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The Chemistry of *O*-alkyl Derivatives of Lactams

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The review gives a general account of the methods of synthesis and chemical properties of *O*-alkyl derivatives of lactams: lactim ethers, lactam acetals, and others. The reactions of *O*-alkyl derivatives of lactams with various nucleophilic and electrophilic reagents are described. Particular attention has been devoted to the possibility of using *O*-alkyl-lactams for the synthesis of various heterocyclic compounds which are of both chemical and biological interest. The bibliography includes 135 references.

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I. INTRODUCTION

The chemistry of *O*-alkyl derivatives of lactams (lactim ethers and lactam acetals) constitutes one of the least investigated branches of the chemistry of lactams in general. The lactams themselves have already been the subject of many investigations in various branches of organic chemistry. In particular extensive and interesting studies have been made on the chemistry of β-lactams [1] (with the aim of investigating the structure and synthesis of penicillins), reactions involving the incorporation of hydroxy- and aminoacyl-groups into lactams with conversion of the latter into the corresponding cyclols, cyclodepsipeptides, or cyclopeptides [2,3], and particularly on the development of methods for the synthesis of lactams for the preparation of various polymeric materials.

An attempt has already been made to give a general account of the available data on the chemistry of lactams as a specific class of heterocyclic compounds [4].

One of the most promising pathways in the development of the chemistry of lactams is the synthesis of various classes of organic compounds on the basis of lactams, associated with the preliminary activation of their amide function [5]. Activation of this kind of functional groups in various organic compounds has already yielded extremely interesting results. It is sufficient to point out that the conversion of ketones into enamines [6] or of acid amides into imino-ethers [7] made it possible to employ these compounds in new, hitherto unknown ways. Similarly the conversion of lactams into lactim ethers and lactam acetals gives rise to new possibilities in the application of lactams in organic synthesis.

The chemical properties of lactim ethers have already been the subject of two short reviews [8,9] but the latter cannot be regarded as sufficiently complete. Lactam acetals have begun to be studied only in recent years and these investigations have not been reviewed at all.

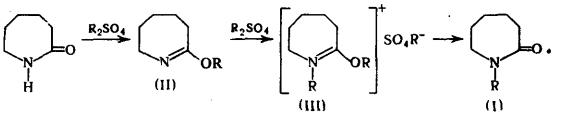
In the present review an attempt is made to give a general account of all the available data on the chemistry of *O*-alkyl derivatives of lactams in order to assess the advances in this field and the likely scope of the application of lactim ethers and lactam acetals in the synthesis of complex organic compounds.

One should also bear in mind that, apart from their use as starting materials for the synthesis of various organic compounds including dyes [10,11], lactim ethers are also of independent interest as biologically active materials [12] and also as accelerating agents in polymerisation processes [13].

II. METHODS OF SYNTHESIS OF LACTIM ETHERS

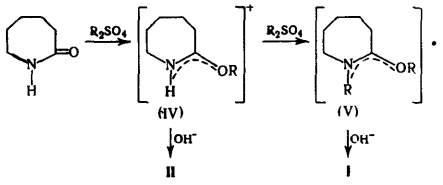
1. Direct Alkylation of Lactams

The methods for the preparation of lactim ethers by direct alkylation of lactams include the interaction of the latter with diazoalkanes [14] and also the alkylation of metal salts of lactams with alkyl halides [15]. Both methods are rarely used for the preparation of lactim ethers, since it is more convenient to use for this purpose the alkylation of lactams by dialkyl sulphates and trialkyloxonium fluoroborates. The alkylation of lactams by dialkyl sulphates was investigated in detail for caprolactam by Benson and Cairns [16], who established that this process depends to a considerable extent on the relative amounts of the components employed in the reaction. An excess of dialkyl sulphate leads, on the one hand, to a sharp reduction of the yield of lactim ethers due to the preferential formation of *N*-alkyl derivatives (I). On the other hand, the slow addition of an equimolar amount of an alkylating agent leads to an increase of the yield of *O*-alkylcaprolactim (II). The authors suggested that a considerable proportion of (I) is formed via compound (II) by the following hypothetical mechanism:



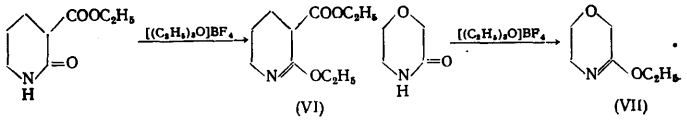
On the basis of the work of Bredereck and coworkers [17,18] on the reaction of acid amides with dimethyl sulphate, one may postulate that the ambidentate cation (IV) is formed

as an intermediate in this reaction and in the presence of an excess of dialkyl sulphate is alkylated further to the *NO*-dialkyl derivative (V). Under the influence of alkaline reagents, compounds (IV) and (V) are converted respectively into compounds (II) and (I). The conversion of compound (V) into (I) can also be achieved by heat treatment with elimination of dialkyl sulphate:

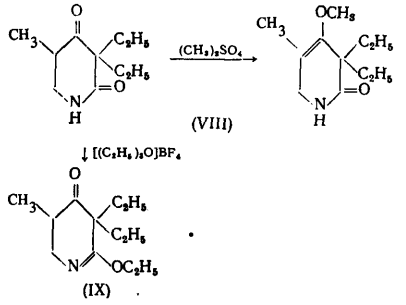


The method of Benson and Cairns is still used for the preparation of lactim ethers from the simplest lactams. However, recently another method of synthesis of lactim ethers has been acquiring increasing importance—alkylation of lactams by tertiary oxonium salts, in particular triethyloxonium fluoroborate [19,20]. This reaction involves the formation of an ambidentate cation, similar to the cation (IV), from which lactim ethers are also obtained by treatment with aqueous solutions of alkaline reagents. By virtue of their high electrophilicity, oxonium salts give better results than other alkylating agents [21].

It is noteworthy that in none of the numerous cases where equimolar amounts of trialkyloxonium fluoroborates were used to alkylate lactams [21-27] were *N*-alkyl derivatives isolated. This suggests the high selectivity of oxonium salts in such reactions. It is interesting that the high tendency towards *O*-alkylation under the action of triethyloxonium fluoroborate, compared with other alkylating agents, is shown also in the alkylation of keto-enols [28], the ambidentate ions of nitro-alkanes [29,30], and also potassium diethyl phosphorothioate [31]. Although special studies dealing with the comparison of the alkylating activities of dialkyl sulphates and trialkyloxonium fluoroborates have not as yet been published, nevertheless the available information suggests that tertiary oxonium salts provide a more univeral means for the synthesis of lactim ethers. Thus it has been noted that the attempts to alkylate 3-ethoxycarbonyl-2-piperidone [25] and 3-morpholinone [32] with dimethyl sulphate were unsuccessful, whereas the use of triethyloxonium fluoroborate resulted in high yields of 2-ethoxy-3-ethoxycarbonyl-3,4,5,6-tetrahydropyridine (VI) and 3-ethoxy-3,4-dehydromorpholine (VII):



The selective properties of triethyloxonium fluoroborate in the alkylation of lactams are shown particularly clearly in its interaction with 3,3-diethyl-5-methylpiperidine-2,4-dione (VIII) [25]. The interaction of compound (VIII) with an equimolar amount of dimethyl sulphate resulted in the alkylation of the carbonyl group in the 4-position, while in the reaction of compound (VIII) with triethyloxonium fluoroborate the corresponding lactim ether (IX) was obtained:



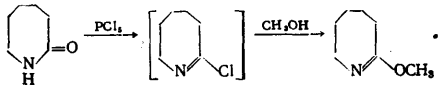
Recently a number of studies have been published on the alkylation of lactam with triethyloxonium fluoroborate when the ring contains, apart from the lactam group, also cyano-, ethoxycarbonyl, and acylated secondary amino-groups [25,33-41]. Selective alkylation of the lactam carbonyl was observed with formation of lactim ethers. In many cases when lactams were alkylated with triethyloxonium fluoroborate, the initial lactams were isolated as well as the lactim ethers, which is in all probability due to hydrolysis [analogous to the conversion of compound (V) into compound (I)] when the ambidentate cation, similar to the cation (IV), is attacked by the hydroxide ion during the isolation of the lactim ether.

