Tetrahedron Vol 44, No 19, pp 5975–5999, 1988
Printed in Great Britain.

0040-4020/88 $5.00 + .00
Pergamon Press plc

TETRAHEDRON REPORT NUMBER 241

CHEMISTRY OF LACTAM ACETALS

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(*Received* 14 *December* 1987)

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1. INTRODUCTION

The synthetic utility of acid amides and lactams as synthons and as reagents was not realised till the development of their activated forms which now include imidoyl chlorides, iminoesters, iminoethers, lactim ethers, lactim thioethers, ketene S,N-acetals and lactam acetals; of these activated forms, lactam acetals are the most reactive and possess great synthetic utility.

Since Meerwein *et al.*'s first reports of the preparation of the acetals of amides and lactams in 1956[1] and of their high chemical reactivity in 1961,[2] a large amount of work has been reported demonstrating their great synthetic utility. Amongst the acetals of amides and lactams, *N,N*-

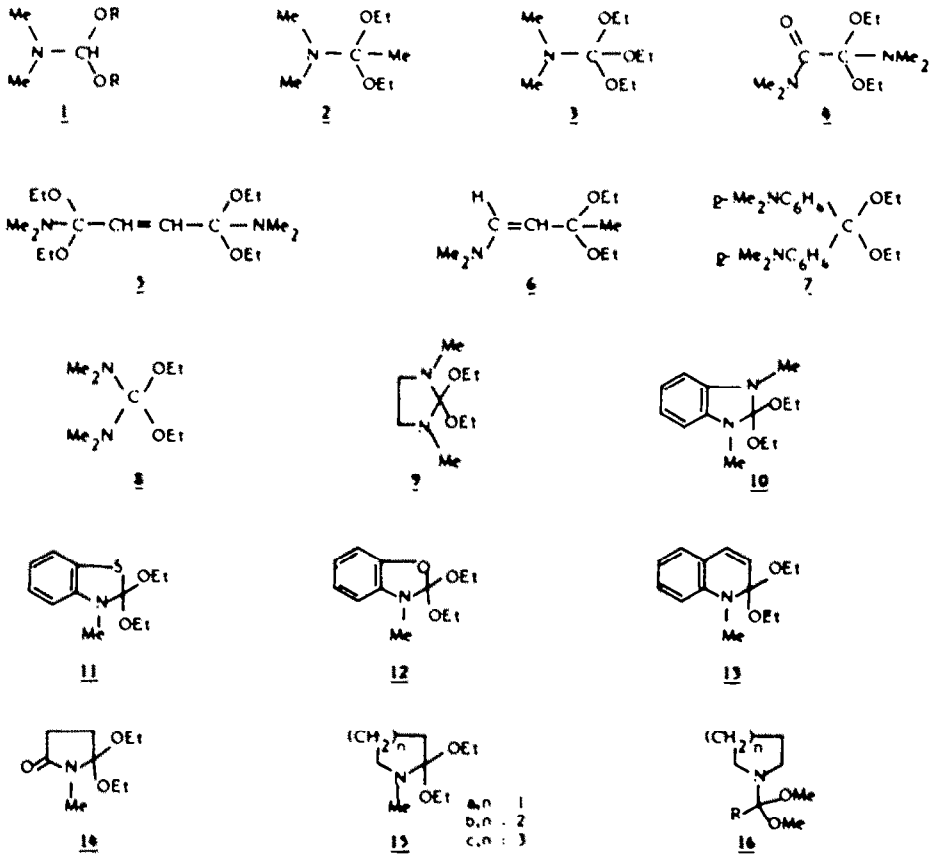


Chart 1.

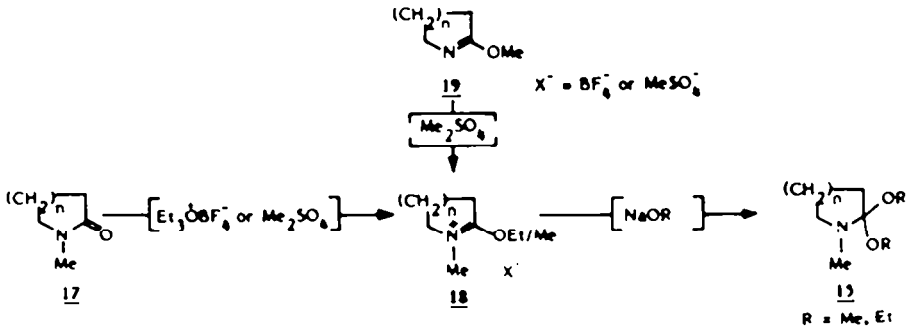
dimethylformamide acetals have been the most extensively studied, which possess a centre for nucleophilic substitution. The higher amide acetals and lactam acetals possess in addition a reactive α-methylene group (relative to carbonyl) available for electrophilic substitution and are capable of undergoing both nucleophilic and electrophilic substitution reactions. This makes them amenable to react with bifunctional and dipolar reagents to yield cycloaddition products and offer easy access to a variety of polycyclic heterocyclic and carbocyclic compounds.

Though acetals of a variety of amides, vinylogous amides, ureas and lactams (**1**–**16**, Chart 1) have been reported,[1-6] only DMF-acetals **1** and lactam acetals **15a–c** have been studied extensively and explored for their chemistry and synthetic utility. The chemistry of DMF-acetals has been reviewed[7] in 1979, while chemistry of amide and lactam acetals was reviewed by Granik *et al.*[8] in 1977. The development of their chemistry since then has been considerable. This review is focused on the major types of reactions entered into by lactam and higher amide acetals, some more recent studies on DMF-acetals and highlights the possibilities offered for novel and convenient synthesis of heterocyclic systems.

2. PREPARATION

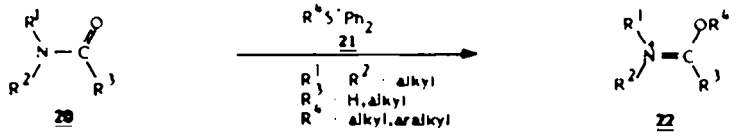
2.1. *From immonium intermediates*

2.1.1. *From α-alkoxyimmonium salts.* Preparation of amide and lactam acetals from immonium intermediates, developed by Meerwein *et al.*[1] still remains the most general and commonly used method for their synthesis (Scheme 1). This involves alkylation of the lactams **17** with trialkyloxonium tetrafluoroborate or dialkyl sulphate followed by treatment of the resulting cationic intermediates **18** with sodium alkoxide in appropriate alcohol to form the lactam acetals **15**. The immonium intermediates **18** can also be generated[9] by *N*-alkylation of lactim ethers **19** with dimethyl sulphate.



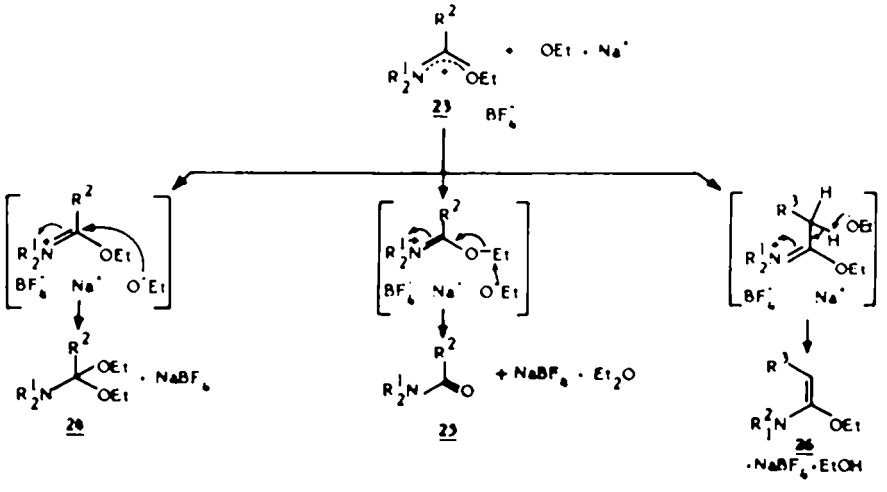
Scheme 1.

