usually by alkylation[197,215], for example,



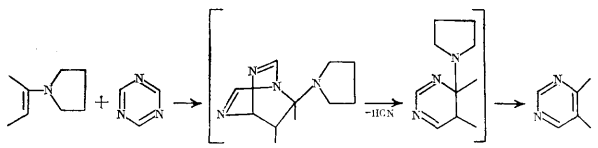
Heterocyclic enaminoesters react with aminoazoles to form azolopyrimidines[216,217]:



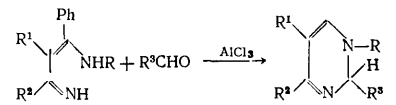
The reactions of enamines with carbonyl isothiocyanates[218] are accompanied by the formation of [1:1] adducts (CXXXII) and [1:2] adducts (CXXXIII):



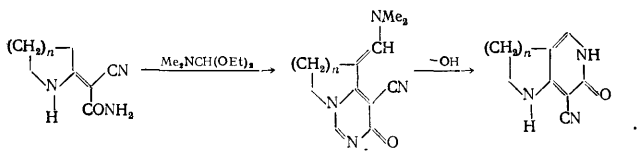
The cycloaddition of enamines to *sym*-triazine leads to pyrimidines[219]:



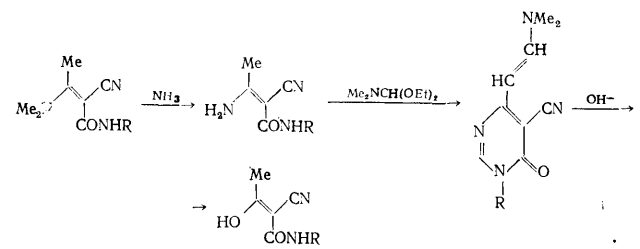
Pyrimidines are also formed when enaminoimines react with aldehydes under the conditions of the Friedel–Crafts reaction[220]:



The condensation of dimethylformamide and dimethylacetamide diethyl acetals with enaminoamides leads smoothly to derivatives of 5-cyanopyrimidine[130,206,210,221–224]. It is significant that the pyrimidines synthesised in this way are readily cleaved in an alkaline medium with subsequent recyclisation to pyridine derivatives. This method of synthesis of pyridine derivatives condensed with a saturated azaheterocycle is in fact preparatively most convenient:

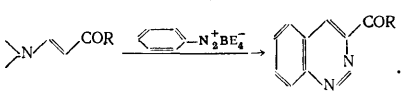


The kinetics of the cleavage of the pyrimidine ring have been investigated[210]. It is of interest that a change in the location of the substituent in the pyrimidine ring lowers the rate of its cleavage and recyclisation does not then occur[224]:



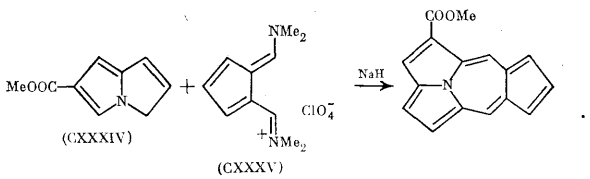
R=PhCH$_2$

A number of studies have been devoted to the closure of six-membered rings other than the pyridine and pyrimidine rings. Thus the interaction of enamines with 1-dialkylaminomethyl-2-hydroxynaphthalenes leads to condensed pyrans[225]. Condensed pyrans are also formed on reduction of 3-(β-ethoxycarbonyl)enamines by lithium tetrahydroaluminate[226]. The reactions of enaminoketones with ketones in the presence of lithiotetramethylpiperidine followed by cyclisation lead to 2,3-dihydro-4-pyrones[227]. Derivates of 2-pyrone have been obtained by the reaction of *N*-carbamidoenaminoketones with cyanoacetic ester and related compounds[228], while 2-morpholino-3-phenyl-3-isoflavene has been obtained by the reaction of 2-hydroxybenzaldehyde with morpholine enamine derived from phenylacetaldehyde[229]. The synthesis of pyridazines, based on the reaction of enaminocarbonyl compounds with diazonium salts[230], and the synthesis of condensed oxadiazines formed when enamines react with diacyldi-imides[231] or with arylacyldi-imides[232] have been described recently:



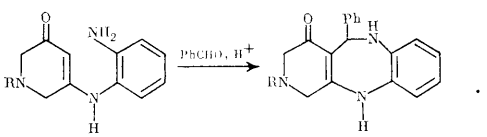
3. The Synthesis of Seven- and Eight-Membered Heterocycles

There have been relatively few studies of the synthesis of heterocycles containing more than six units from enamines. The interaction of *H*-pyrrolizinones (CXXXIV) with the enaminoimmonium salt (CXXXV) in the presence of sodium hydride has been described[233]:

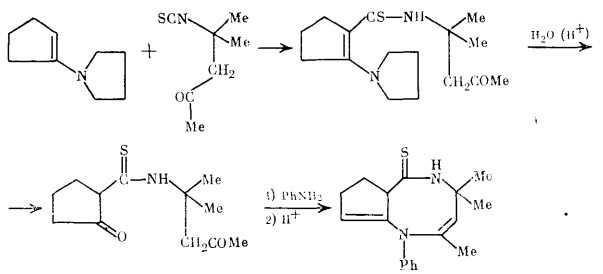


(CXXXIV) (CXXXV)

Condensed diazepines have been synthesised by the reaction of 3-ethoxycarbonylcyclopentanone with 4-nitro-o-phenylenediamine[234] or by the interaction of *N*-arylenamine derived from piperidinedione (CXXXVI) with benzaldehyde[123]:



Finally we shall mention yet another study in which condensed diazocines have been obtained by the reaction of isothiocyanates with the cyclopentanone-based enamine[235] and subsequent treatment with aniline:



Thus the results, presented above, of studies of the properties and the possibility of the employment of enamines in organic synthesis indicate the desirability and likely usefulness of the development of the chemistry of compounds of this class. Further development of studies directed towards the synthesis of various classes of heteromonocyclic, heterobicyclic, and heterotricyclic systems on the basis of enamines is of special interest.

During the preparation of this article for the press, a review was published on the chemistry of enamines[236], which, in contrast to the present review, is concerned mainly with enamines without electron-donating or electron-accepting substituents in the β-position.

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