Summarising, we may note that the use of triethyloxonium fluoroborate has real advantages over other alkylating agents both because of better yields of lactim ethers and because, when there is a choice between a possible attack on the lactam and other carbonyls, the former takes place preferentially (see above). This is also confirmed by the studies of Meerwein et al. [42], who classify carbonyl compounds in accordance with their capacity for alkylation by oxonium salts in the following series:

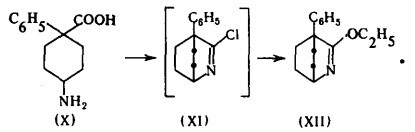
lactams > non-cyclic acid amides > lactones > carboxylic acid > esters > ketones > aldehydes.

2. Other Methods for the Synthesis of Lactim Ethers

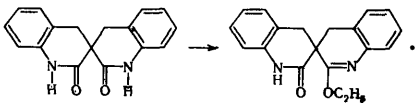
An important method for the preparation of lactim ethers consists in the conversion of lactams into the corresponding chlorinides followed by treatment with alcohols. Thus the interaction of caprolactam with phosphorus pentachloride and subsequent treatment of the reaction mixture with methanol led to the synthesis of *O*-methylcaprolactim [43]:



Similarly in the interaction of 4-amino-1-phenylcyclohexane-1-carbocyclic acid (X) with phosphorus pentachloride cyclisation takes place with formation of the chlorimide (XI), the alcoholysis of which yielded the lactim ether (XII) [44]:

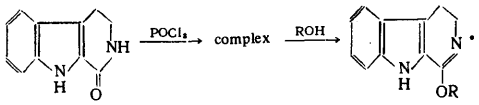


Similarly the interaction of the bishydrocarbostyryl-spirane (XIII) with phosphorus trichloride and phosphorus oxychloride followed by alcoholysis gave the corresponding lactim ether (XIV), which is also formed as a by-product in the reduction of di-(*o*-nitrobenzyl)malonic ester[45]:



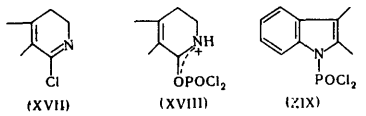
(XIII) (XIV)

Another example of the synthesis of lactim ethers from lactams and phosphorus oxychloride is the conversion of 3,4-dihydro-β-carbolin-1-one (XV) into 1-alkoxy-3,4-dihydro-β-carboline[46,47] (XVI):



(XV) (XVI)

Although the structure of the intermediate complex has not been accurately established, on the basis of the general properties of acid amides and lactams[48-52], one may suggest that, under the action of phosphorus oxychloride, the piperidone component of the molecule of compound (XV) is converted into compound (XVII) or (XVIII):

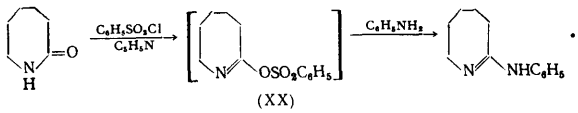


(XVII) (XVIII) (XIX)

However, one must remember that the indole component of the molecule is also capable of interacting with $POCl_3$ to form the phosphoramidic dichloride (XIX)[33].

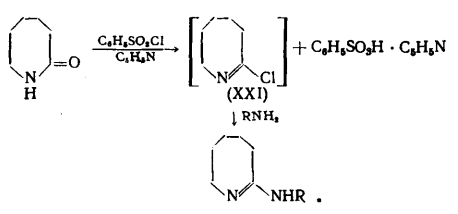
The reaction of the simplest lactams with benzenesulphonyl chloride probably takes place similarly as the reaction of β-carbolin-1-one (XV) with phosphorus oxychloride.

In their study of the synthesis of cyclic amidines from lactams, Oxley et al.[53] proposed a mechanism according to which, on treatment with benzenesulphonyl chloride in the presence of pyridine, caprolactam is converted into the intermediate *O*-benzenesulphonate of the caprolactim (XX), which readily reacts with amines, forming cyclic amidines:



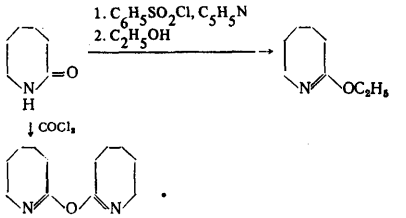
(XX)

However, later, in connection with the development of the synthesis of αβ-pentamethylenetetrazole[54], a detailed study of the first stage of this mechanism showed that this hypothesis is incorrect, since a high yield of the salt of benzenesulphonic acid and pyridine and not pyridinium chloride was isolated from the reaction mixture. Therefore a different mechanism was put forward, postulating the intermediate formation of the chlorimide of the caprolactam (XXI):



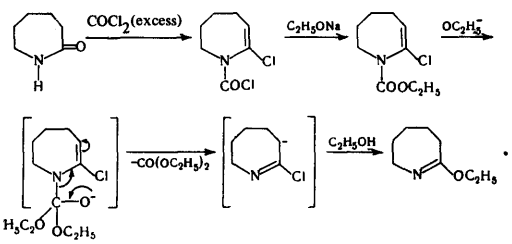
(XXI)

It is noteworthy that the intermediate chlorimide is extremely labile and is readily hydrolysed to caprolactam, all attempts to isolate it proving unsuccessful. This last study suggests that the syntheses of lactim ethers based on the interaction of lactams with reagents such as benzenesulphonyl chloride, chlorocarbonic ester, and phosgene[55-57] also probably takes place via the intermediate formation of chlorimides:

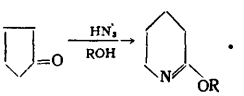


The interaction of sulphonyl chlorides with cycloalkanone oximes in pyridine probably also takes place similarly. In the first stage of this reaction the oxime evidently undergoes the Beckmann rearrangement and the lactam formed is converted into the chlorimide, from which the corresponding lactim ether is obtained by reaction with alcohol[58].