A recent method[10] for the preparation of the immonium intermediates involves the reaction of amides **20** with alkyldiphenylsulphonium salts **21**. These alkylating agents are somewhat less powerful than oxonium salts; however, these are readily available and unlike oxonium salts, are crystalline and non-hygroscopic (Scheme 2).



Scheme 2.

The mode of reaction of the immonium intermediate with sodium ethoxide depends[11] on the nature of the substituent R^2 and the reaction may proceed in three different ways (Scheme 3); (a) simple counter-ion association to form the acetal **24**; (b) O—C cleavage of the immonium intermediate **23** in the presence of OEt to form dialkyl ether and starting amide (**25**); (c) abstraction of a proton available at β-position to form the α-alkoxyenamine **26**. The process (a) takes place most readily since it involves simple counter-ion association and the activation energy is significantly lower compared to the processes (b) and (c). However, in case of bulky R^2 groups such as *t*-butyl or dichloromethyl, the formation of stable molecules such as diethyl ether and amide (**25**) is favoured via process (b). If R^2 is relatively small and possesses a proton sufficiently activated to be abstracted by OEt, the formation of α-alkoxy enamine (**26**) takes place.

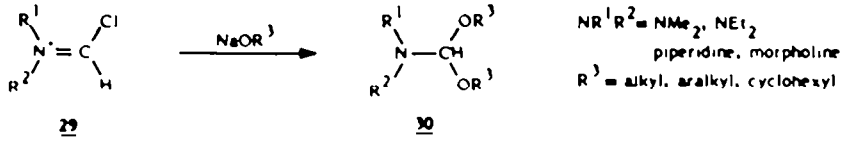


Scheme 3.

The process (c) has, in fact, been observed[9] in the reaction of 2-ethoxy-3-ethoxycarbonyl-1-methyltetrahydropyridinium fluoroborate (**27**) with sodium alkoxide, which results in the formation of α-alkoxy-β-enamino ester **28** (Scheme 4).

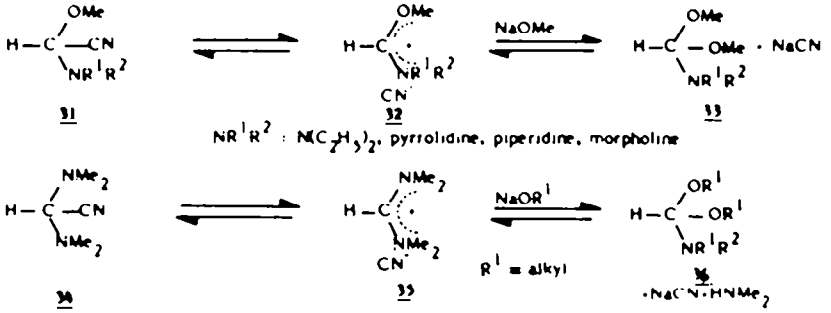
Scheme 4.

2.1.2. *From imidoyl chlorides.* Eilingsfeld *et al.*[3] reported the synthesis of amide acetals **30** from imidoyl chlorides **29**; the latter are prepared by the reaction of tertiary amides with phosgene, thionyl chloride or phosphorus pentachloride (Scheme 5).



Scheme 5.

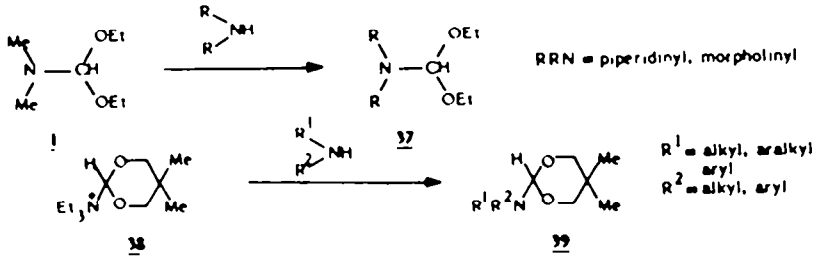
2.1.3. *From α-dialkylamino-α-methoxyacetonitriles.* α-Dialkylamino-α-methoxyacetonitriles (**31**) dissociate[4] into a cyanide ion and an immonium cation **32** which react with alkoxides to form amide acetals **33**. Similarly bisdimethylaminoacetonitrile **34** forms the amide acetals **36** on its reaction with sodium alkoxides (Scheme 6), presumably via the immonium intermediate **35**.



Scheme 6.

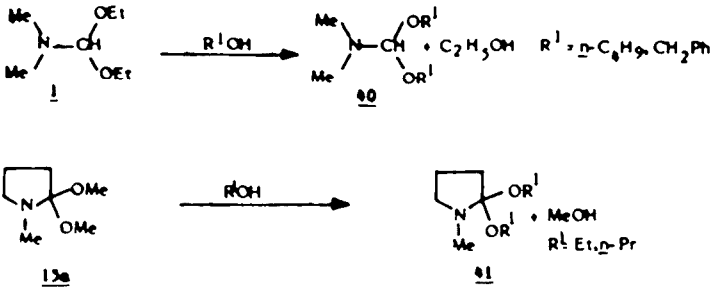
2.2. *By transfer reaction from lower homologues*

2.2.1. *By transamination.* Lower dialkylamide acetals **1** undergo transamination reaction[2] on treatment with higher secondary amines to give the corresponding amide acetals **37**. Similarly the reaction[12] of dialkoxymethylammonium salts **38** with secondary amines gives the amide acetals **39** (Scheme 7).



Scheme 7.

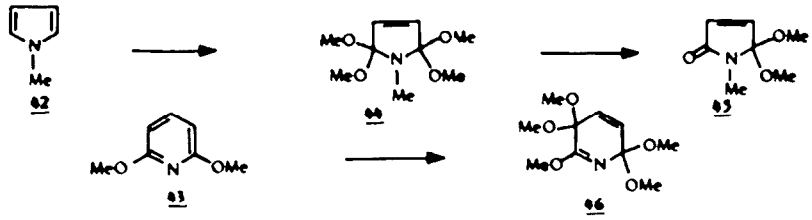
2.2.2. *By transacetalization.* Lower dialkoxy acetals **1** and **15a** undergo transacetalization[2,13] reaction on treatment with high boiling alcohols to give the corresponding acetals **40** and **41** respectively (Scheme 8).



Scheme 8.

2.3. *By anodic oxidation of heteroaromatics*

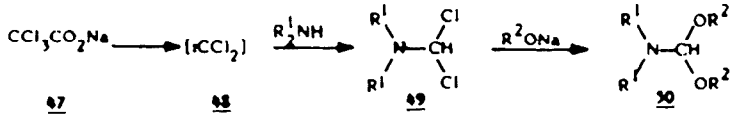
Acetals **44–46** of unsaturated lactams can be prepared by anodic oxidation[14] of the parent heterocycle; a methanolic solution of *N*-methylpyrrole **42** and 2,6-dimethoxypyridine **43**, on electrochemical oxidation gave the corresponding lactam acetals **44–46** (Scheme 9).



Scheme 9.

2.4. *Miscellaneous*

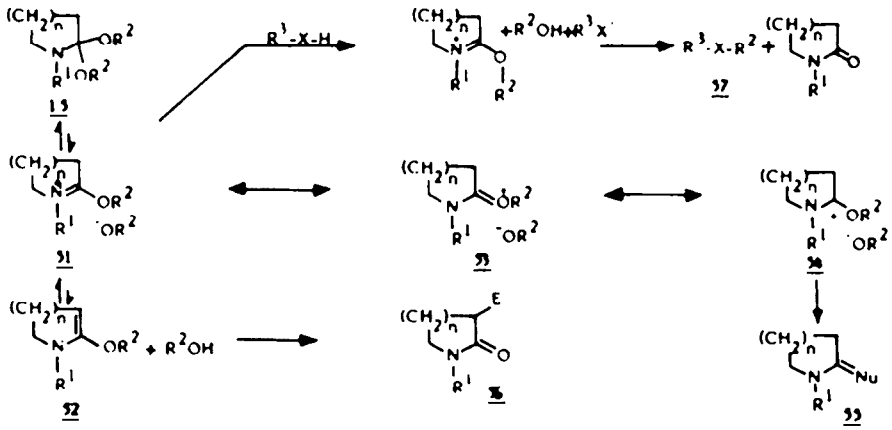
Amide acetals have also been synthesized[15] from dichloramine intermediates **49** which, in turn, were prepared by the reaction of dichlorocarbene **48** with dialkylamines. The dichloramines on treatment with alkoxide give the amide acetals **50** (Scheme 10).



