Translated from *Uspekhi Khimii*, **46**, 685-711 (1977) U.D.C. 547.27-318

# Advances in the Chemistry of the Acetals of Acid Amides and Lactams

V.G.Granik, A.M.Zhidkova, and R.G.Glushkov

Data on the chemistry of the acetals of acid amides and lactams published during the period between 1969 and 1974 are surveyed. The reactions of the acetals of acid amides and lactams with various nucleophiles and electrophiles are considered, particular attention being devoted to the possibility of using such amide and lactam acetals in the synthesis of heterocyclic compounds which are of interest both chemically and biologically.
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## I. INTRODUCTION

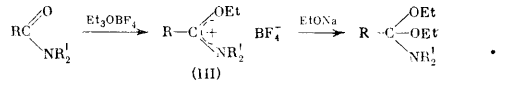
During the last two decades, the chemistry of acid amides and latcams has become enriched in new data associated primarily with the study and utilisation for synthetic purposes of "activated forms" of these compounds. Such "activated forms" include iminoesters [1], lactim ethers [2], complexes of acid amides with alkylating and acylating agents [3-6], keten *ON*-acetals [7,8], aminals [9,10], and extremely readily available at the same time very highly reactive compounds which Meerwein called the acetals of acid amides [11,12].

The acetals of acid amides were obtained for the first time in 1956 [11], but their properties were not described in detail until 1961. [12] In recent years, the chemistry of these compounds has been developing so vigorously that the review [13] published in 1969 no longer reflects the advances achieved in this field.

The present review surveys data on the chemistry of amide acetals published during the period between 1969 and 1974. Earlier studies are discussed only in those instances where this is required for the description of new material or when relevant studies were not considered in the review mentioned above [13].

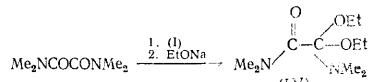
## II. THE SYNTHESIS OF THE ACETALS OF ACID AMIDES AND LACTAMS

One of the most general methods for the synthesis of the acetals of acid amides and lactams involves the interaction of amides or lactams with alkylating and acylating agents followed by the treatment of the resulting complexes with alkali metal alkoxides [13]. The most frequently used alkylating agents are triethyloxonium fluoroborate (I) and dimethyl sulphate (II). Although a quantitative comparison of the reactivities of these alkylating agents in the synthesis of amide acetals has not so far been made, one should note an important qualitative difference between them, consisting in the fact that the interaction of acid amides with compound (I), in contrast to the reaction with compounds (II), proceeds irreversibly [14]. The study of the alkylation of acid amides by compound (I) has been shown [14] that the steric effects of the substituents in the amides do not have an appreciable influence on the reactions; an exception to this rule is provided by those cases where the steric hindrance is accompanied by a significant destabilisation of the cation (III):

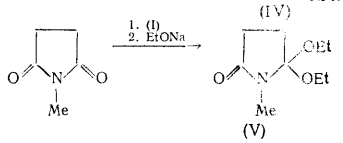


(III)

Thus $Cl_3CCON(CH_3)_2$, in which the amide group is linked to the extremely bulky and highly electronegative trichloromethyl group, does not react with compound (I). In those instances where the molecule contains two amide functional groups, the "acetalisation" of both is possible only in the presence of bridging groups between them [15]. Thus only the monoacetals (IV) and (V) can be synthesised from the bisdimethylamide of oxalic acid [14] and *N*-methylsuccinimide [16] with the aid of compound (I):

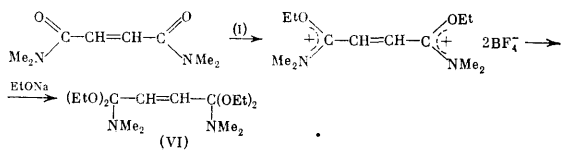


(IV)



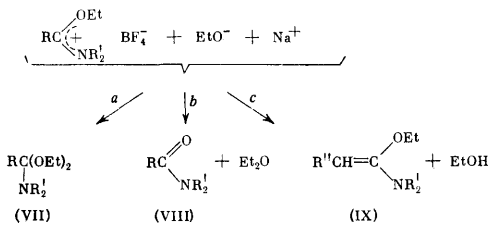
(V)

The separation of the amide groups by the -HC=CH- bridge ensures the possibility of the formation of the bisacetal (VI) [14]:



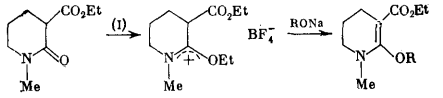
(VI)

The interaction of the intermediate complexes (III) with sodium alkoxides [14] can proceed in three ways depending on the nature of the substituent R: (a) the formation of the amide acetal (VII); (b) the regeneration of the initial amide (VIII); (c) the formation of the $\alpha$-alkoxyenamine (IX):



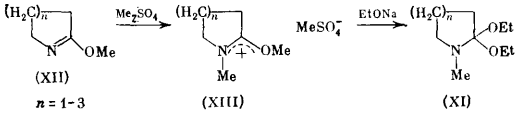
(VII) (VIII) (IX)

Reaction *a* should proceed most readily. This process involves the simplest ion association, since its activation energy is apparently significantly lower than in cases *b* and *c* and the acetal (VII) should be formed rapidly, provided that, for example, the steric hindrance to attack by the alkoxide anion is not too great. If R is a bulky substituent such as the t-butyl or dichloromethyl group, the reaction is directed via the thermodynamically favourable pathway *b* with formation of stable molecules such as the amide (VIII) and an ether. Finally, if R is a relatively small and highly electron-accepting group, a proton may be abstracted from the $\alpha$-position (relative to the amide group) and the $\alpha$-alkoxyenamine (IX) may be formed. One should note that the synthesis of enamines of type (IX) had also been observed earlier when 2-ethoxy-3-ethoxycarbonyl-1-methyl-3,4,5,6-tetrahydropyridinium fluoroborate (X) was treated with sodium alkoxide [17]:



(X).

A new version of the synthesis of lactam acetals (XI) involves the use of lactim ethers (XII) as the starting materials [18,19]:

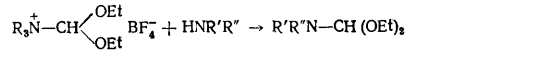


(XII) (XIII) (XI)

$n = 1$-3

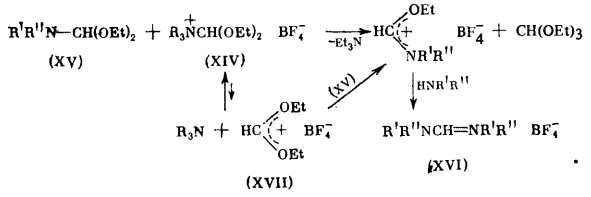
The study of the alkylation of compound (XII) by dimethyl sulphate using the method of competing reactions with analysis of the reaction mixtures by gas–liquid chromatography (GLC) showed that the rate of formation of the complexes (XIII) depends significantly on the size of the ring in compound (XII): the highest rate of alkylation is observed for *O*-methylbutyrolactim (XII, $n = 1$) and the lowest for *O*-methylcaprolactim (XII, $n = 3$). Examination of the *N*-alkylation of lactim ethers with the aid of molecular models showed that the difference between the rates of reaction is determined mainly by conformational factors [19].