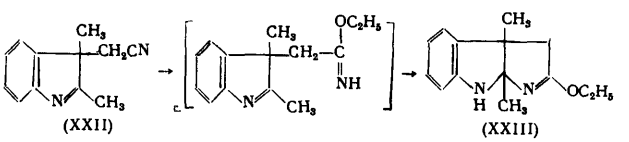
Tetenbaum's study[59] of the interaction of caprolactam with phosgene and the alcoholysis of 2-chloro-1-chlorocarbonyl-4,5,6,7-tetrahydro-1*H*-azepine also demonstrates the possibility of synthesising lactim ethers via the intermediate formation of compounds containing the chlorimide N=C–Cl group:



Among other methods of synthesis of lactim ethers, mention should be made of the procedure which consists in the interaction between cyclic ketones and hydrazoic acid in the presence of alcohol[60]:

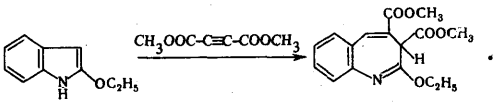


Apart from the general methods for the synthesis of lactim ethers described above, the ethers can also be obtained using the individual properties of particular organic compounds. An example is provided by the conversion of 3-cyanomethyl-2,3-dimethylindolenine (XXII) into the tricyclic lactim ether (XXIII)[61] under the influence of a solution of sodium ethoxide or hydrogen chloride in alcohol. In particular, in this case use was made of the capacity of indolenines to react with imines at the 2-position of the indolenine molecule:



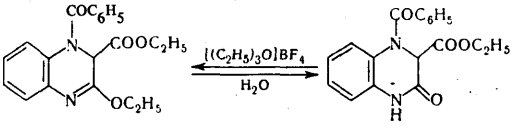
(XXII) (XXIII)

Mention can also be made of the synthesis of a lactim ether by the expansion of the indole ring to a benzazepine ring by the mechanism[62]:

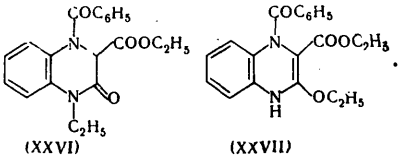


III. CHEMICAL PROPERTIES AND REACTIONS OF LACTIM ETHERS

Lactim ethers are extremely reactive towards nucleophilic agents, which readily distinguishes them from *N*-alkyl-lactams and other isomeric compounds. One may quote as an example the lactim ether derived from 4-benzoyl-3-ethoxycarbonyl-1, 2, 3, 4-tetrahydro-2-quinoxalinone (XXIV)[63]. The reaction of triethyloxonium fluoroborate with 4-benzoyl-3-ethoxycarbonyl-1, 2, 3, 4-tetrahydro-2-quinoxalinone (XXV) yielded a substance to which one of the following three isomeric structures (XXIV), (XXVI), or (XXVII) could be ascribed, bearing in mind the possibility to alkylation with transfer of the reaction centre:



(XXIV) (XXV)

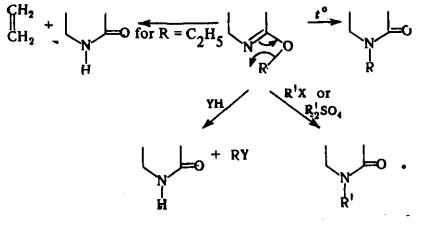


(XXVI) (XXVII)

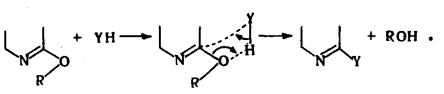
On the basis of infrared and NMR spectroscopic data, the structure (XXVII) was eliminated. However, the spectroscopic data did not allow an unambiguous choice between structures (XXIV) and (XXVI). Therefore the compound obtained was hydrolysed under exceptionally mild conditions (in water at 20°C) which gave an almost quantitative yield of the initial lactam (XXV). Such mild hydrolysis conditions undoubtedly indicate that the compound obtained is a lactim ether, this being confirmed subsequently also by its reactions (see below).

The reactions of lactim ethers with participation of the lactim ether group can be divided into two principal classes.

1. Reactions accompanied by the elimination of the *O*-alkyl residue and the formation of lactam derivatives:

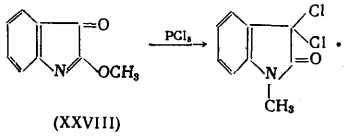


2. Reactions involving the lactim carbon atom with elimination of the alkoxy-group:



Reactions of the first type include the thermal rearrangement of lactim ethers into *N*-alkyl-lactams. In particular it was noted that 2-methoxy-3-oxoindolenine (XXVIII) undergoes on heating thermal isomerisation to *N*-methylisation[64]. In the paper by Benson and Cairns[16] mentioned above, a similar conversion of *O*-methyl(ethyl)caprolactim into the *N*-methyl(ethyl) derivative was described.

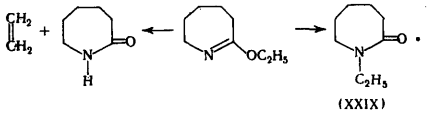
Another example of this type of rearrangement is the interaction of the lactim ether derived from isatin (XXVIII) with phosphorus pentachloride, which is also accompanied by the substitution of the oxo-group in the 3-position by two chlorine atoms[66]:



(XXVIII)

According to many investigators[16,65], this rearrangement is a common property of lactim ethers, similar to the analogous rearrangement of the simplest imino-ethers[7].

New data on this problem were obtained by Ralls and Eliger[67] in a study of the thermal isomerisation of *O*-ethylcaprolactim. In this investigation it was shown that the lactim ether remains unchanged at 193°C and only after prolonged heating (21 h at 237°C) is a small amount converted into *N*-ethylcaprolactam. The principal reaction product is caprolactam formed from the lactim ether on elimination of ethylene:

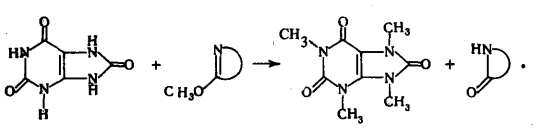


(XXIX)

The authors suggested that the rearrangement of the lactim ether into *N*-ethylcaprolactam (XXIX) is caused by traces of dialkyl sulphate and demonstrated this by the heat treatment of *O*-ethylcaprolactim in the presence of diethyl sulphate; the *N*-alkyl derivative (XXIX) was isolated as the main product. Similar behaviour was observed also with *O*-methylvalerolactim[67].

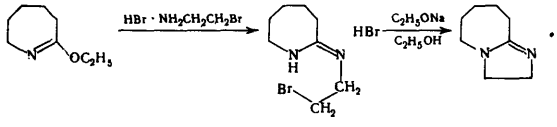
The need for the presence of dialkyl sulphate in the rearrangement of lactim ethers into *N*-alkyl-lactams is also consistent with the finding that similar isomerisation was achieved earlier in the interaction between *O*-methylcaprolactim and dimethyl sulphate[16]. The process probably involves the intermediate formation of compound (V) (see Russ. p. 914).

Reactions of the first type include also alkylation by lactim ethers of compounds with definite acid properties. Thus lactim ethers have been used as alkylating agents in reactions with compounds containing imino-groups[68], such as uric acid, xanthines, and hypoxanthines, and also for the esterification of organic acids[69]:

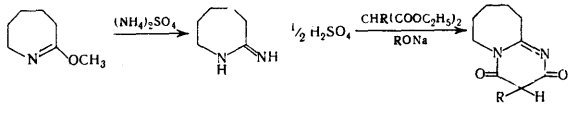


Among reactions of the second type the most common and probably the most promising for the synthesis of heterocyclic systems are reactions with various amino-derivatives and also with compounds having active methylene groups.