Scheme 10.

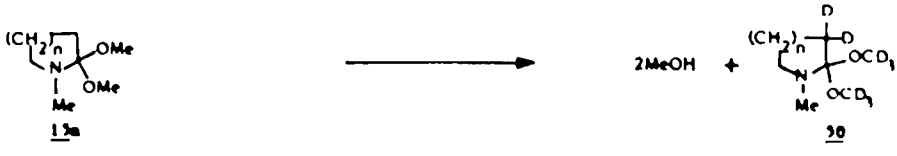
3. STRUCTURE AND REACTIVITY

Lactam acetals possess the unique property of reacting under mild conditions with both nucleophiles and electrophiles, with the former at position C-2 and with the latter at C-3. This high and bifunctional reactivity of lactam acetals cannot be explained on the basis of their ground state structure **15**. The solutions of amide and lactam acetals have been shown to possess conducting properties[2,16] and this phenomenon can be explained assuming the dissociation of the acetals into immonium cation **51** and an alkoxide ion (Scheme 11). In a polarographic study,[16] Granik *et al.* have shown that a solution of lactam acetals in methanol contains up to 0.3% of the ambident cation **51**. Although the proportion of this species at equilibrium is small, but enough to initiate and promote reaction with nucleophiles and also lead to the formation of enamine **52** resulting from



Scheme 11.

proton abstraction by the alkoxide ion. To obtain some direct evidence for the presence of these species, IR and ^{1}H NMR spectra of lactam acetals were studied.[17] NMR which has a much slower time scale as compared to IR, could not detect these species. The IR spectrum of the acetal **15a** in anhydrous chloroform, however, displayed strong absorption band at 1675 and 1730 cm^{-1} and a group of weak bands around 2450 cm^{-1} indicating the presence of the enamine and immonium species respectively. Serial ^{1}H NMR spectra of the acetal **15a** in CD_3OD at ambient temperature and at $-40°$ showed the presence of the deuterated derivative **50** even in spectra taken soon after mixing, indicating very fast exchange of 3-CH_2 by deuterium as well as replacement of OCH_3 by OCD_3 (Scheme 12). These results supported the suggested formation of the immonium intermediate **51**, the alkoxide ion and the enamine **52** in the solutions of lactam acetals. These reactive intermediate species enable the lactam acetals to undergo a variety of chemical reactions as shown in Scheme 11. The immonium cation **51** which would, in principle, be stabilized by the canonical forms **53** and **54**, possesses a centre at C-2 for facile attack by nucleophiles to form 2-substituted derivatives **55**. As the reactive intermediate in this reaction is the ambient cationic imino ether, it is sometimes advantageous to use the intermediate immonium salt **18** prepared *in situ* for this reaction, particularly in cases where the lactam acetals are not reactive enough for a particular reaction (*loc. cit.*). Besides this, the 2-alkoxy function in **51** is capable of undergoing *O*-alkyl bond fission to provide an alkyl cation which can alkylate suitable substrates R^3XH to give the alkylated products **57**. The alkoxide ion can act as a nucleophile as in anhydride opening or as a base and abstract a proton depending on the nature of the substrate. The 2-alkoxyenamines **52** possess an electrophilic substitution site at C-3 and on reaction with electrophiles can give 3-substituted lactams **56**. The presence of reactive sites both at C-2 and C-3, makes the lactam acetals capable of reacting with bifunctional reagents possessing suitably disposed nucleophilic and electrophilic centres to form 2,3-annulated products. The reactivity of lactam acetals varies with the ring size; the order of reactivity appears to be five-membered > six-membered > seven-membered as would be expected because of the better overlap of the lone pair of electrons of nitrogen with the π-electrons in the enamine species in the five-membered acetals due to greater planar character of the latter than that of six- and seven-membered acetals. The difference in reactivity of lactam acetals of different ring sizes leads to the formation of different products in their reaction with various nucleophiles and electrophiles as described in the appropriate sections below.



Scheme 12.

4. REACTIONS WITH NUCLEOPHILES

Lactam acetals possess a highly electrophilic carbon at C-2 which enables them to react with a variety of nucleophiles including N, C, O, and phosphorus nucleophiles. The alkoxide ion available in the equilibrium mixture of lactam acetals can act as a base to abstract a proton from a substrate possessing an activated proton and, in turn, generates an anion which can act as a powerful nucleophile.

4.1. *Amino compounds*

Lactam and amide acetals **15** and **16** react readily under mild conditions with primary amines and amides to yield amidines and acylamidines (**59–61**) respectively, which constitutes a convenient method for their synthesis. Acid hydrazides react[26] in a similar fashion with lactam acetals to give the hydrazones **62**. Although lactam acetals **15** did not react with ammonia, the immonium salt **18** reacted with ammonia to form 2-iminopyrrolidine **63**. The types of mono- and bis-amides **59–61** synthesized by the reaction of lactam acetals with primary aliphatic, aromatic and heteroaromatic amines are given in Chart 2.[13,18-25]

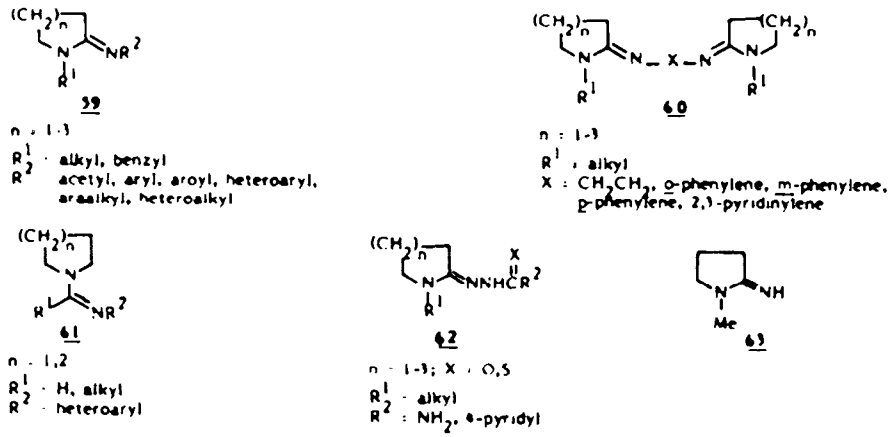


Chart 2.

Many of these amidines exhibit interesting biological activities. Guanidine derivative[27] **64** prepared from 1-methyl-2-pyrrolidone via the imino pyrrolidine **63** have been found to possess marked hypoglycemic activity. Amidines **65** prepared from pyrrolidone acetal **15a** have been shown to be potential antianginal agents.[28] 2-Iminopyrrolidine (**63**) reacted with aryl isocyanates to form pyrrolodinylidene ureas **66** which are a new class of agents acting on the central nervous system (Chart 3).[29]

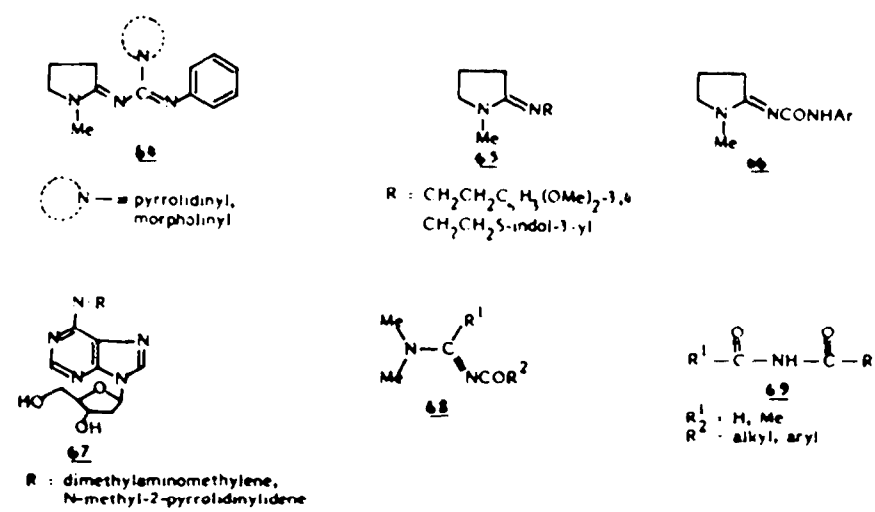


Chart 3.