New methods for the synthesis of acid amide acetals include the interaction of dialkyoxymethylammonium salts (XIV) with secondary amines [20]:



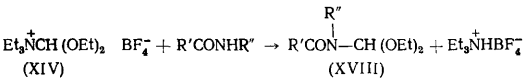
(XIV) (XV)

The acetals (XV) can react further with the salts (XIV) to form an orthoformate ester and amidinium salts (XVI):



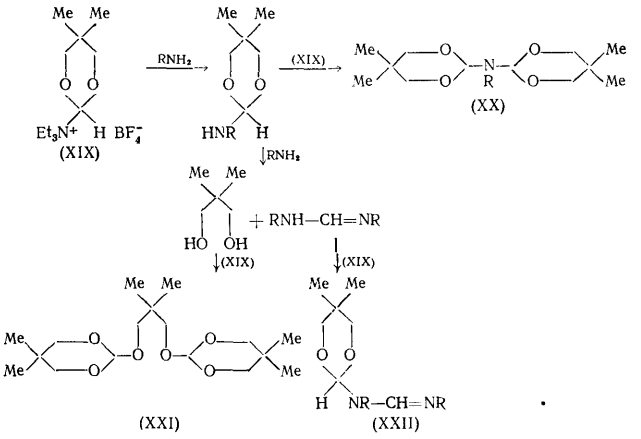
(XVII) (XVI)

It has been suggested [20] that the above side reactions occur owing to the dissociation of the dialkyoxmethylammonium salts (XIV) into a tertiary amine and a dialkoxycarbonium salt (XVII), which reacts with the acetal (XV). This is confirmed by the finding that an excess of the corresponding tertiary amine, which displaces the equilibrium towards compound (XIV), leads to an appreciable increase of the yield of the acetals (XV). *N*-Acylamidoacetals (XVIII) have been obtained by the reaction of the salts (XIV) with acid amides [21]:



(XIV) (XVIII)

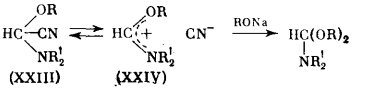
The reaction of dialkoxymethylammonium salts (XIX) with primary amines proceeds in an interesting manner and the following mechanism has been proposed [22]:



(XIX) (XX) (XXI) (XXII)

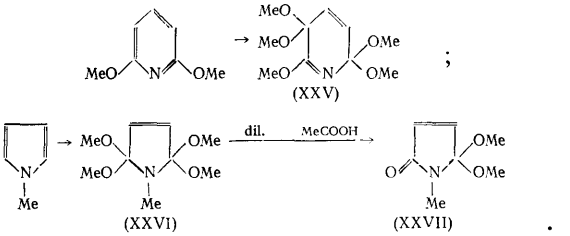
When the molar ratio of the salt (XIX) and the amine is 2 : 1, the main reaction product is the bisacetal (XX), while in the presence of an excess of the amine mainly the amidine-acetals (XXII) are formed, compound (XXI) having also been isolated as a side product.

A new method of synthesis of amide acetals, consisting in the interaction of $\alpha$-dialkylamino-$\alpha$-methoxyacetonitriles (XXIII) with sodium alkoxide has been published recently [28]. The reaction evidently proceeds via a stage involving the dissociation of compound (XXIII) with subsequent attack by the alkoxide anion on the cation (XXIV):



(XXIII) (XXIV)

In addition, the synthesis of the acetals of unsaturated lactams (XXV)–(XXVII) in the anodic oxidation of pyrrole and pyridine derivatives in methanol has been described [24]:

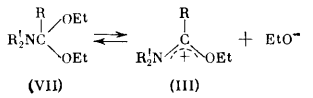


(XXV) (XXVI) (XXVII)

## III. THE PROPERTIES AND REACTIONS OF THE ACETALS OF ACID AMIDES AND LACTAMS

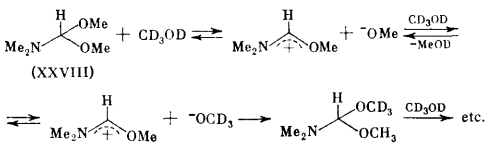
The structure of amide acetals, represented by formulae (VII) and (XI), does not justify the assumption that these compounds can be highly reactive in relation to nucleophiles [25] and electrophiles.

In 1961, Meerwein et al.[12] and subsequently also other investigators[13,26] showed that solutions of the acetals of acid amides and lactams are conducting. This phenomenon can be explained by the fact that amide acetals dissociate in solution into an ambident cation (III) and an alkoxide anion. It must be emphasised that the alkoxide anion is capable of interacting, for example, with compounds having an active methylene group, forming carbanions and therefore facilitating the nucleophilic addition reaction



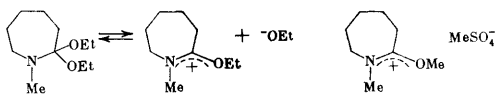
(VII) (III)

This treatment is nowadays generally accepted[13] and provides a satisfactory explanation of the properties of amide acetals. In particular, the only explanation of the readily cccurring exchange of the hydrogen atoms of the *O*-methyl groups of the dimethyl acetal of dimethylformamide (XXVIII) for deuterium in the presence of an excess of $CD_3OD$ is its preliminary dissociation[27]:



(XXVIII)

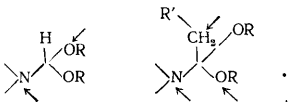
An attempt has been made[26] to estimate quantitatively by the polarographic method the degree of dissociation of the diethyl acetal of *N*-methylcaprolactam (XII, $n = 3$). Comparison of the polarographic behaviour of this acetal and the methyl sulphate complex of *N*-methylcaprolactam (XIII) showed that the content of the ambident cation (XXIX) in methanol solution does not exceed 0.3%:



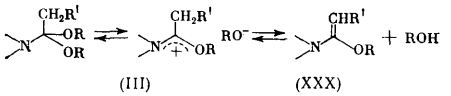
(XII) $n=3$ (XXIX) (XIII)

Bearing in mind the high reactivity of cations of this type in relation to reagents bearing a negative charge or having a lone electron pair, one may conclude that even the above insignificant degree of dissociation is sufficient to ensure the interaction of the acetals with various nucleophiles.

Investigations have shown that there are significant differences between the acetals of dimethylformamide, on the one hand, and their homologues and the acetals of lactams with the extremely reactive $CH_2$ groups in the $\alpha$-positions, on the other. Thus electrophiles can attack only the nitrogen atom in the acetals of dimethyl-formamide or the $RO^-$ anion formed following the dissociation of the acetal. On the other hand, together with the processes described above, the acetals of homologous amides as well as lactam acetals can undergo also reactions involving the $\alpha$-$CH_2$ groups (alkylation, acylation, etc.).

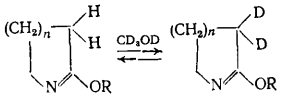


The ability of amide and lactam acetals to undergo $\alpha$-*C*-alkylation (acylation) has been explained[13,28,29] by the fact that the ambident cation (III) can interact with the alkoxide anion, the process involving the abstraction of a proton from the activated $\alpha$-$CH_2$ group in the cation (III) and the formation of an $\alpha$-alkoxyenamine (XXX), which readily reacts with electrophiles like other enamines[30]:



(III) (XXX)

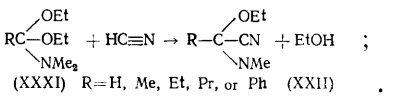
This hypothesis is supported also by data indicating a considerable mobility of the $\alpha$-protons in lactim ethers[31]:



## 1. REACTIONS OF AMIDE AND LACTAM ACETALS WITH NUCLEOPHILES

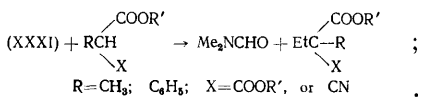
### a. Reactions of the Acetals Via Activated CH, $CH_2$, and $CH_3$ Groups

Numerous studies have been made on the reactions of amide and lactam acetals with compounds having activated methyl, methylene, or methylidyne groups[13,14,32-50]. The interaction of amide acetals with anhydrous hydrocyanic acid is accompanied by the substitution of [one of] the alkoxy-groups of the acetal by the cyano-group with formation of $\alpha$-alkoxyaminonitriles (XXIII)[32]:

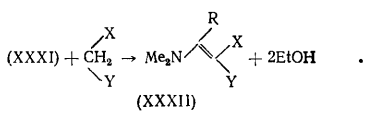


(XXXI) R=H, Me, Et, Pr, or Ph (XXII)