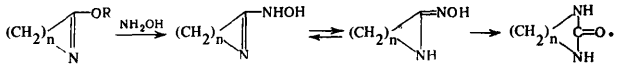
The synthesis of amidines from lactim ethers and amines takes place very readily and with high yields [8,9,16,21,70-76]. As an example, one may quote the synthesis of derivatives of imidazo[1,2-*a*]azepines carried out by Stolle et al.[77] by the reaction of *O*-ethylcaprolactim with β-bromoethylammonium bromide followed by cyclisation under the action of sodium ethoxide of the resulting β-bromoethylamidine derived from the caprolactim:



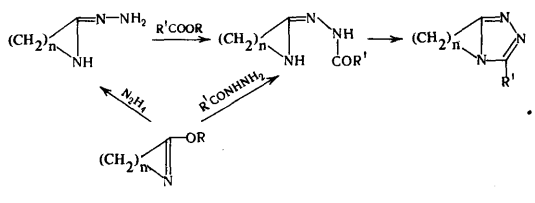
and also the synthesis of derivatives of pyrimidino[1,2-*a*]-azepines from *O*-methylcaprolactim[70]:



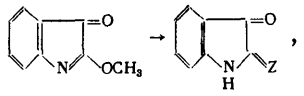
Lactam oximes have been synthesised by the interaction between lactim ethers and hydroxylamine [9,72,73,78]. This reaction became particularly important after it had been established that, under the influence of polyphosphoric acid, lactam oximes undergo the Beckmann rearrangement with formation of polymethyleneureas[79]:



The reaction of lactim ethers with hydrazine hydrate and substituted hydrazines [5,54,76,80-82] takes place even more readily because of the even more pronounced nucleophilic properties of the latter reagents. The "hydrazidines" formed in this process are extremely active and can take part in various cyclisations involving the amino-group of the side chain and the ring nitrogen. Thus, when the hydrazine of caprolactim was treated with nitrous acid, αβ-pentamethylenetetrazole (corazole) was synthesised [54,80,81], while the syntheses employing hydrazidines derived from other lactim ethers gave analogues of this compound [32,35]. It should also be mentioned that polymethylenetetrazoles may be synthesised by the action of an excess of hydrazoic acid on lactim ethers[83] as well as by the reaction of this acid with *O*-acyl-lactims (or lactam chlorimides) obtained from lactams and sulphonyl chlorides or phosphorus oxychloride[84]. Other possibilities which arise when similar "hydrazidines" are obtained may be demonstrated using as an example their conversion into polymethylenetriazoles [85-87]:



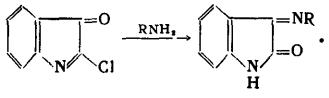
The reactions of the lactim ether of isatin (XXVIII) with amines, hydroxylamines, and substituted hydrazines [76,88] require special consideration. When compound (XXVIII) reacts with the above reagents, the condensation involves only the lactim ether group but not the oxo-group:



(XXVIII)

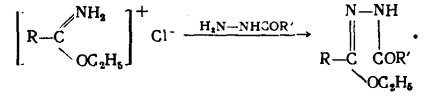
where Z = RN^-, $RNH-N^-$, or $-N-OH$.

From this, one may conclude that the lactim ether group in compound (XXVIII) is extremely reactive. We may also mention that the lactim ether group in this compound is probably even more reactive than the chlorimide group. Thus, it has been stated that, under the action of tosylhydrazine and aniline on isatin chlorimide, the oxo-group in the 3-position is attacked; the reaction is accompanied by the hydrolysis of the chlorimide to the lactam[89]:



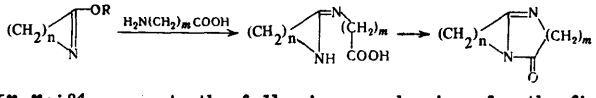
The reactions of lactim ethers with semicarbazides, thiosemicarbazides, and sulphonyl hydrazides as a rule stop at the amidrazone stage.

It is interesting that the reaction of aliphatic imino-ethers with the above components take place by a completely different mechanism: not with the elimination of alcohol and the formation of a C=N bond, but with the dissociation of the C=N bond and the elimination of ammonia [90-92]:

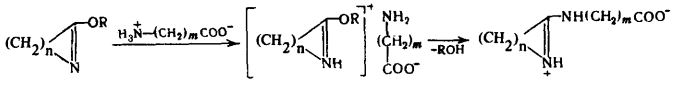


The reactions of lactim ethers with amino-acids have been investigated in fair detail [21,23,93]. It has been established that these reactions take place very readily, substituted amidino-acids, the cyclisation of which leads to various condensed dihydropyrimidines or imidazolines, being formed.

The cyclisation of aliphatic amino-acids requires fairly severe conditions, while with aromatic or heterocyclic amino-acids, where a fairly high degree of aromatisation of the diazine ring is attained, the process takes place readily so that the intermediate amidines cannot be isolated:



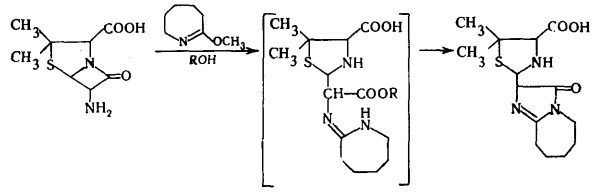
Körösi[94] suggests the following mechanism for the first stage of this process:



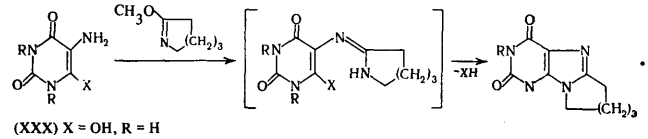
According to this mechanism, the reaction begins with the protonation of the lactim nitrogen, which is achieved more readily when the acid properties of the amino-acid carboxyl are enhanced (i.e. in the case of aromatic and heterocyclic amino-acids). The protonation of the lactim nitrogen increases the electrophilicity of the adjacent carbon atom and is responsible for the ease of the subsequent nucleophilic substitution of this atom. Consequently, when lactim ethers are condensed with amines, account must be taken not only of the basicity of the initial amines but also of the possibility of the formation of a salt by the lactim ether group.

The reactions of lactim ethers with amino-acid esters[95] lead to the corresponding amidino-acid esters. The principal factor which determines the course of this process is the basicity of the amino-group, which is clearly illustrated, for example, by the condensation of lactim ethers with the aminocrotonic ester, which either does not occur at all[21,95], or takes place with a relatively low yield[70].

The interaction of *O*-methylcaprolactim with 6-aminopenicillanic acid takes place with the opening of the β-lactam ring and subsequent cyclisation of the derivative of penicilloic acid involving the ester group and the endocyclic nitrogen of the azepine ring[96]:

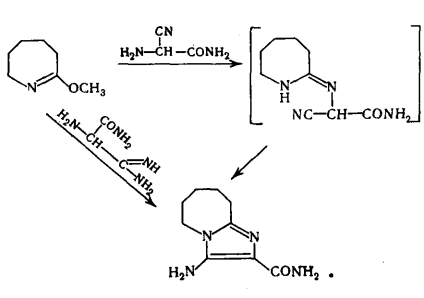


The ease of formation of amidines in the reactions of lactim ethers with amines was used in the synthesis of 8,9-polymethylenepurines. The attempts to condense *O*-methylcaprolactim with uramil (XXX) and 4,5-diamino-1,3-dimethyluracil (XXXI), undertaken to obtain 8,9-pentamethylenexanthine showed that lactim ethers do not react with 5-aminouracil derivatives, probably because of the low basicity of their amino-groups:



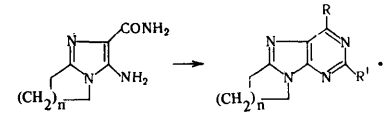
(XXX) X = OH, R = H
(XXXI) X = NH_2, R = CH_3