DMF and 1-methyl-2-pyrrolidone acetals **1** and **15a** have also been used as *N*-protecting groups[30] in nucleoside synthesis. The *N*-methyl-2-pyrrolidinylidene group of *N*-protected nucleoside **67** was shown to be more stable towards acid catalysed depurination than *N*-benzoyl derivative. It is easy to prepare and can be removed rapidly and quantitatively using ethylene diamine–phenol.

N-Acylamidines **68** resulting from the condensation[31] of DMF-acetal **1** and amides, undergo facile hydrolysis leading to a new synthesis of diacylamines **69**.

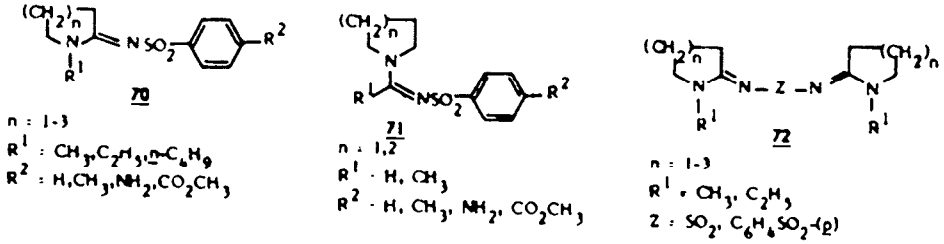
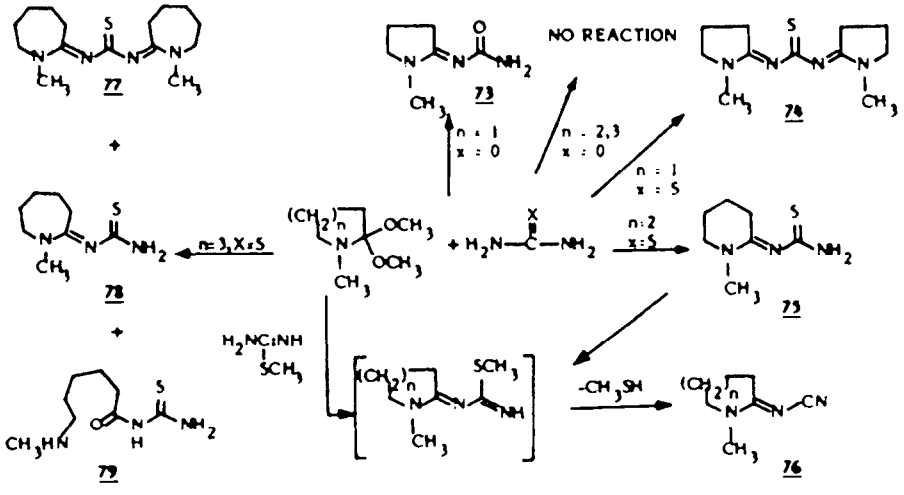


Chart 4.

4.2. *Sulphamide, sulphonamides, urea and thiourea*

The amide and lactam acetals reacted[32] with sulphamide and benzenesulphonamides to form *N*-sulphonyl amidines **70–72** (Chart 4). However, the products formed on reaction with urea and thiourea are dependent on the ring size of the lactam (Scheme 13).[32] While pyrrolidone acetal **15a** reacted with urea and thiourea to form *N*-monosubstituted urea **73** and *N,N'*-disubstituted thiourea **74** respectively, the piperidone and caprolactam acetals (**15b** and **15c**) failed to react with urea. Reaction of piperidone acetal **15b** with thiourea yielded a mixture of *N*-(1-methyl-2-piperidinylidene)thiourea **75** and a cyanamide derivative **76** ($n = 2$), which is an unprecedented observation. The formation of **76** presumably occurs by *S*-alkylation of the monocondensation product **75** by the immonium cation followed by elimination of a molecule of methyl mercaptan. This was supported by the formation of the cyanamide derivative **76** ($n = 1$), in the reaction of lactam acetal **15a** with *S*-methylpseudothiourea. The reaction of caprolactam acetal **15c** with thiourea gave a mixture of monocondensation product **78** and the acyclic compound **79** which appears to be formed by hydrolytic ring opening of **78**. Heating of thiourea with excess of caprolactam acetal **15c** without any solvent yielded in addition to **78** and **79**, the diamidine **77**.



Scheme 13.

4.3. *Carbanions*

Lactam acetals condense under very mild conditions with activated methylene compounds such as nitroalkanes, ethyl cyanoacetate, ethyl acetoacetate, acetylacetone, benzyl cyanide, malonodinitrile, 2,4-dinitrotoluene, acetophenones and other *C*-acetylheteroaromatics, which provides a

convenient route to the synthesis of β-functionalized enamines such as enaminoketones, enaminoesters, enaminonitriles and β-nitroenamines **80**;[2,6,33-40] similarly, reaction of cyclic activated methylene compounds[2,41] gives the corresponding condensation products **81** [Chart 5]. The β-functionalized enamines possess an interesting constellation of reactive sites, and serve as useful synthons for the synthesis of different types of carbocyclic and heterocyclic systems, which is discussed later in this review.

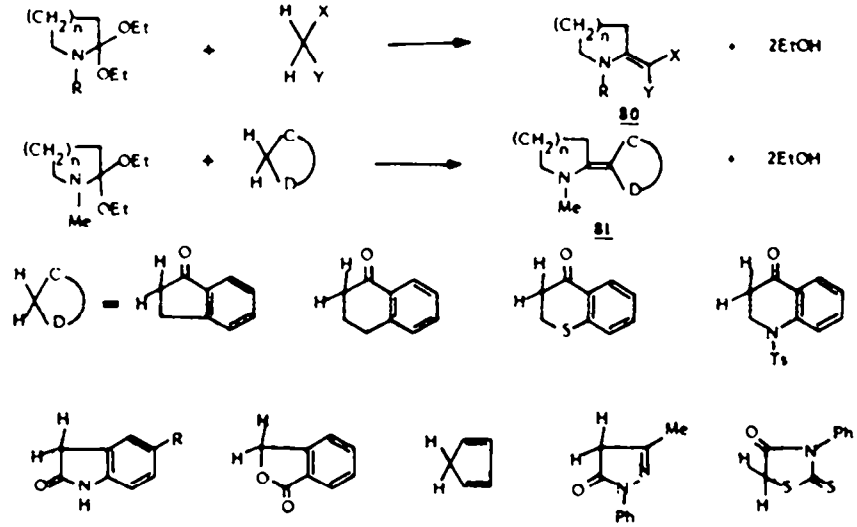
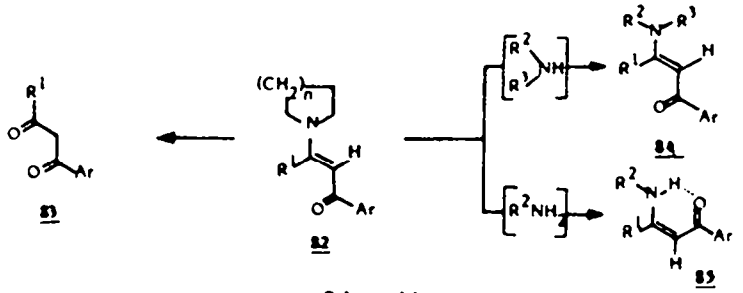


Chart 5.

Similarly, the reaction[6] of amide acetals **16** with acetophenones yields enaminones **82** which are, in fact, enamines of 1,3-diketones, and on acid treatment gave good yields of the diketones **83**, and this constitutes a useful method for their preparation (Scheme 14).