On the other hand, when the acetals react with C–H acids such as ethyl- or phenyl-malonic and cyanoacetic esters, the latter undergo *C*-alkylation[32]:



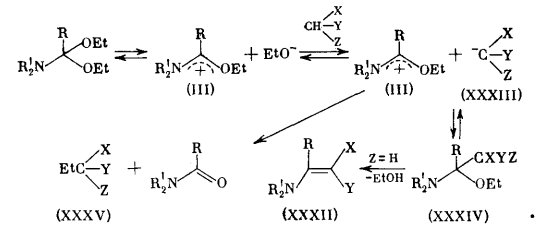
When compounds with active methylene or methyl groups are made to react with amide or lactam acetals, a third type of interaction takes place involving the formation of enamines (XXXII)[13]:



(XXXII)

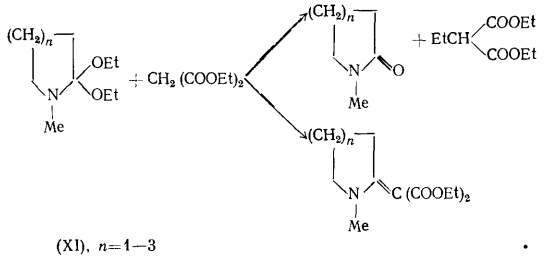
Bredereck et al.[32] believe that the first step in the interaction of amide acetals with compounds having activated CH or $CH_2$ groups involves the abstraction of a proton from the latter and the formation of the anion (XXXIII). The reaction of the anion (XXXIII) with the ambident cation (III) can proceed via the irreversible association of (III) and (XXXIII) with formation of compound (XXXIV). Subsequently, depending on the structure of the anion (XXXIV), the enamine (XXXII) (with Z = H) may be formed or *C*-alkylation may take place, which

results in the formation of compound (XXXV), and the corresponding amide:



In the presence of the weakly stabilised anion (XXXIII) (for example, $^-C{\equiv}N$), the addition product (XXXIV) is thermodynamically more favourable and the equilibrium is displaced towards its formation. On the other hand, when the anion is stabilised by conjugation, compound (XXXIV) is present in the equilibrium mixture in only a small amount; if one of the substituents (X, Y or Z) is a hydrogen atom, conditions are created for the elimination of an alcohol with formation of an enamine (XXXII). Simultaneously with this process (but more slowly), the cation (III) may alkylate the anion (XXXIII) with formation of the *C*-alkyl derivative (XXXV). When the anion does not contain a hydrogen atom, the latter process becomes dominant and the main reaction product is compound (XXXV). Thus, by postulating the equilibrium (XXXIII) $\rightleftharpoons$ (XXXIV), one can account for the possible reactions occurring when amide acetals react with CH acids. However, one must stipulate the case where the formation of compound (XXXIV) is prevented by steric factors. Under these conditions, the only reaction pathway becomes *C*-alkylation† with formation of compound (XXXV).

It follows from the above mechanism that the formation of the enamine (XXXII) must be accompanied by *C*-alkylation. Indeed, a study of the reaction of lactam acetals[33-35] with malonic ester showed that the process proceeds in two ways, C–C condensation predominating:

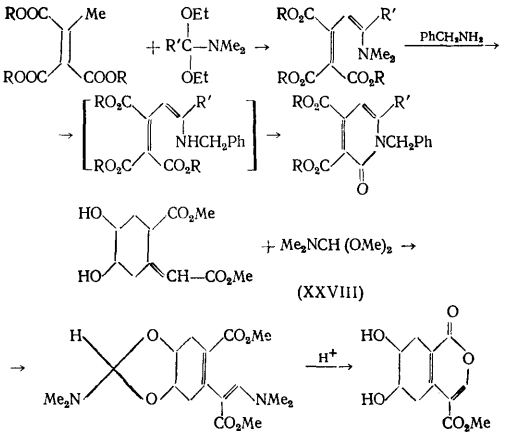


(XI), $n$=1–3

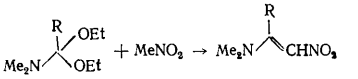
A study of the reactions of lactam acetals (XI) with compounds having active methylene or methyl groups[33-35] established that the rate of reaction depends both on the size of the lactam ring and on the strength of the CH acid: the highest reactivity is shown in this process by the diethyl acetal of *N*-methylbutyrolactam (XI, $n$ = 1), the increased mobility of the hydrogen atoms in the $CH_2XY$ group promoting a higher reaction rate.

†The initial amide and an ether may be formed in a side reaction (see above).

The ability of amide acetals to react readily with compounds having active $CH_2$ or $CH_3$ groups has been used in new syntheses of 2-pyridones[36] and condensed $\alpha$-pyrones[37]:



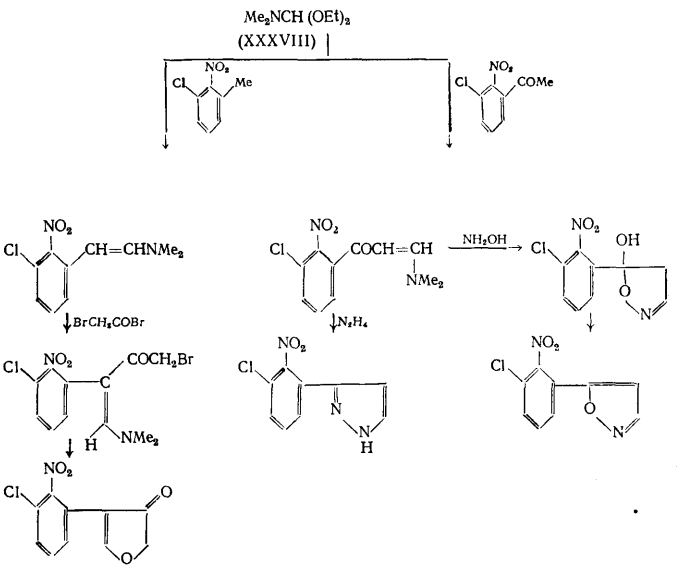
Bredereck et al.[14] compared the reactivites of the acetals (XXXVI) and (XXXVII) in condensation with nitromethane:



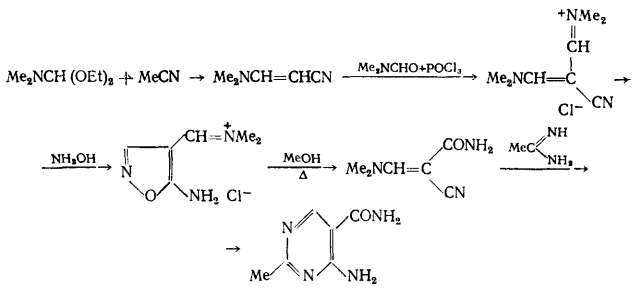
(XXXVI), R=$CONMe_2$ ;
(XXXVII), R=$CO_2Et$ .

Whereas in the first case the reaction proceeds with a yield of 96% (80°C, 1 h), in the second the yield does not exceed 37% even after prolonged heating (80°C, 5 h). According to the authors, this difference between the reactivities of the acetals (XXXVI) and (XXXVII) is due to the much greater destabilising effect of the $CO_2Et$ group compared with that of the $CONMe_2$ group.