The synthesis of 1,2-polymethylene derivatives of 5-amino-4-carbamoylimidazoles, which are key compounds in the synthesis of 8,9-polymethylenepurines, was achieved by condensing lactim ethers with α-amino-α-cyanoacetamide. It was found that, despite the presence of an active methine unit in the latter compound, the reaction involves selectively the amino-group, as shown by the physicochemical properties of the products, further reactions, and, in the case of *O*-methylcaprolactim, also by synthesis—the condensation of the caprolactim with the dihydrochloride of α-amidino-α-aminomalonamide[97]:



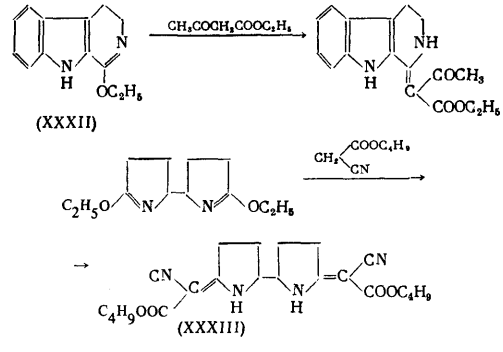
When this reaction was extended to butyro- and valerolactims, it was found[98] that an additional enhancement of the electrophilicity of the attacking carbon atom of the lactim group is necessary, and this was achieved by carrying out the reaction in alcohol containing catalytic amounts of hydrogen chloride.

The reaction of lactim ethers with α-amino-α-cyanoacetamide thus developed permitted the synthesis of a group of polymethyleneimidazoles and made it possible to convert the latter into 8,9-polymethylenepurines:



The general features of this reaction have also been compared using more complex examples such as 1-ethoxyisoindolenine[24] and also lactim ethers containing an additional hetero-atom in the lactam ring[32,35,99]. When α-amino-α-cyanoacetamide was condensed with lactim ethers derived from 3-morpholinone[32], 3-thiazanone[99], and 2-piperazinone[35], it was shown that the introduction of a second hetero-atom in the 4-position of the lactam ring does not alter significantly the reactivity of lactim ethers.

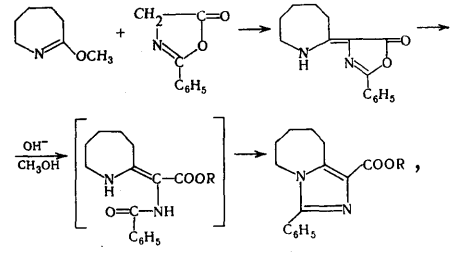
The high reactivity of lactim ethers is shown particularly clearly in their capacity to form a new carbon–carbon bond in the reaction with compounds containing active methylene groups, such as acetoacetic, cyanoacetic, and malonic esters and their derivatives, acetylacetone, barbituric acid, rhodanine, nitromethane, oxindole, and others[8,9,33,100–102]. One may quote as examples the condensation of the lactim ether derived from 3,4-dihydro-β-carbolin-1-one (XXXII) with acetoacetic ester[103] and also the condensation of the bislactim ether derived from 2,2′-di-5-pyrrolidone (XXXIII) with butyl cyanoacetate[26]:



(XXXII)

(XXXIII)

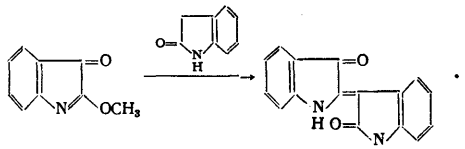
Another example of the reaction of lactim ethers with compounds having an active methylene group is the condensation of *O*-methylcaprolactim with 2-phenyl-5-oxazolone[104] which leads to the synthesis of 3,4-pentamethyleneimidazoles via the intramolecular rearrangement of the intermediate 2-phenyl-4-(2′-homopiperidylene)-5-oxazolone:



where R = H or CH_3.

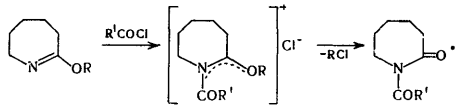
The condensation of the lactim ether derived from isatin (XXVIII) with oxindole in an anhydrous medium (benzene, acetic anhydride) in the presence of a catalytic

amount of concentrated sulphuric acid involves the active α-methylene unit with formation of indirubin (XXXIV)[102]:

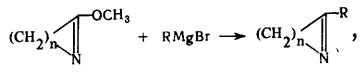


(XXVIII) (XXXIV)

In the literature there are contradictory data on the interaction between lactim ethers and acid chlorides. In 1956 a patent was published in which it is stated that this interaction leads to the corresponding *O*-acyl-lactams[105]. In another study on this problem[106] it was shown for a large number of examples, using spectroscopic methods, that the reaction products are *N*-acyl-lactams:

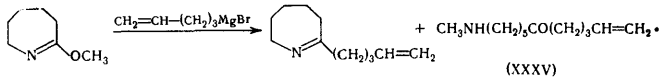


Numerous studies have been made on the interaction between lactim ethers and Grignard reagents[72,73,107-112]. It has been stated that this reaction depends on the size of the lactam ring. Thus, whereas *O*-methylbutyro- and *O*-methylvalero-lactims give bases of the same type:



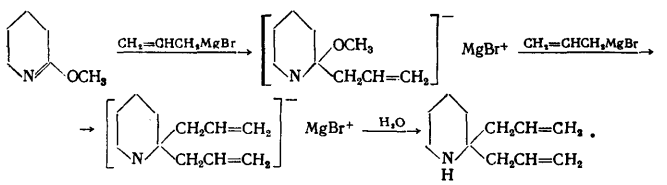
(*n* = 2,3)

in the case of *O*-methylcaprolactim, in addition to similar bases, *N*-methylaminoketones of type (XXXV) are sometimes formed, which can be explained by the conversion of *O*-methylcaprolactim into *N*-methylcaprolactam and subsequent interaction of the latter with a Grignard reagent[109]:

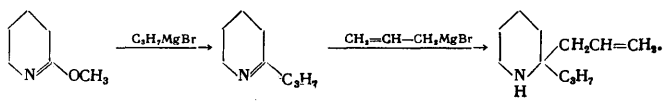


(XXXV)

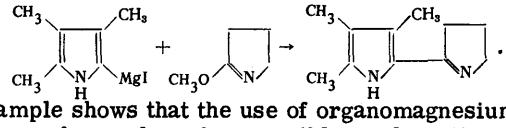
In the general case (where R in RMgX is a simple alkyl or aryl) it is suggested that the reaction does not take place via the addition of the Grignard reagent to the C=N bond but involves the direct substitution of the alkoxy-group of the lactim ether by the alkyl residue. In this connection, the reaction of *O*-methylvalerolactim with allylmagnesium bromide constitutes an unusual case[112]. This reaction yields only the gem-derivative, which is probably due to the addition of the Grignard reagent to the C=N bond:



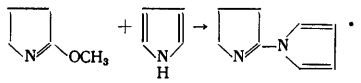
This mechanism is consistent with the capacity of allylmagnesium bromide to add to the double bond of 2-propyl-3,4,5,6-tetrahydropyridine:



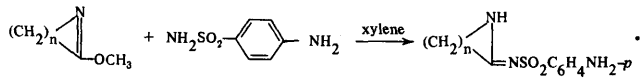
An interesting example of the reaction of lactim ethers with organomagnesium compounds is the synthesis of 2,2′-pyrrolylpyrrolines[108]:



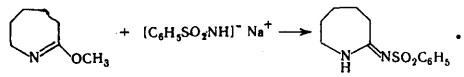
This example shows that the use of organomagnesium derivatives of pyrrole makes possible condensation involving the α-position of the pyrrole ring. When pyrrole itself reacts with the lactim ether, the condensation involves the pyrrole nitrogen with formation of a C–N bond[113]:



Sulphonamides enter into a similar condensation with lactim ethers and in the presence of an aromatic amino-group and a sulphonamide group the reaction of the lactim ether involves preferentially the sulphonamide group[114]:

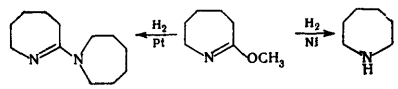


The interaction of lactim ethers with ammonium benzenesulphonate leads to the corresponding amidine salt and that with sodium benzenesulphonate yields the benzenesulphonyl derivative of amidinocaprolactim[71]:



An important property of lactim ethers is the relative (compared with lactams) ease of their reduction to cyclic imines. The reduction of lactams involves considerable difficulties and is as a rule carried out with lithium aluminium hydride. In this connection, the comparatively easy hydrogenation of lactim ethers is promising[16,72,109].