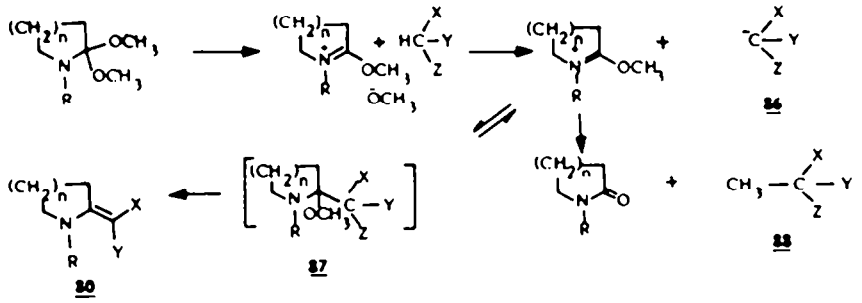
Scheme 14.

The stereochemistry of the enaminones formed by the reaction of lactam/amide acetals with reactive methylene compounds has been studied[6,41] using Lanthanide shift reagents and in most of the cases exclusive formation of the *E*-isomer was observed.

Enaminones **82** undergo facile transamination reaction on treatment with primary and secondary amines, thus providing a convenient method for obtaining a variety of enaminones from a common intermediate (Scheme 14). The product **84** obtained by reaction with secondary amines had the same stereochemistry as the starting enaminone **82**. With primary amines, however, the product **85** obtained had the *Z*-stereochemistry, very likely due to the stabilising effect of intramolecular H-bonding in the *Z*-isomer.

It has been suggested[42] that the first step in the reaction of acetals with the activated methylene compound HCXYZ is the generation of the carbanion **86**, which would form the intermediate **87** by reversible association with the immonium cation. Subsequently, if a proton is available in the CXYZ moiety, the reaction would result in the formation of a stable enamine **88**, otherwise it would

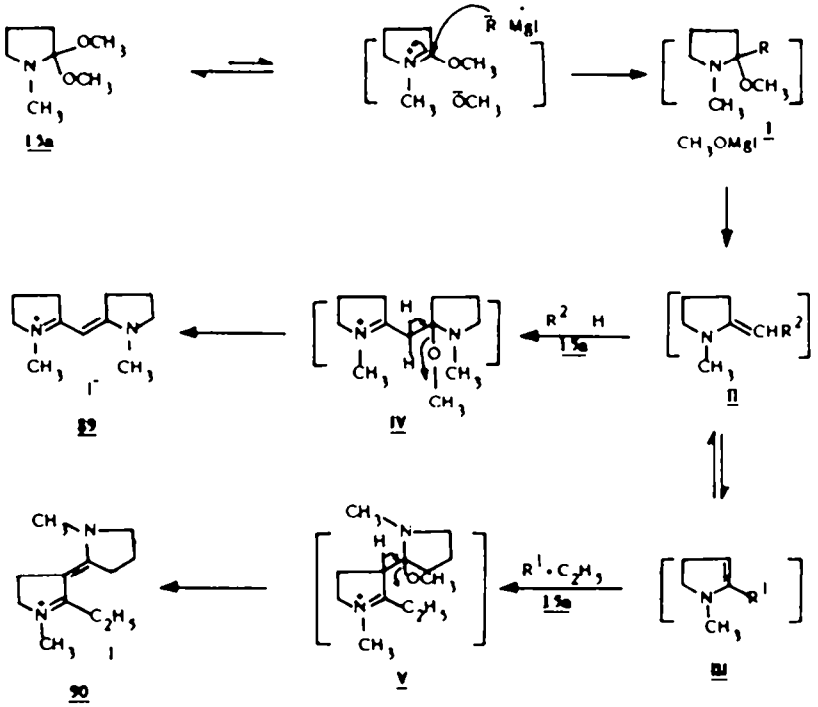
end up in the formation of the C-alkylated product **88** and regeneration of the original lactam (Scheme 15).



Scheme 15.

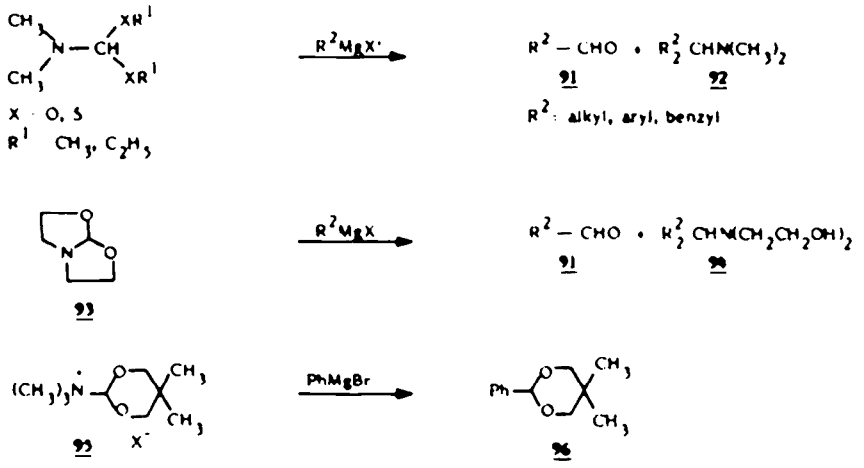
4.4. *Grignard reagents*

Reaction of pyrrolidone acetal **15a** with methylmagnesium iodide led[43] to the formation of 2-(1-methyl-2-pyrrolidinylidene)methylene-1-methyl-Δ^1-pyrrolinium iodide **89**, while reaction with ethylmagnesium iodide resulted in the formation of 2-ethylpyrrolinium salt **90**. The probable mechanism for the formation of linear and angular immonium salts **89** and **90** involves the nucleophilic attack of the Grignard reagent on C-2 of the lactam acetal. The resulting intermediate **I** may form an enamine with an exocyclic (II) or endocyclic (III) double bond which further reacts with a second molecule of lactam acetal to form the immonium salts via the intermediate IV or V (Scheme 16).



Scheme 16.

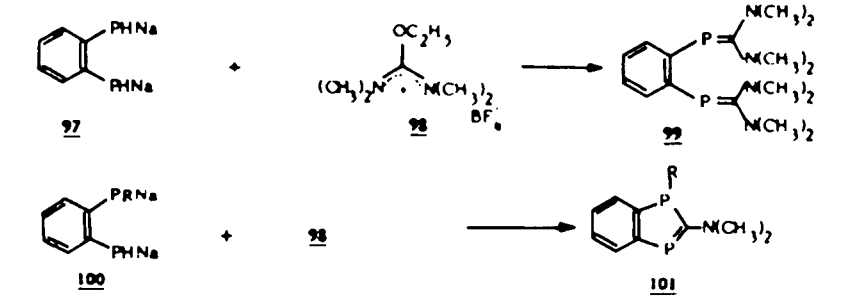
The reaction of Grignard reagents with DMF-acetal and thioacetal, however, formed[44] the aldehyde **91** and tertiary amine **92**. The cyclic acetal **93** formed the aldehyde **91** and amine **94** in its reaction with Grignard reagents, while 2-(trimethylammonium)-5,5-dimethyl-1,3-dioxane (**95**) reacted with phenylmagnesium bromide to give 5,5-dimethyl-2-phenyl-1,3-dioxane **96** (Scheme 17).



Scheme 17

4.5. *Phosphorus nucleophiles*

Reaction with P-nucleophiles has not been studied at great length. A recent report[45] describes the reaction of sodium salt of benzophosphine (**97**) with immonium salt **98** which gives rise to 1,2-bisdimethylaminoalkylidenephosphinobenzene **99**. However, the P-alkylated derivative **100** of benzophosphine reacted with equimolar amount of immonium salt **98** to form 1,3-benzodiphosphole **101** (Scheme 18).



Scheme 18.