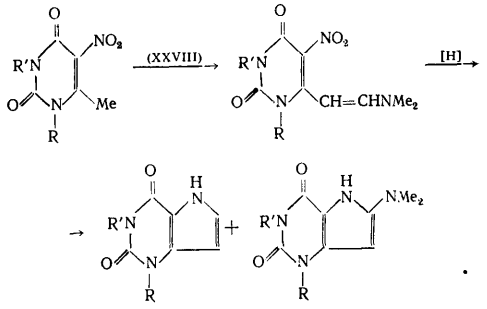
The diethyl acetal of dimethylformamide (XXXVIII) has also been used in the synthesis of pyrrolnitrin analogues[38]:



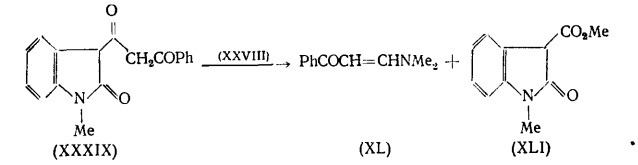
Isoxazole and pyrimidine derivatives have been synthesised from the acetal (XXVIII) [39]:



as well as pyrrolo[3,2-*d*]pyrimidines [40]:

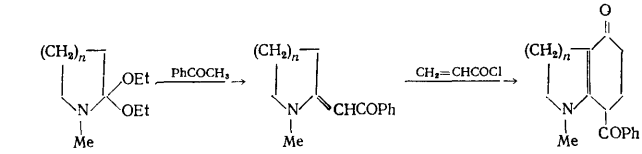


The reaction of the acetal (XXVIII) with 3-benzoylacetyl-1-methyloxindole (XXXIX) proceeds in a very unusual manner. The C–C bond is ruptured with formation of *NN*-dimethylaminomethyleneacetophenone (XL) and 3-methoxycarbonyl-1-methyloxindole (XLI) [41]:



(XXXIX) (XL) (XLI)

The interaction of the lactam acetals (XI) with acetophenone led to the synthesis of the enaminoketones (XLII) from which a new synthesis of hydrogenated derivatives of indole, quinoline, and benzazepine (XLIII) was achieved by reaction with acryloyl chloride [42]:



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

A series of studies on the reactions of amide acetals with nitromethane derivatives [43], acetonitrile [44,45], malonic ester [46], and β-benzoylpropionic ester [47] have been published in recent years. They involved the synthesis of a number of substituted enamines, which can be used as the starting materials for the preparation of various heterocyclic compounds (see, for example, Spencer et al. [48]).

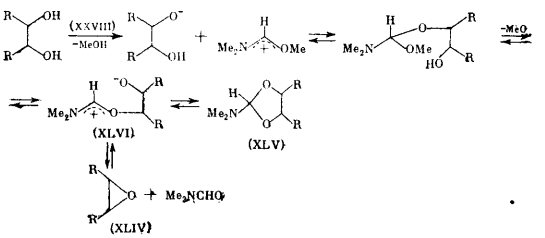
The above data permit the conclusion that lactam acetals react more smoothly with nucleophiles than do amide acetals [25]. A clear example is provided by the finding that lactam acetals react readily with phenylacetic ester, giving satisfactory yields [25,49], while the diethyl acetal of *NN*-dimethylacetamide could not be made to undergo this reaction [50].

b. Reactions with Alcohols and Mercaptans

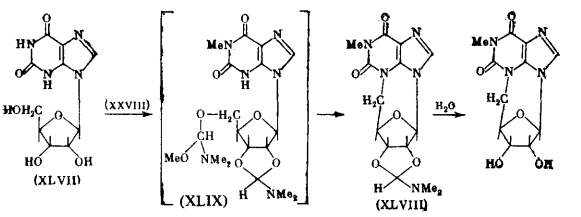
One of the methods for the synthesis of amide acetals involves the transesterification of the dimethyl acetal of dimethylformamide (XXVIII) with alcohols [13]. Compound (XXVIII) and other amide acetals react similarly with alkanethiols and arylalkanethiols, forming the thioacetals of acid amides [51]:

$$Me_2NCH(OMe)_2 + 2RSH \rightarrow Me_2NCH(SR)_2 + 2MeOH .$$

The reaction of amide acetals with alcohols constitutes the basis of a new method for the synthesis of epoxy-compounds (XLIV). [52] The process mechanism is consistent with the usual concepts concerning the interaction of amide acetals with alcohols:

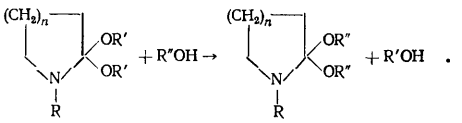


It is seen from the above mechanism that the reaction may involve the formation of cyclic amide acetals (XLV). One of the main factors determining the nature of the products formed is the configuration of the initial diol. For example, the reaction of the acetal (XXVIII) with *cis*-cyclohexanediol results in the formation of the cyclic acetal [XLV, R,R = $-(CH_2)_4-$] only, while its *trans*-isomer is converted smoothly into the epoxy-compound (XLIV). The cyclic acetal (XLVIII) has also been obtained in the reaction of xanthosine (XLVII) with the dimethyl acetal of dimethylformamide (XXVIII) [53]:



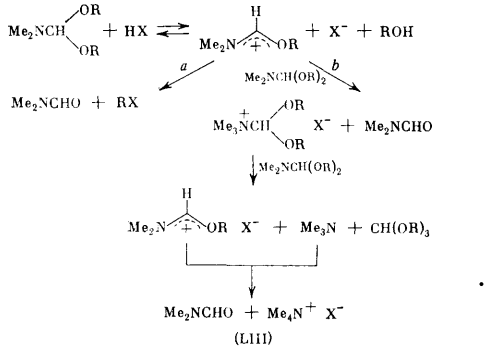
The above mechanism shows that the amide acetal (XXVIII) reacts not only with the vicinal secondary hydroxyls but also with the primary hydroxy-group. Owing to the high polarisation of the $O-CH_2$ group in the intermediate bisamide acetal (XLIX), the xanthine fragment undergoes intramolecular *N*-alkylation with formation of the cyclonucleoside (XLVIII). This is accompanied by the *N*-methylation of xanthosine by the acetal (XXVIII) (see above).

It is noteworthy that lactam acetals are readily transesterified by alcohols, like amide acetals[54,55]:

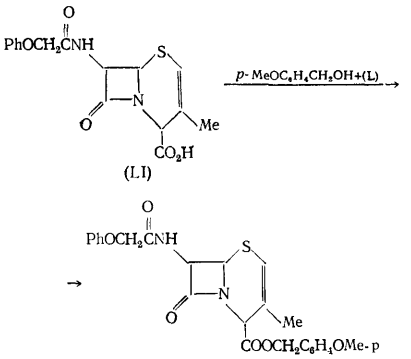


c. Reactions with Phenols and Carboxylic Acids

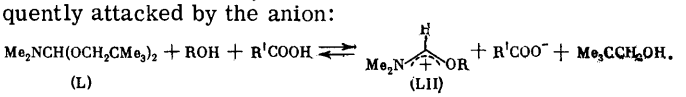
The esterification of carboxylic acids and phenols in their reactions with amide and lactam acetals takes place even more readily than the *C*-alkylation of compounds having an acid $CH_2$ group (see above)[12,33-35,55-57]. When the molecule contains a phenolic hydroxyl and a carboxy-group, the alkylation proceeds very selectively at the carboxy-group[56,57]. Despite its apparent simplicity, the reaction of amide acetals with carboxylic acids may be accompanied by a series of side processes[56]:



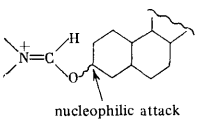
The relative contributions of the main process *a* and the side reactions *b* depend to a large extent on the nature of the substance alkylated HX.[58] Thus, in the interaction of the dimethyl acetal of dimethylformamide (XXVIII) with phenol, the reaction proceeds almost exclusively via pathway *a*. The reaction with picric acid proceeds mainly via pathway *b*. Similar behaviour has been observed also for a series of carboxylic acids: the formation of methyl benzoate predominates in the reaction involving benzoic acid, while only tetramethylammonium trifluoroacetate was isolated in the reaction with trifluoroacetic acid. However, the acidity of HX is not the only factor determining the mode of the process. The concentration of the reactants plays an important role in these processes. Thus, when solutions of the reactant are diluted and the steady-state concentration of compound (XXVIII) is reduced, it is possible to increase sharply the yield of alkylation products[56]. It was found that the rate constant for the esterification of *p*-nitrobenzoic acid by the dimethyl acetyl of *N*-formylpyrrolidine is almost twice as high as the rate constant obtained when compound (XXVIII) is used in this reaction. The dineopentyl acetal of dimethylformamide (L) has been used successfully in the alkylation of carboxylic acids[13]. Its employment for this purpose is based on the fact that derivatives of neopentyl alcohol are capable of undergoing $S_N2$ reactions to only a very slight extent[56]. As an example, one may quote the esterification of $\Delta^2$-diacetoxycephalosporin (LI), which proceeds under mild conditions[59]:



The mechanism of the esterification reaction with the aid of comopund (L) provides for the intermediate formation of the cation (LII), in which the residue R is subsequently attacked by the anion:



Naturally, when the residue R contains in this instance an asymmetric centre linked to the oxygen atom, the nucleophilic attack should involve an inversion of configuration ($S_N2$ mechanism). Epimerisation of this kind has been achieved for a series of derivatives of 3$\alpha$-hydroxycholestane and androstane[56]:




This method can probably be used for the inversion of configuration also in other optically active alcohols.