The studies of Benson and Cairns[16] showed that the hydrogenation of *O*-methyl and *O*-ethylcaprolactims over Raney nickel, ruthenium oxide, and the barium–copper–chromite catalyst give high yields of hexamethyleneimine. When platinum is used in this case, an amidine is formed by the mechanism:

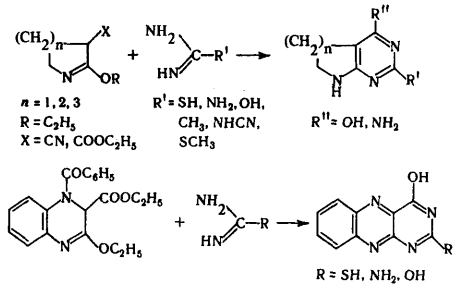


The catalytic hydrogenation of *O*-methylvalerolactim over platinum oxide yielded piperidine[109] and the hydrogenation of *O*-methylbutyrolactim over platinum in acetic acid resulted in the formation of pyrrolidine[72]. In addition, the reduction of lactim ethers with lithium aluminium hydride has also been described—cyclic imines were obtained in all cases[109].

So far we have considered the reactions of monofunctional lactim ethers involving mainly their imino-ether group. In such cases new heterocyclic rings are formed from the carbon and nitrogen of the lactim ether group.

Recently a number of studies have been published, in which di- (or tri-) functional lactim ethers were used for this purpose[25,38-41,115]. The first example of this type of synthesis was the interaction of the lactim ether derived from 3-ethoxycarbonyl-2-piperidone (XXXVI) with thiourea in the presence of an alcoholic solution of sodium ethoxide[25]. A detailed study of this reaction was carried out for

lactim ethers derived from 3-ethoxycarbonyl-2-piperidone (XXXVI), 3-cyanocaprolactam (XXXVII), 3-ethoxycarbonylcaprolactam (XXXVIII), 3-ethoxycarbonyl-2-pyrrolidone (XXXIX), and ethoxycarbonyl-4-benzoyl-1,2,3,4-tetrahydro-2-quinoxalinone (XL) [35-38,40,115].



It was shown that this reaction constitutes a general synthesis of condensed pyrimidines and that the pyrimidine cyclisation depends both on the structure of the lactim ethers and on the properties of the "amidine" component. The use of guanidine and thiourea as the "amidine" component gives the best results in all cases of the synthesis of the corresponding condensed pyrimidines. It is noteworthy that, whereas in the condensation of compounds (XXVIII)–(XL) with urea condensed uracils were obtained in a low yield, in a similar condensation of compound (XXXVI) hydrogenated 2,4-dihydroxypyrido[2,3-*d*]pyrimidine was obtained in a satisfactory yield, comparable to that of the product obtained in the reaction of compound (XXXVI) with acetamidine.

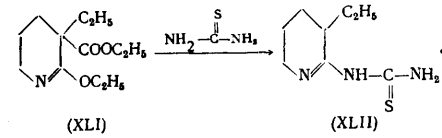
The reactivity of other "amidine" components is as a rule intermediate between the above extremes and the components can be arranged in the following sequence:

guanide ≃ thiourea > cyanoguanidine > acetamidine > *S*-methylisothiourea > urea.

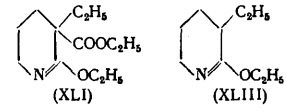
If one disregards the anomalously low yields when *S*-methylisothiourea is used, then the relative reactivities of the amidine components in the above series are the same as in the usual pyrimidine cyclisations [116-119]. Furthermore the condensation of lactim ethers derived from 3-ethoxycarbonyl-lactams with amidine components greatly depends on the stability of the reactants, as in the analogous reaction of malonic esters [120].

Like aliphatic imino-ethers, lactim ethers are very labile both in acid and alkaline media. Therefore the reaction depends in many respects on the relative rates of the main process (pyrimidine cyclisation) and the side reactions associated with the instability of the starting materials. When the "amidine" components are substances with high basicity and high capacity for enolisation under the process conditions, pyrimidine cyclisation predominates and the yields of the condensed pyrimidines are high. On the other hand, when the "amidine" components do not have these properties (or have them to a much smaller extent), the lactim ethers are probably alcoholysed to lactams with subsequent rupture of the lactam ring [121]. Comparison of the reactivities of the lactim ethers derived from 3-cyano- and -3-ethoxycarbonyl-caprolactams shows that, as in the usual pyrimidine cyclisations [120], the latter are more reactive. Whereas the condensation of the lactim ether derived from 3-cyanocaprolactam with urea does not occur at all, in the condensation of the 3-ethoxycarbonyl derivative condensed uracil was obtained, albeit in a low yield.

The use of bifunctional lactim ethers in the synthesis of condensed pyrimidines made it possible to achieve the synthesis of a new heterocyclic system—pyrimido[4,5-*b*]-tetrahydroazepine [36,37] and also to develop new methods for the synthesis of alloxazines [41], 7*H*,5,6-dehydropyrrolo[2,3-*d*]pyrimidines [38,39], and 8*H*,piperidino[2,3-*d*]pyrimidines [25,115]. A further development of these studies was the investigation of the condensation of the lactim ether derived from 3-ethoxycarbonyl-3-ethyl-2-piperidone (XLI) with thiourea, guanidine, and other amidine components [115]. The aim was to synthesise condensed piperidino[2,3-*d*]-pyrimidines with an angular ethyl group, which are cyclic analogues of the biologically active 5,5-disubstituted barbituric acids. The study of the interaction of compound (XLI) with thiourea showed that the condensation does not occur when an equimolar amount of sodium alkoxide is employed, while in the presence of an excess of this reagent *N*-(3-ethyl-3,4,5,6-tetrahydropyrid-2-yl)thiourea (XLII) was isolated:

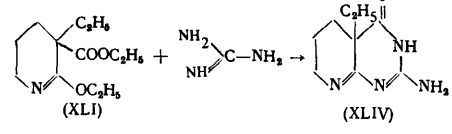


The above mechanism shows that in this reaction the ethoxycarbonyl group is eliminated, probably as a result of its alcoholysis with formation of diethyl carbonate, as was observed earlier for disubstituted cyanoacetic esters in the synthesis of iminobarbituric acids [122,123]. Comparison of the reactivities of the lactim ethers (XLI) and (XLIII) shows that the former should be more reactive in nucleophilic substitution reactions than compound (XLIII) because of the negative inductive effect of the ethoxycarbonyl group and the associated higher partial positive charge on the "lactim" carbon atom:



On this basis, one may suppose that the first stage in this process is attack by thiourea on the "lactim" carbon atom and consequently the lactim ether group is more reactive under the conditions of this reaction than the ethoxycarbonyl group. The need for an excess of sodium hydroxide in this reaction is probably due to the low dissociation constant of thiourea.