5. REACTIONS WITH ELECTROPHILES

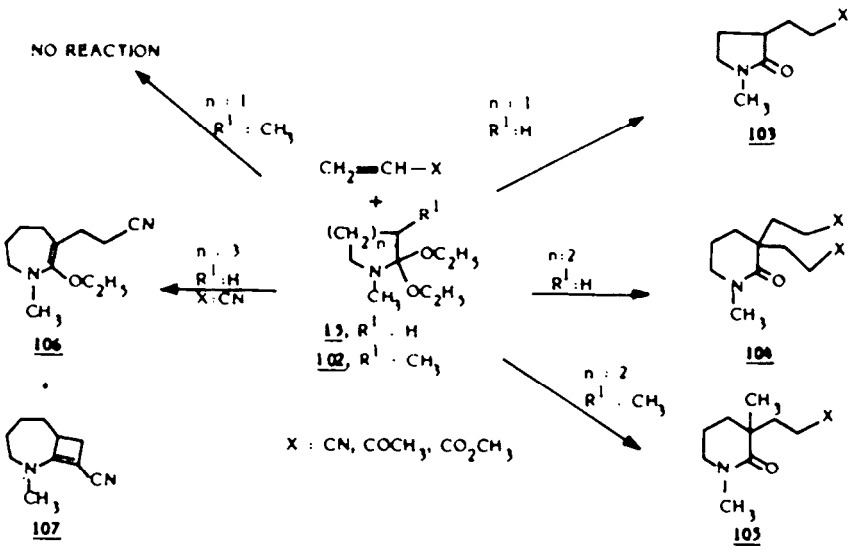
An important and recently explored facet of the chemistry of lactam acetals is their reaction with electrophilic reagents to give 3-substituted lactams.

5.1. *Michael acceptors*

Lactam acetals condense very readily with Michael acceptors, leading to the formation of 3-substituted lactams. Pyrrolidone acetal **15a** reacts[39,46] with acrylonitrile, methyl acrylate and methyl vinyl ketone furnishing 3-monosubstituted lactams **103** while piperidone acetal **15b** furnished 3,3-disubstituted derivatives **104** of the lactams. Similarly the diethyl acetal (**102**, $n = 1$) of 1,3-dimethyl-2-pyrrolidonone did not react with methyl acrylate, the acetal (**102**, $n = 2$) of 1,3-dimethyl-2-piperidone yielded 3,3-disubstituted product **105** in this reaction. Reaction[47] between caprolactam acetal **15c** and acrylonitrile furnished 2-alkoxyenamine **106** and a bicyclic product **107** (Scheme 19).

Reaction of 2,2-dimethoxy-1-methylpyrrolidine with dimethyl azodicarboxylate led to the formation of 3-substituted product **108**.[39]

Reaction of *N*-methyl-2-pyrrolidone acetal **15** with dimethyl acetylene-dicarboxylate in refluxing dioxane and benzene gave a different set of compounds in the two cases; indoline derivative **109**, isomeric pyrrolidinones **110** and **111** and tetracarbomethoxy-1,3-butenylpyrroline **112** were obtained



Scheme 19.

when the reaction was carried out in refluxing dioxane, while 1 : 1 adduct **113** was found to be the main product in the case of benzene (Chart 6).[48]

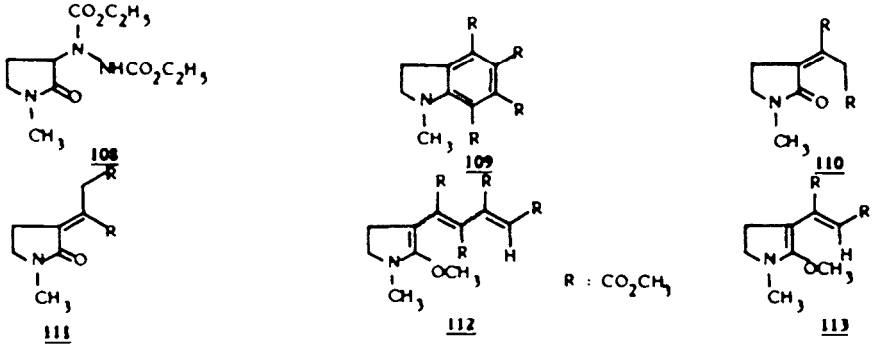
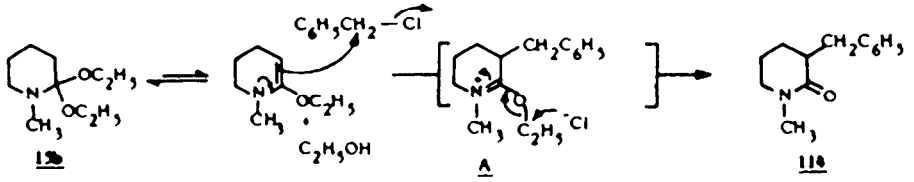


Chart 6.

5.2. *Alkyl and acyl halides*

In contrast to the reaction with acrylonitrile, piperidone acetal **15b** reacted[49] with benzyl chloride to yield monosubstituted lactam derivative **114**. This reaction has been explained by the ability of the intermediary immonium salt A (Scheme 20) to undergo *O*-alkyl cleavage by the chloride ion formed.



Scheme 20.

Lactam acetals react with benzoyl chlorides to form a number of products **115–119** arising from *C*-, *N*- and *O*-acylations (Chart 7).[49–51]

Similar reaction[52] of dimethylacetamide acetal 2 with methyl acrylate, acrylonitrile, methyl vinyl

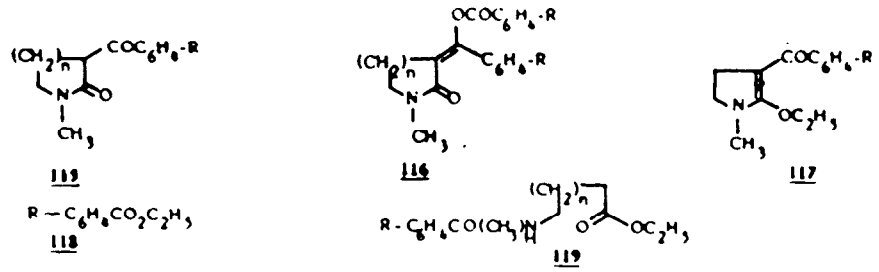


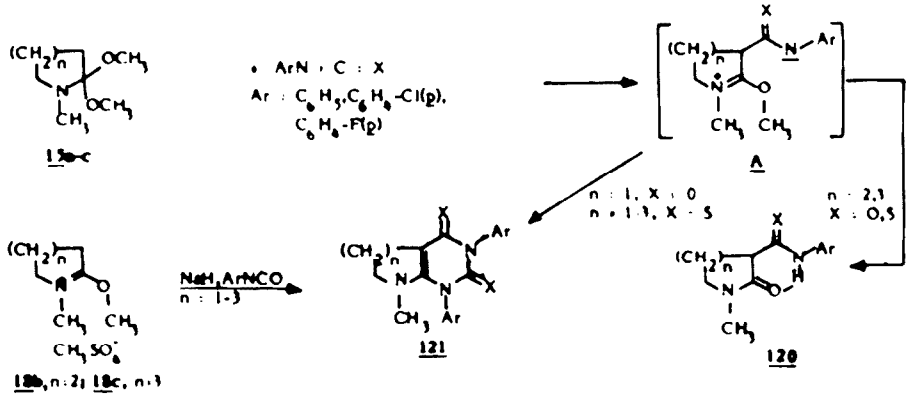
Chart 7.

ketone, benzyl chloride and benzoyl chloride resulted in the introduction of substituents at β-position of the amide group.