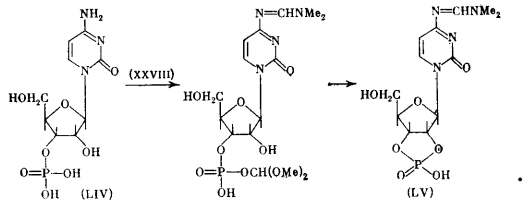
d. Reactions of Amide Acetals with Other Acid Compounds

The study of the interaction of the acetal (XXVIII) with other acid agents[58] confirmed that there is a definite (although not direct) relation between the mode of reaction and the acid $pK_a$. The study of the reaction of compound (XXVIII) with amides has shown that, as a rule, both pathways *a* and *b* (see above) operate and that pathway *a* is fully inhibited only in the reaction with $Tos_2NH$. A similar behaviour has been observed for hydrochloric and phosphorus-containing acids (alkylation and the formation of quaternary salts are both observed to some extent). When toluene-*p*-sulphonic acid or $HClO_4$ are used in the reaction with compound (XXVIII), the only products are the corresponding NNN'N'-tetramethylformamidinium salts (LIII).

e. Reactions with Phosphorus-Containing Compounds

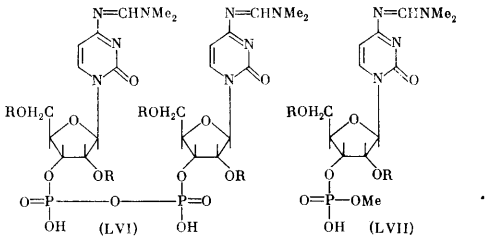
The interaction of the dimethyl acetal of dimethylformamide with nucleoside phosphates is a special case of reactions of compound (XXVIII) with OH and CH acids. When the aglycone of the nucleoside phosphate contains the $NH_2$ group, as, for example, in cytidine phosphate

(LIV), the reaction via the phosphate group is accompanied in this case also by condensation via the 4-amino-group[60]:

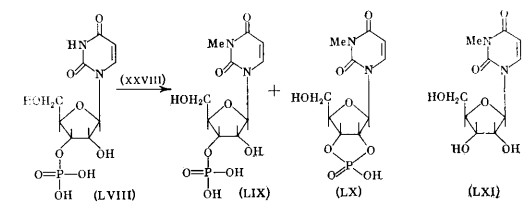


The mechanism of the formation of compound (LV) has been represented as one involving the activation of the P–O bond with subsequent closure of the five-membered ring.

The study of this reaction in other systems[60] showed that in all cases cyclic compounds of type (LV) are formed. Thus the reaction constitutes a convenient method for the synthesis of compounds containing only one unprotected OH group in the 5′-position. It is noteworthy that, in those cases where the OH groups in the 2′- and 5′-positions had been protected beforehand, the reactions of ribonucleoside phosphates with compound (XXVIII) lead to the formation of pyrophosphates (LVI) and the methyl esters (LVII) as the side products (the main reaction involves the protection of the 4-amino-group of the pyrimidine base):

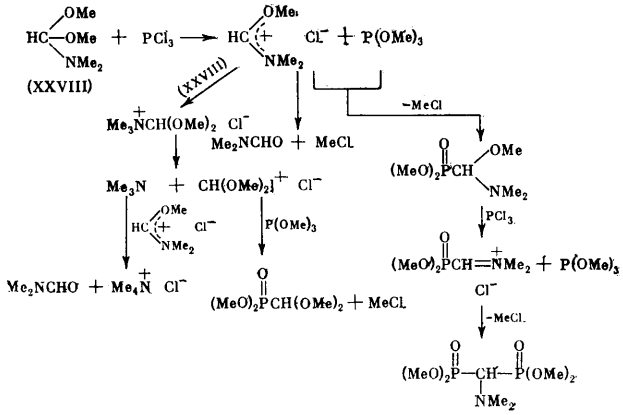


When the neopentyl acetal (L) is used in reactions with aminonucleoside phosphates, the condensation proceeds selectively via the $NH_2$ group, without involving the hydroxy-groups. It was noted that dephosphorylation with formation of compound (LX) is observed in the interaction of uridine phosphate (LVIII) with compound (XXVIII) in addition to the *N*-methylation of compound (LIX) and the cyclisation of the phosphate group at the 2′-hydroxy-group in compound (LX)[60]:

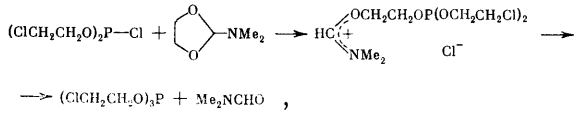


Furthermore, certain reactions of amide acetals with diribonucleoside phosphates may involve the dissociation of internucleotide linkages[61].

The reactions with phosphorus halides and with the esters of phosphorus-containing acids occupy a special place in the chemistry of amide acetals[62-64]. The following mechanism has been proposed for the reaction of the acetal (XXVIII) with $PCl_3$[62]:



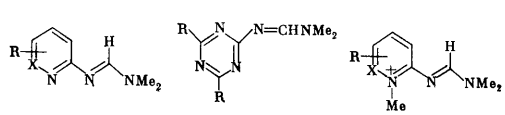
The reactions of amide acetals with other chlorophosphines have also been described[63]:



as well as the reactions with phosphite esters and phosphine oxides[63,64].

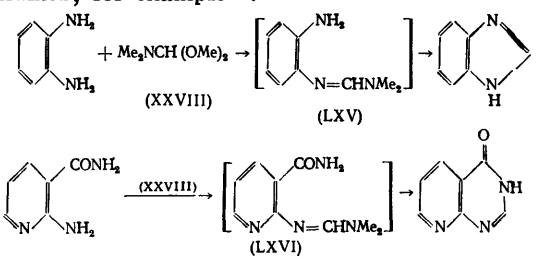
## f. Reactions with Amines

The synthesis of amidines from amide and lactam acetals has been investigated in fair detail[13]. A number of studies on the reactions of lactam acetals with aniline derivatives[25,55,65-68] and heterocyclic[60,69-73] and aliphatic[74,75] amines have been published in recent years. The interaction of amide and lactam acetals with amines constitutes a simple and convenient approach to the synthesis of various amidines, which is particularly important in connection with the fact that a number of substances exhibiting a high biological activity have been discovered in recent years among representatives of this class of compound (see, for example, Refs. 76–78). A series of 6-formamidinopenicillanic acids have been obtained by the reaction of amide acetals with aminopenicillanic acid[74]. It has been shown that animal-esters can be obtained by the interaction of compound (XXVIII) with secondary amines[75]. Various aminoheterocycles have also been successfully made to react with acetals, which led to the synthesis of the heterocyclic amidines (LXII)–(LXIV)[70]:



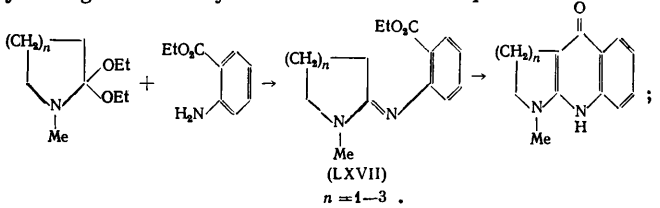
Amide acetals have been used successfully in recent years also as cyclising agents in the synthesis of various heterocyclic compounds. Thus, on heating with the dimethyl acetal of dimethylformamide, *o*-diamines or

*o*-aminocarboxamides form condensed imidazoles of pyrimidines, for example [70]:

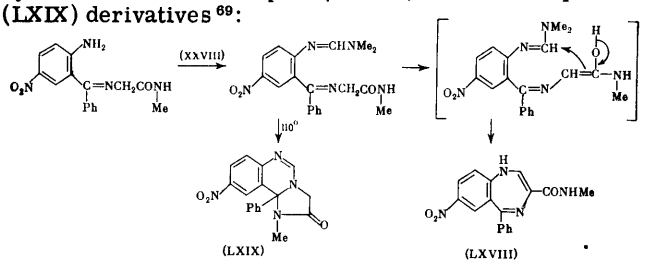


The reaction probably proceeds via the intermediate formation of the amidines (LXV) and (LXVI).

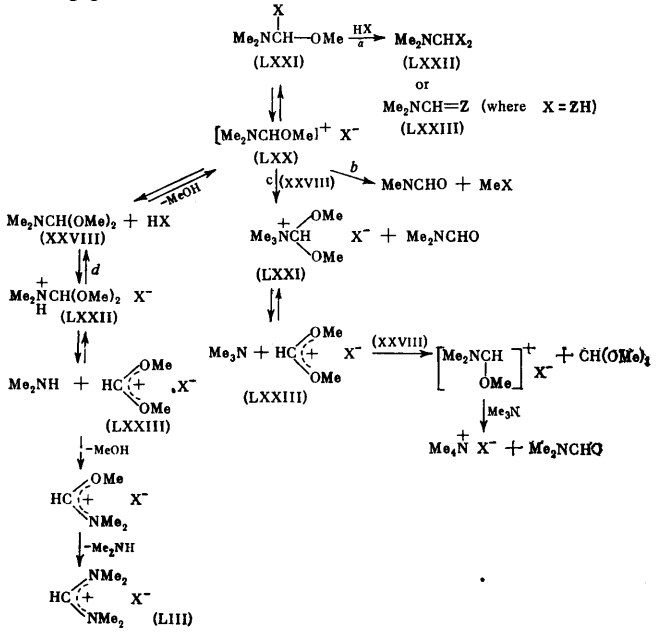
When lactam acetals react with an anthranilate ester, the corresponding amidines (LXVII) are again formed, cyclising to the tricyclic derivatives of 4-quinolone [66]:



The acetal (XXVIII) has been used successfully in the synthesis of benzodiazepine (LXVIII) and imidazoquinazoline (LXIX) derivatives [69]:



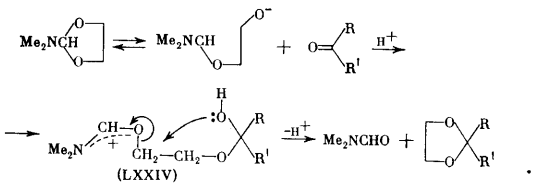
The data presented above show that the majority of studies on the reactions of amide and lactam acetals with nucleophiles are based on the interaction of amide acetals with compounds containing active C–H, O–H, S–H, and N–H groups. These reactions can be represented by the following general mechanism [58]:



As mentioned above, one of the main factors determining the mode of the process (pathways *a*–*d*) is apparently the acidity of the initial HX. Pathway *a* is characteristic of weak acids, such as HC≡CR or AlkOH [with formation of compound (LXXII)] or $H_2O$, $RNH_2$, and $RR'CH_2$ [with formation of compound (LXXIII)]. The reactions of ArOH or certain carboxylic acids proceed mainly via pathway *b*. Stronger acids ($CF_3COOH$, $Tos_2NH$, and picric acid) react via pathway *c*. Finally, pathway *d* is characteristic of sulphonic acids and $HClO_4$.

### g. Reactions with Aldehydes and Ketones

As mentioned above, amide and lactam acetals condense with compounds having activated $CH_2$ or $CH_3$ groups (including ketones [13]) with formation of enaminocarbonyl compounds. However, amide acetals are also capable of reacting with aldehydes and ketones via another mechanism—with formation of the corresponding acetals and ketals [56]:



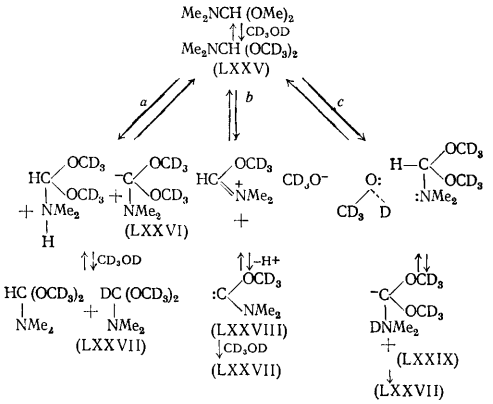
The reaction of compounds with a highly polarised carbonyl group (for example $CCl_3CHO$) is possible also in the absence of acid catalysis. It must be emphasised that the intermediate compound is sterically hindered. This factor makes it possible to use amide acetals as selective agents for the protection of keto-groups. For example, in the steroid series this process proceeds readily via the carbonyl group in the 3-position without affecting the keto-groups in the 17- and 20-positions [56].

## 2. REACTIONS OF AMIDE AND LACTAM ACETALS WITH ELECTROPHILES

### a. Reactions Involving Dimethylformamide Acetals

The simplest reaction of amide acetals with electrophiles is deuterium exchange. It was noted previously that, in solution of the dimethyl acetal of dimethylformamide (XXVIII) in deuteromethanol, the protons of the *O*-methyl groups of the acetal are rapidly exchanged for deuterium [27]. It is of interest that the formyl proton of the acetal is exchanged for a deuteron, albeit more slowly. This process requires a detailed examination, since many features observed in the study of this phenomenon proved to be common also to the reactions of dimethylformamide acetals with other electrophiles. A mechanism has been proposed [27] for the deuteration of amide acetals via the intermediate formation of carbenes. Three possible

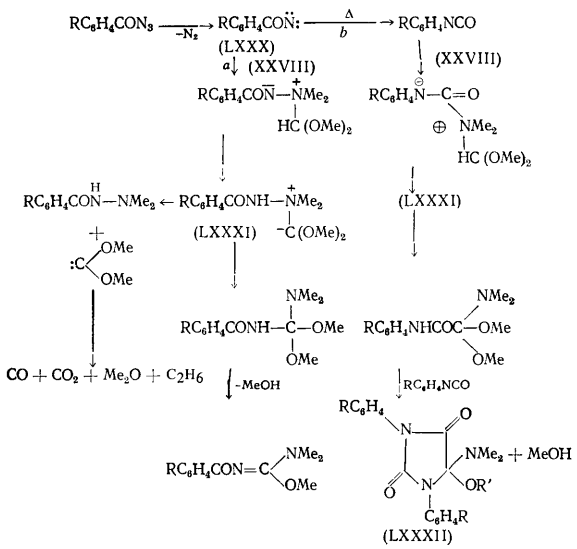
mechanisms of the deuterium exchange (pathways *a–c*) were examined in another investigation[79]:



Mechanism *a*, which provides for the abstraction of the formyl proton already in the first stage with formation of the anion (LXXVI), is unsuitable for the following reasons: under the conditions governing the formation of the deuteroacetal (LXXVII), orthoesters, in which the overall $-I$ effect of the alkoxy-groups is greater than in amide acetals, do not undergo deuterium exchange, and even chloroform is deuterated under these conditions more slowly than compound (LXXV). Mechanism *b*, according to which the intermediate is the carbene (LXXVIII), conflicts with the finding that the complexes $[MeOCH{=}NMe_2]X^-$ (where X = $MeSO_4^-$ or $BF_4^-$) do not undergoe deuterium exchange.