The interaction of compound (XLI) with guanidine, which is a stronger base, now leads to the product of cyclisation involving the ethoxycarbonyl group, 2-amino-4-hydroxy-10-ethyl-4,5,6,7,8,10-hexahydropyrido[2,3-*d*]pyrimidine (XLIV) with an angular alkyl group in the 10-position of the bicyclic compound being formed. In this case the yield is lower than in the condensation of compound (XXXVI) with guanidine, which can probably be accounted for by the incomplete aromatisation of the pyrimidine ring in compound (XLIV):



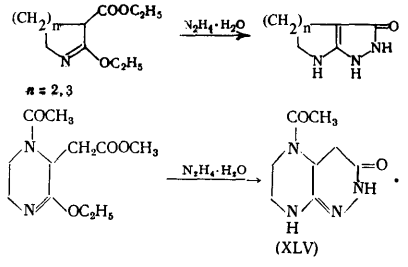
The last factor is evidently decisive in cyclisations of this type, involving the formation of a diazine ring. This is also confirmed by the fact that the attempts to condense

the lactim ether derived from 4-acetyl-3-methoxycarbonylmethyl-2-piperazinone with "amidine" components proved to be unsuccessful[40].

It is striking that the reaction of compound (XLI) with urea does not occur at all, probably because of the lower tendency of the latter to enolise under the reaction conditions compared with thiourea[113]. In all these cases one should also bear in mind the slightly reduced reactivity of the lactim ether group of compound (XLI) compared with compound (XXXVI) in consequence of the electron-donor effect of the alkyl group in the 3-position of the lactam ring.

In this connection it is also interesting to note that the reduced reactivity of compound (XLI) compared with compounds (XXXVI)–(XL) is confirmed by its higher stability to alcoholysis under the conditions of condensation with "amidine" compounds, since, in contrast to compounds (XXXVI)–(XL), compound (XLI) is partially regenerated in almost all cases.

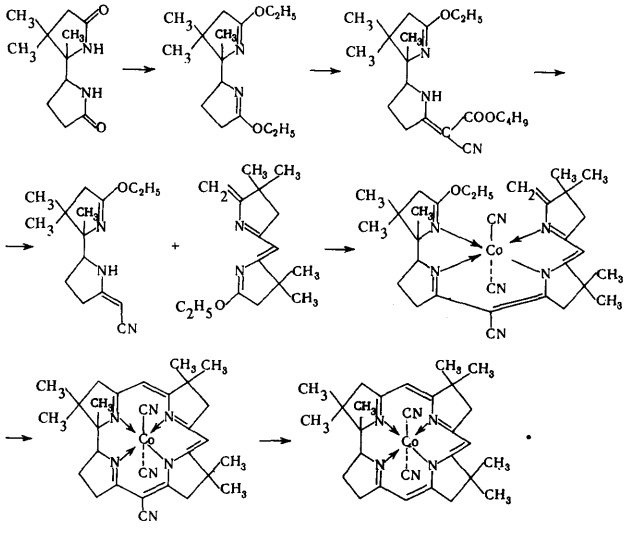
The condensation of bifunctional lactim ethers with "amidine" reagents does not exhaust the vast possibilities created by these compounds for the synthesis of various heterocycles. As an illustration, one may quote the condensations of certain lactim ethers with hydrazine hydrate, giving condensed pyrazoles[25,37] and pyridazines[40]:



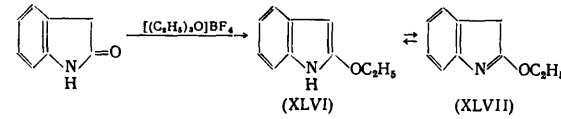
(XLV)

The "amidine" structure of compound (XLV) was demonstrated by infrared and NMR spectroscopy.

The high reactivity of lactim ethers made it possible to use these compounds in the study of the synthesis of complex organic compounds such as representatives of the corrin system[124-127]. As an example, one may quote the synthesis of racemic dicyano(1,2,2,7,7,12,12-heptamethylcorrin)cobalt (III)[125]:

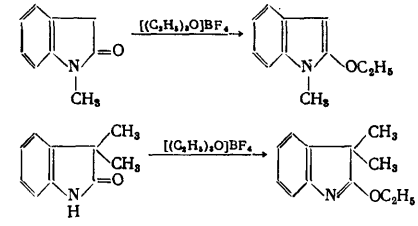


The ethylation of oxindole and its derivatives with triethyloxonium fluoroborate occupies a special place in the chemistry of lactim ethers. Harley-Mason and Leeney[22] established that the interaction of oxindole with triethyloxonium fluoroborate yields 2-ethoxyindole (XLVI) which isomerises on sublimation to the lactim ether (XLVII) derived from oxindole. When the latter is heated above the melting point, the reverse conversion of compound (XLVII) into compound (XLVI) can be achieved:



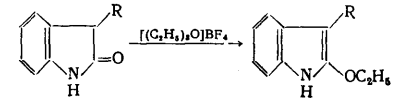
(XLVI) (XLVII)

2-Ethoxy-1-methylindole and 2-ethoxy-3,3-dimethylindolenine were prepared as models for the investigation of these reactions:



The study of the NMR and infrared spectra of the compounds obtained and their comparison with the spectra of the model compounds convincingly demonstrated the occurrence of the tautomerism (XLVI) ⇌ (XLVII).

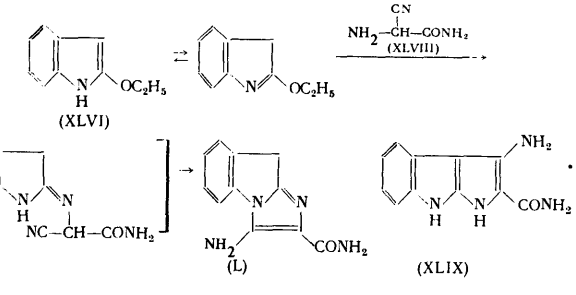
In another study an attempt was also made to obtain the lactim ether derived from oxindole (XLVII) and 3-ethoxycarbonylindole[33]. However, in both cases indole and not indolenine derivatives were isolated:



where R = H or $COOC_2H_5$.

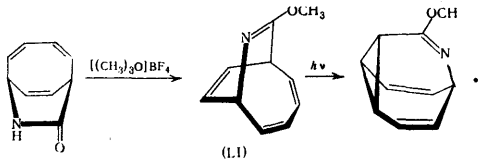
Bearing in mind the capacity of compound (XXXVI) for isomerisation to compound (XLVII), the capacity of lactim ethers to condense with α-amino-α-cyanoacetamide (XLVIII), and also the capacity of the α-alkoxy-derivatives of certain enamines for nucleophilic substitution of alkoxy-groups[128], an attempt was made in this investigation to condense compound (XLVI) with compound (XLVIII) in alcohol in the presence of catalytic amounts of hydrogen chloride.