5.3. *Aryl isocyanates and aryl isothiocyanates*

Lactam acetals **15** react[51] with aryl isocyanates and aryl isothiocyanates to form 3-*N*-arylcarbamoyl lactams,**120** and/or azacycloalkano[2,3-*d*]pyrimidines **121** depending upon the ring size of the lactam and the reaction conditions (Scheme 21). *N*-Methylpyrrolidone acetal (**15a**) reacted with both isocyanates and isothiocyanates to form pyrrolo[2,3-*d*]pyrimidines (**121**), as the only product; reaction of 6- and 7-membered acetals (**15b** and **15c**) with aryl isothiocyanates furnished a mixture of 3-*N*-arylthiocarbamoyl lactams **120** and pyrido- and azepino [2,3-*d*]pyrimidines **121**, but reaction with aryl isocyanates yielded only the 3-*N*-arylcarbamoyl lactams. However, when the reaction of phenyl isocyanate was carried out with immonium salts (**18b** and **18c**) in anhydrous dichloromethane in the presence of sodium hydride, the corresponding fused pyrimidines **121** were formed in fair yield. The reaction very likely proceeds by generation of 2-methoxyenamine which *in situ* reacts with two molecules of aryl isocyanate to give the fused pyrimidine derivatives.

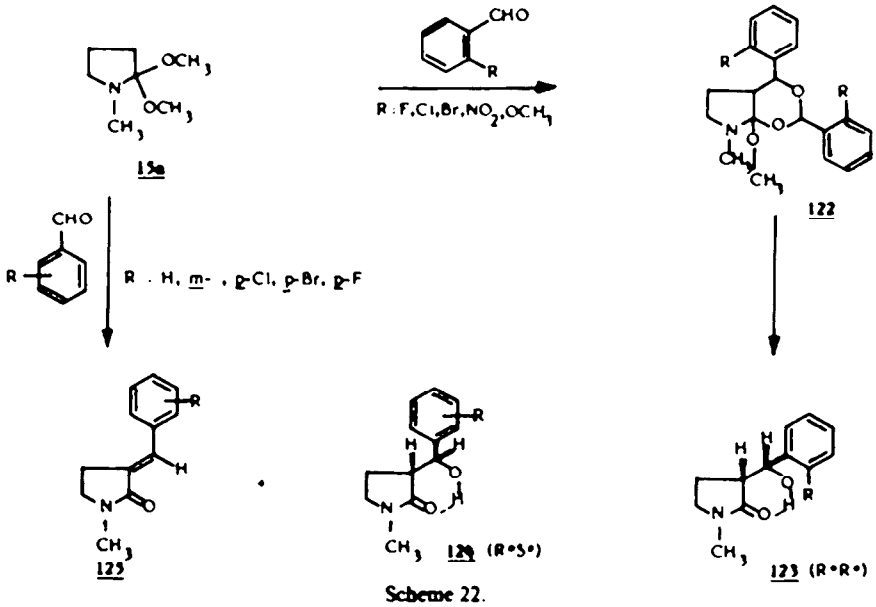
The difference in the nature of the products formed in the reaction of lactam acetals **15** with aryl isocyanates and aryl isothiocyanates may be explained by difference in the stability of the intermediate zwitterionic species (**A**, Scheme 21) formed, leading either to the fused pyrimidinediones/dithiones or to the 3-arylcarbamoyl/thiocarbamoyl derivatives. In the thio-zwitterionic species, which would be relatively more stable than the oxo-analogues because of the *d*-orbital participation, charge neutralization on the thiocarbamoyl nitrogen would take place by both the routes, the preferred course being the neutralization with the electrophilic carbon of a second molecule of ArNCS, as evident from greater yield of the products thus formed. While in the oxo-zwitterionic species the charge is preferably neutralized by protonation apparently arising from the methanol liberated during the reaction. However, on excluding the formation of methanol by using methosulphate salts **18b** and **18c** and sodium hydride, the charge is neutralized by the second molecule of aryl isocyanate.



Scheme 21.

5.4. *Araldehydes*

Lactam acetal **15a** reacted under mild conditions with araldehydes to form[54,55] dioxino-pyrrole **122**, the benzylhydrols **123** and/or **124** and the benzylidene **125** (Scheme 22). The products formed were dependent on the substituent pattern of the araldehyde and reaction conditions; *o*-substituted araldehydes, in general, yielded dioxinopyrroles **122** and (*R**,*R**)-benzhydrol derivatives **123** while araldehydes without *o*-substituent formed *E*-benylidene lactams **125** as the major product along with (*R**,*S**)-benzhydrol derivatives **124** as the minor product.



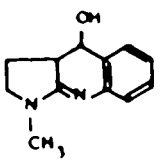
Scheme 22.

With a view to study the course of the reaction, ^{1}H NMR study of the reaction mixture was carried[55] out to identify the possible intermediates leading to the formation of different products in the two cases. The results of this study indicate that in case of *o*-substituted araldehydes dioxinopyrrole **122** is the first product formed which is gradually hydrolysed to (*R**,*R**)-benzhydrol **123**, which dehydrate only under drastic condition using 50% sulphuric acid to benzylidene **125**, while in the case of araldehydes without *o*-substituent only one mole of aldehyde is condensed to first form (*R**,*S**)-benzhydrol **124** which undergoes facile dehydration to form the benzylidene derivative **125**. However, the reaction of *o*-anisaldehyde with lactam acetal was very slow and careful work-up of the reaction mixture yielded a mixture of dioxinopyrrole **122**, (*R**,*R**)- and (*R**,*S**)-benzhydrols **123** and **124** and benzylidene derivative **125**.

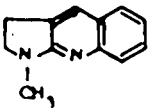
Although the precise reason for this effect of *o*-substituent is difficult to delineate at this stage, it appears that the *o*-substituent exerts a buttressing effect which does not allow the formation of the transition state necessary for the formation of the *R**,*S**-benzhydrol or the dehydrated product. However, the fact that the electron withdrawing substituent in *o*-position gives exclusively the dioxinopyrrole and thus the *R**,*R**-benzhydrol, while *o*-anisaldehyde yields all the possible products viz. dioxinopyrrole, *R**,*R**- and *R**,*S**-benzhydrols and benzylidene derivative, suggests that the reactivity of the aldehyde may also play some role in the outcome of the reaction.

Reaction of pyrrolidone acetal **15a** with *o*-aminobenzaldehyde gave a mixture of tetrahydroquinolinol **126** and dihydropyrroloquinoline **127**, thus providing a useful one-step synthesis of pyrroloquinolines. In contrast, reduction of the *o*-nitrobenzhydrol **123** (R = NO_2) furnished the corresponding aminobenzhydrol **123** (R = NH_2) which did not cyclize to dihydropyrroloquinoline **127**, thus showing that the amino benzhydrol **123** (R = NH_2) does not possess the stereochemistry suitable for cyclization. Reaction of pyrrolidone acetal **15a** with phthalaldehyde led to the formation of hemiacetal **128** (Chart 8).

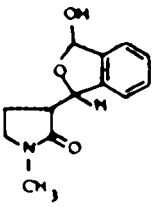
In contrast to lactam acetals, amide acetals (**16**) reacted[56] with araldehydes with or without *o*-substituents, to give cinnamamide derivatives **129** as the only isolable products possessing *E*-geometry.