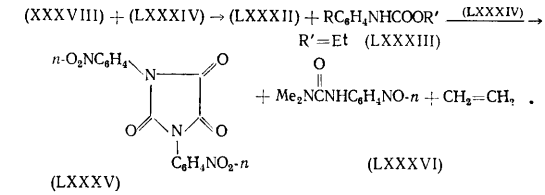
The "ylid" mechanism *c* is supported by the following data: (1) the enhancement of the electron-donating properties of the *N*-alkyl residues leads to an increase (up to a certain limit) of the rate of deuterium exchange; (2) the enhancement of the acid properties of the deuterating agent accelerates the deuterium exchange (the deuterium exchange proceeds to the extent of 25% after 196 s in $CD_3OD$ and after 705 s in t-BuOD); (3) the presence of strong bases in the system retards the deuterium exchange owing to a competing reaction.

Bedereck et al.[80] proposed mechanisms for the thermal and photochemical reactions of the acetal (XXVIII) with benzoyl azides:

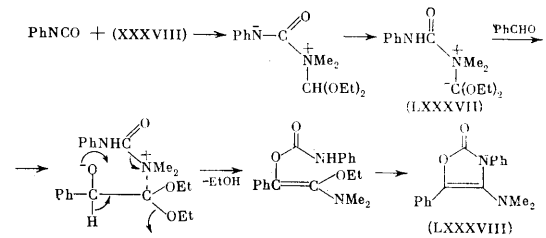


According to this mechanism, the intermediate nitrene (LXXX) interacts under mild conditions with the acetal (XXVIII), this being followed by a rearrangement to the ylid (LXXXI), from which the final reaction products are formed (photochemical reaction—pathway *a*). On heat treatment (pathway *b*), the nitrene (LXXX) rearranges to the isocyanate, which reacts further with compound (XXVIII). In this case, the synthesis on the *ON*-acetal of parabanic acid (LXXXII, R′ = Me) is also preceded by the formation of the ylid (LXXXI).

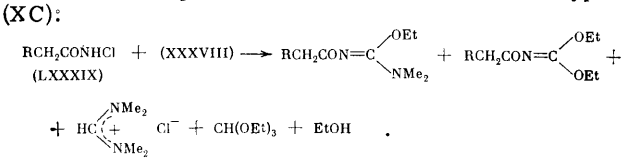
The mechanism of the reactions of amide acetals with isocyanates has been demonstrated in relation to the diethylacetal of dimethylformamide [compound (XXXVIII)].[81] It was found that, as in the thermal reaction with benzoyl azides, the main products are the *ON*-acetal (LXXXII, R′ = Et) and the carbamic ester (LXXXIII, R′ = Et). The highly reactive *p*-nitrophenyl isocyanate (LXXXIV, R = *p*-$NO_2$) reacts further, forming derivatives of parabanic acid (LXXXV), urea (LXXXVI), and ethylene:



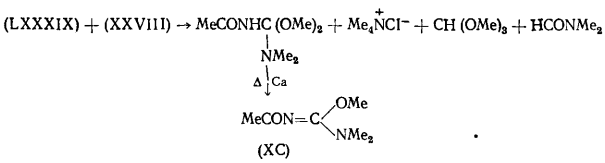
To demonstrate the intermediate formation of the ylid (LXXXVII), this reaction was carried out in benzaldehyde, a preliminary test having established that the latter does not react either with the dimethylformamide acetal (XXXVIII) or with the *ON*-acetal (LXXXII, R′ = Et). The product isolated in this reaction was 4-dimethylamino-3,5-diphenyloxazolin-2-one (LXXXVIII), for the formation of which the following mechanism has been proposed:



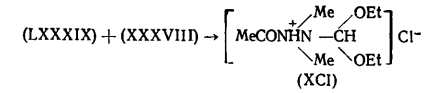
The interaction of the diethyl acetal of dimethylformamide (XXXVIII) with *N*-halogenoamides, *N*-halogenoureas, and *N*-halogenourethanes (LXXXIX)[82] proceeds with formation of multicomponent mixtures of substances, in which the main products are keten *ON*-acetals of type (XC):



It is of interest that, when the dimethyl acetal of dimethylformamide (XXVIII) is used in the reaction, the nature of the side products changes:



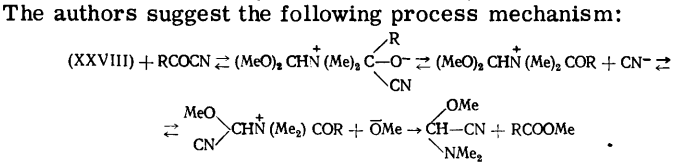
By allowing the acetal (XXXVIII) to react with *N*-chloroacetamide (LXXXIX, R = H), Bredereck et al.[83] succeeded in isolating the intermediate (XCI):



(XCI)

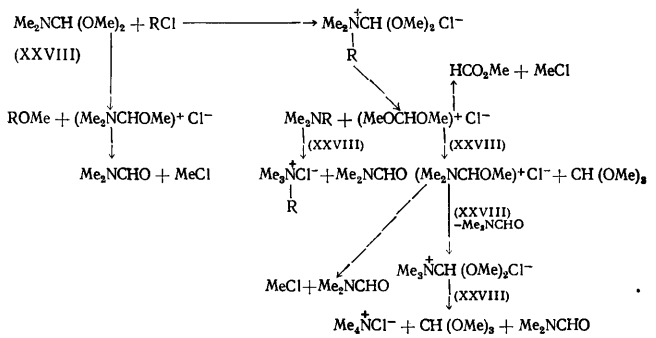
On the basis of the structure of the salt (XCI) and the probable formation of the ylid (LXXXI) from the latter, the authors suggested that the conversion of the ylid into the final product (XC) proceeds via an $S_E1$ or an $S_Ni$ mechanism.

The reaction of the dimethyl acetal of dimethylformamide (XXVIII) with an acyl cyanide leads smoothly to the formation of α-dimethylamino-α-methoxyacetonitrile [84]. The authors suggest the following process mechanism:



The reaction of acyl cyanides with orthoesters proceeds with a much lower yield even under much more severe conditions.

A detailed study of the reactions of the dimethyl acetal of dimethylformamide (XXVIII) with alkylating and acylating agents has been published recently[85]. It was shown that the alkylation proceeds exclusively via the nitrogen atom of the amide acetal, while the ratio of the *O*- and *N*-acylation products depends significantly on the nature of the acyl halide used. The authors proposed the following general reaction mechanism:

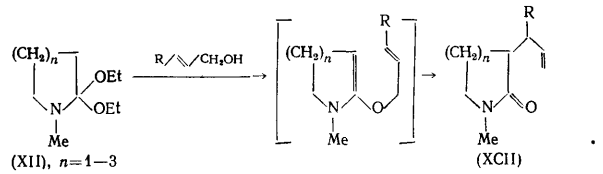


Experimental data led to the conclusion that the reactivity of acyl halides in the *O*-acylation of the amide acetal (XXVIII) increases in the sequence

$$AlkCOCl < ArCOCl < RSO_2Cl < (RO)_2P(=O)Cl \sim R_2PCl \sim R_3SiCl .$$

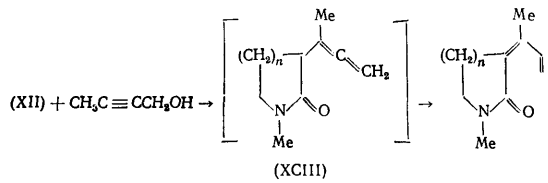
b. Reactions of the Homologues of the Dimethylformamide Acetal and Lactam Acetals