A detailed study of the physicochemical properties of the product and in particular its NMR spectrum, showed that it is not 3-amino-2-carbamoyl-pyrrolo[2,3-*b*]indole (XLIX) but the "normal" product of the reaction of lactim ethers with compound (XLVIII)—3-amino-2-carbamoylimidazo[1,2-*a*]indoline (L). This process may be represented by the following mechanism:



(XLVI) (L) (XLIX)

Together with high reactivity in relation to nucleophilic reagents, the lactim ether group is sufficiently stable to achieve certain sometimes very complex reactions. As an illustration one may quote the isomerisation of the lactim ether (LI) in which the lactim ether group is preserved[27]:

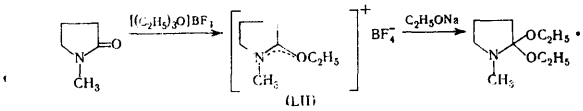


(LI)

IV. METHODS OF SYNTHESIS AND CHEMICAL PROPERTIES OF OTHER *O*-ALKYL DERIVATIVES OF LACTAMS

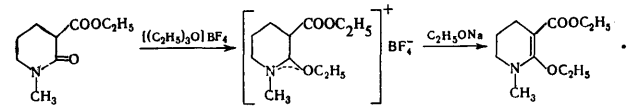
The activation of the amide group in lactams by their conversion into lactim ethers greatly extended the range of applications of lactams and made it possible to synthesise examples of various classes of organic compounds. However, the above reactions are always subject to a constant limitation in the choice of the lactam, since in the synthesis of lactim ethers only lactams unsubstituted at the nitrogen atom must be employed.

A further extension of the application of *O*-alkyl derivatives of lactams in organic chemistry was achieved in the study of a new branch of lactam chemistry—that of lactam acetals[50,129-132]. Lactam acetals were synthesised for the first time by Meerwein and coworkers[130,131] by the alkylation of *N*-substituted lactams with triethyloxonium fluoroborate, followed by the decomposition of the resulting fluoroborate complex (LII) with sodium ethoxide:

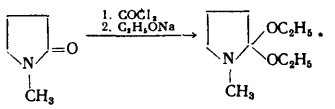


(LII)

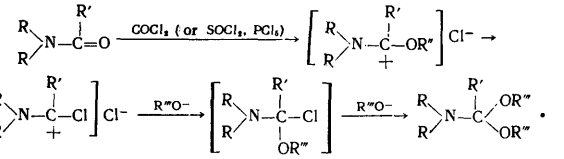
In the presence of an electron-acceptor substituent in the 3-position of the lactam ring, the decomposition of the intermediate fluoroborate complex by sodium ethoxide is accompanied by the elimination of a proton from the 3-position and the formation of a 2,3-dehydro-derivative, as happens, for example, in the case of 3-ethoxycarbonyl-*N*-methyl-2-piperidone[133]:



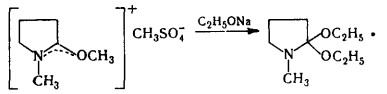
Another method for the synthesis of lactam acetals consists in the interaction of *N*-substituted lactams with phosgene, resulting in the formation of the corresponding amide-chlorides, from which the acetals are obtained by treatment with sodium ethoxide or triethylamine in alcohol[50,132]:



It has been stated that this reaction takes place by the following hypothetical mechanism[132]:

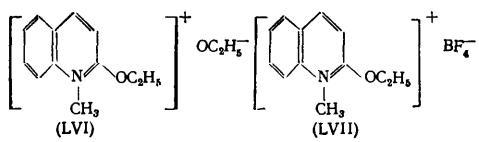


The preparation of lactam acetals by the interaction of the complex of *N*-methyl-2-pyrrolidone and dimethyl sulphate with sodium ethoxide, similar to the procedure where lactim ethers are obtained by treating lactams with triethyloxonium fluoroborate or dimethyl sulphate, has been also described[129]:



The chemical properties of lactam acetals have been inadequately investigated, although there is an indication[130] that these compounds are similar in their chemical behaviour to the acetals of non-cyclic acid amides, which have been investigated in greater detail[130,134,135]. Like lactim ethers, lactam acetals enter fairly readily into nucleophilic substitution reactions. In particular, on reaction with water, these compounds are hydrolysed relatively easily with formation of the corresponding lactams.

In this connection the comparative reactivities of the acetals of *N*-methyl-2-quinolone (LIII), *N*-methyl-2-benzothiazolone (LIV), and *N*-methyl-2-benzoxazolone (LV) should be mentioned[130]. It has been established that compound (LIII) hydrolyses so readily that it is difficult to isolate it in a pure form. In contrast to compound (LIII), compounds (LIV) and (LV) are relatively stable to hydrolysis. In order to account for this phenomenon, it has been suggested that the acetal (LIII) exists partially in the ionised form (LVI):

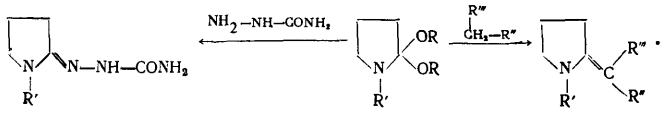


(LVI) (LVII)

The formation of compound (LVI) is facilitated in this case by the complete aromatisation of the quinoline ring and the presence of the above ionised species leads of course to an enhanced reactivity in relation to nucleophilic reagents [compared with compounds (LIV) and (LV)]. This hypothesis was confirmed by the relatively high electrical conductance of solutions of compound (LIII) in nitrobenzene and dimethylformamide and also by the fact that the fluoroborate complex (LVII) is much more stable to hydrolysis than the corresponding complex obtained from *N*-methyl-2-benzoxazolone and *N*-methyl-2-benzothiazolone. Similar relative reactivities of compounds (LIII), (LIV), and (LV) are observed also in other nucleophilic substitution reactions.

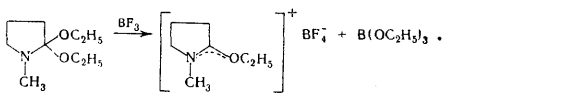
Among the reactions of lactam acetals with nucleophilic reagents, the interaction of the acetals of *N*-methyl-2-pyrrolidone with semicarbazide, with formation of the corresponding semicarbazone, as well as reactions with

compounds having active methyl or methylene groups have also been reported[130]:

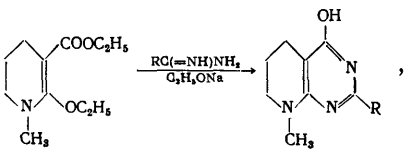


It is noteworthy that the last reaction takes place as a rule extremely readily, which suggests that the acetals are more reactive than lactim ethers.

The high reactivity of the acetals is also shown in the reaction of the diethylacetal of *N*-methyl-2-pyrrolidone with boron trifluoride accompanied by the elimination of one alkoxy-residue and the formation of the fluoroborate complex (LII)[131]:



In conclusion we may quote the condensation of 3-ethoxycarbonyl-2-ethoxy-*N*-methyltetrahydropyridine with guanidine and thiourea, resulting in the formation of 2-substituted 4-hydroxy-8-methyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidines[133]:



where R = NH_2 or SH.

This reaction shows that the conversion of lactim ethers to *O*-alkyl derivatives of lactams with a substituent at the ring nitrogen atom gives rise to the possibility of the synthesis of condensed heterocyclic compounds with predetermined positions of the substituents.

The use of *O*-alkyl derivatives of lactams in organic synthesis has led to important results both as regards synthesis and theory. A large number of heterocyclic compounds, in particular examples of new heterocyclic systems which are of interest both biologically and chemically, have been synthesised on their basis. The wide choice of reagents and their relative availability combined with high reactivity give rise to a wide range of applications of *O*-alkyl derivatives of lactams as starting materials in the synthesis of a wide variety of organic compounds.

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