The introduction of alkyl or acyl groups in the α-positions of amides and lactams is known to proceed with difficulty as a rule. In this connection, a convenient method for the synthesis of α-alkyl(acyl)amides or α-alkyl(acyl)lactams is provided by the interaction of the corresponding amide or lactam acetals with alkylating or acylating agents. Thus the reaction of lactam acetals with unsaturated alcohols leads to the formation of 3-allyllactams (XCII) [54]:



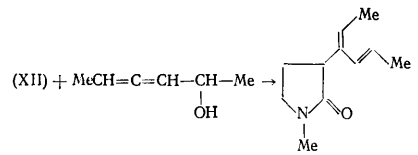
(XII), $n$=1–3 (XCII)

The conjugated lactam (XCII) has been synthesised by the reaction of compound (XII, $n$ = 1) with butynol. When the acetal of *N*-methylcaprolactam was used in this reaction, the intermediate allene (XCIII) could be isolated:

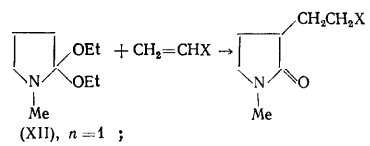


(XCIII)

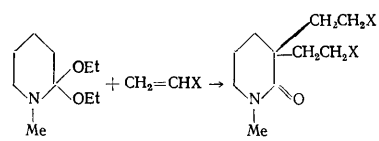
The reaction with allenes proceeds similarly[54]:



The reactions of lactam acetals with compounds such as acrylonitrile have been investigated in fair detail[29]. It has been shown that, when compound (XII, $n$ = 1) interacts with $CH_2$=CHX (where X = CN, $CO_2Me$, or COMe), only the products of monosubstitution in the 3-position of the lactam ring are formed, while compound (XII, $n$ = 2) forms 3,3-disubstituted lactams under these conditions:

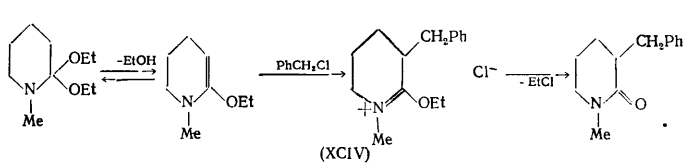


(XII), $n$ = 1 ;



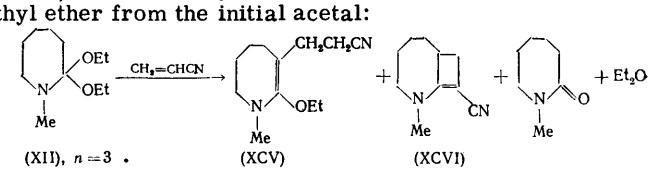
(XII), $n$ = 2 X=CN, $CO_2Me$, or COMe

Alkylation of compound (XII, $n$ = 2) with benzyl chloride leads to a monoalkylation product. Such specificity of the benzylation of compound (XII) has been explained[29] by the ability of the intermediate immonium salt (XCIV) to split off ethyl chloride:



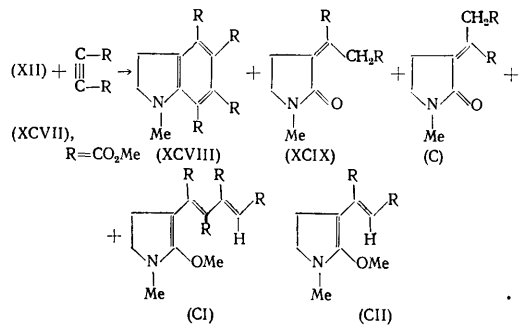
(XCIV)

The diethyl acetal of *N*-methylcaprolactam (XII, $n = 3$) reacts with acrylonitrile[35], forming the $\alpha$-alkoxyenamine (XCV), the cyclic product (XCVI), and *N*-methylcaprolactam, the last compound as a result of the elimination of ethyl ether from the initial acetal:



(XII), $n = 3$ . (XCV) (XCVI)

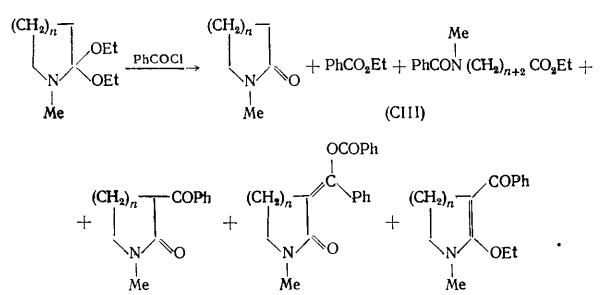
When the acetal (XII, $n = 1$) was allowed to react with the acetylenedicarboxylate ester (XCVII), a number of substances, (XCVIII)–(CI), were isolated[86]:



(XCVII), R=$CO_2$Me (XCVIII) (XCIX) (C) (CI) (CII)

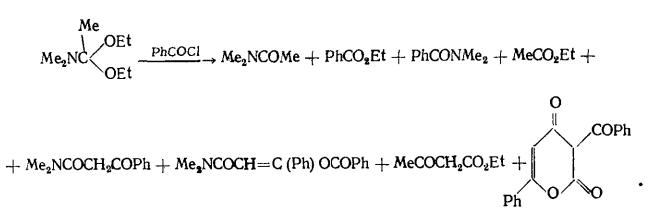
It was shown that the primary product of this reaction is the enamine (CII), which is converted into the isomers (XCIX) and (C) under mild conditions, for example in chromatography on silica gel, while on heating with the ester (XCVII) it gives rise to the indoline (XCVIII).

Among the reactions of amide and lactam acetals with electrophiles, those with benzoyl chloride have been investigated in greatest detail[28,35,87,88]. As was to be expected, these reactions proceed unambiguously with formation of *C*-, *N*-, and *O*- acylation products:

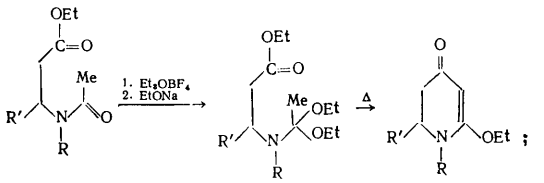


(CIII)

The benzoylation of the dimethylacetamide acetal (CIV) proceeds in an even more complex manner; its mechanism has been examined in detail[88]:

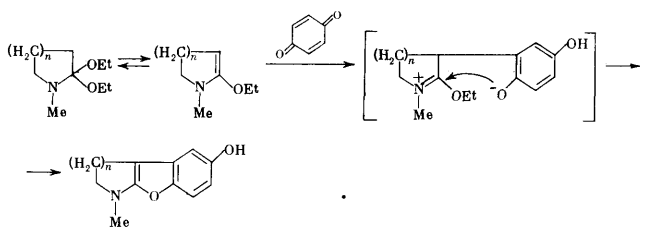


The ability of amide acetals to react with electrophiles has been used in the synthesis of heterocyclic compounds, for example for the preparation of 2,4-dioxopiperidine derivatives[50]:



R=Me, R′=H, or (RR′)=$-(CH_2)_4-$ .

It has been found recently that lactam acetals condense readily with *p*-benzoquinone, cyclising subsequently to condensed benzofurans[89]:



Thus the data described show that the discovery of amide and lactam acetals, a new class of organic compounds, initiated a new field in organic chemistry, which is of great promise from both synthetic and theoretical points of view. There is no doubt that the scope of the applications of amide acetals in organic synthesis is far from exhausted and that the chemistry of these exceptionally reactive compounds will continue to attract the attention of many organic chemists.

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