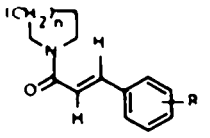
126



127



128



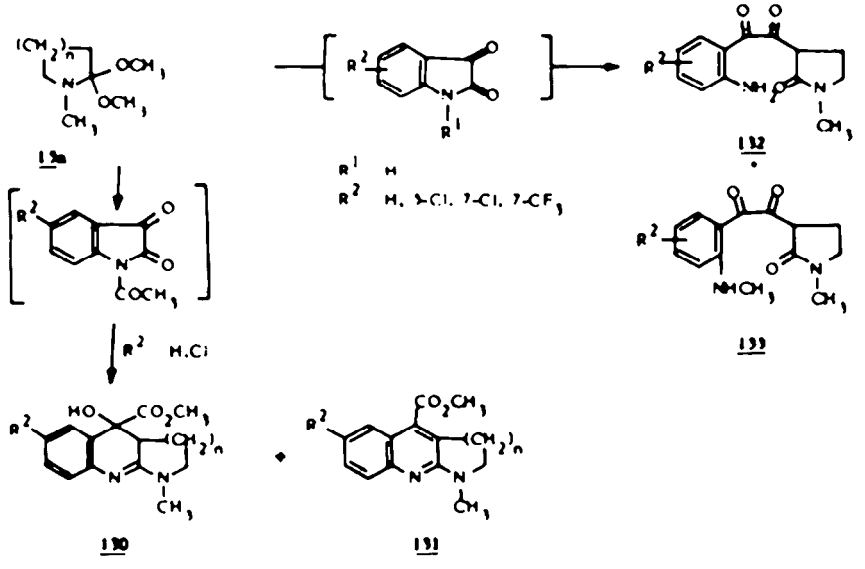
129

R H, o-NO_2, o-Br, o-Cl, p-NO_2, p-Br, p-Cl

Chart 8

5.5. *Isatins and* N-*acetylisatins*

Pyrrolidone acetal **15a** reacted[31] with *N*-acetylisatins to yield 4-methoxycarbonylpyrrolo[2,3-*b*]quinolines **131** ($n = 1$, R^1 = H, Cl) along with the hydroxy intermediate **130** ($n = 1$, R^2 = H). Treatment of **130** ($n = 1$, R^2 = H) or **131** ($n = 1$, R^2 = H) with alcoholic alkali yielded the acid **134** which decarboxylated readily to 2,3-dihydropyrrolo[2,3-*b*]quinoline **127**, a product obtained by the reaction of pyrrolidone acetal **15a** with *o*-aminobenzaldehyde. The reaction of piperidone acetal **15b** with *N*-acetylisatins was sluggish and gave only poor yield (~10%) of the tetrahydropyrido[2,3-*b*]quinolines **131** ($n = 2$, R^1 = H, Cl) while caprolactam acetal **15c** reacted to give an intractable mixture (Scheme 23).

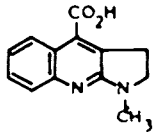


Scheme 23.

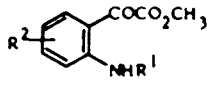
In contrast to the reaction with *N*-acetylisatins, pyrrolidone acetal **15a** reacted with isatin, 5-chloro-, 7-chloro-, 7-trifluoromethylisatins to form 3-(2-methylaminoaroylformyl)-2-pyrrolidones **132** and the *N*-methyl derivatives **133**, the latter arising obviously from *N*-methylation of isatin along with condensation. *N*-Methylisatin also furnished the same product **133** (R^2 = H) on reaction with pyrrolidone acetal **15a**. However, piperidone and caprolactam acetals **15b** and **15c** reacted with isatin to give only *N*-methylisatin.

The possible mechanism for the formation of the ring-cleaved products **132** and **133** and 2,3-

annulated lactams 130 and 131 in the reaction of lactam acetal with isatins could be the cleavage of the N—C bond of isatin owing to nucleophilic attack of the methoxide ion available in the solution of lactam acetal on C-2 position of isatin, very likely leading to the formation of the intermediate 135. 2-Methoxyenamine 52 which would be generated from immonium cation, would attack preferentially on ester carbonyl of the intermediate 135 ($R^1 = H$) because α-carbonyl (relative to aromatic ring) would be less reactive due to its conjugation with the lone pair of the nitrogen, leading to the formation of 3-substituted lactams 132 and 133.



134



135

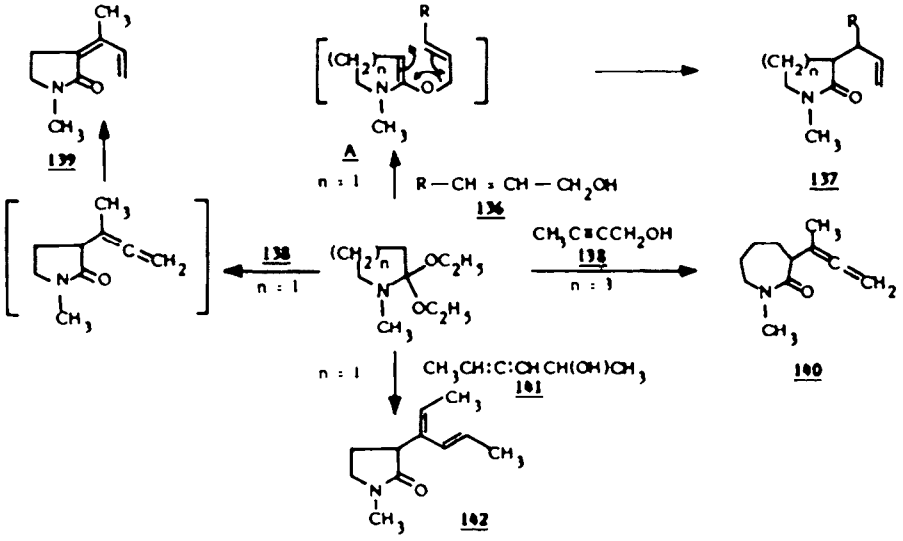
Chart 8a.

In case of six- and seven-membered lactam acetals preferential formation of *N*-methylisatin may be due to the apparently low reactivity of the corresponding 2-methoxyenamines and hence its failure to attack the ester carbonyl of the intermediate 135. Alternatively, the preferred route in these cases appears to be *N*-methylation and recyclization of the intermediate 135 to form *N*-methylisatin.

However, in the reaction of lactam acetals with *N*-acetylisatins, the 2-methoxyenamine species would attack preferentially on the α-carbonyl of the intermediate 135 ($R^1 = COCH_3$), followed by intramolecular cyclization to form 130 and 131.

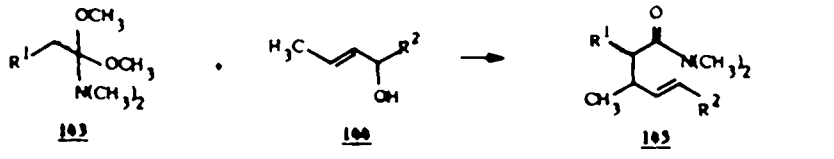
5.6. *Electrophilic substitution through transacetalization reaction*

Ability of lactam acetals to undergo transacetalization reaction has been used to introduce substituents at C-3 via Claisen rearrangement. Allyl alcohols 136 reacted with lactam acetals resulting in the formation[38] of 3-allyllactams 137 via intermediary enamine A (Scheme 24). Pyrrolidone acetal



Scheme 24.

15a reacted with 2-butynol (138) to furnish conjugated lactam 139 while caprolactam acetal 15e furnished 3-allenyl derivative 140. 3-Substituted lactam 142 has been formed in the reaction of acetal 15a with allenyl alcohol 141. Electrophilic substitution products 145 of amide acetals 143 were obtained in their reaction[39] with allyl alcohols 144 (Scheme 25).



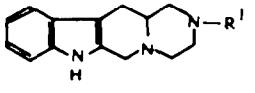
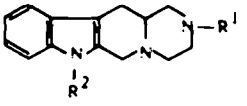
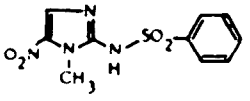
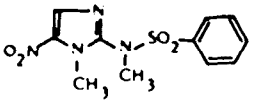
Scheme 25.

6. USE IN ALKYLATION AND ESTERIFICATION REACTIONS

Lactam/amide acetals, due to their ability to undergo *C*-alkoxy and *O*-alkyl bond fission, are very useful reagents for *N*-, *O*- and *S*-alkylations and esterifications. *C*-Alkylation of malonic acid and esterification of benzoic acid by lactam acetals have been described by Granik *et al.*[34] In more extensive study of the use of lactam acetals for alkylation and esterification, it has been observed that *N*-methylation of 3-formylindole, 3-acetylindole, pyrazinopyridonindoles and imidazole could be achieved[60,61] by reaction with 2,2-dimethoxy-1-methylpyrrolidine **15a**, while dimethoxy acetal of *N*-methyl caprolactam, **15c** was found to be an effective reagent for *N*-methylation of isatin. Similarly, pyrrolidone acetal **15a** could be used for *N*-alkylation[13] of hindered —SO_2NH in a 1,2,5-trisubstituted imidazole where conventional methods failed to alkylate (Table 1).

Simultaneous esterification and alkylation has been observed[60] in the reaction of pyrrolidone acetal **15a** with isatoic anhydride which led to the formation of methyl *N*-methylanthranilate along with small amount of methyl anthranilate. Similar reaction of **15a** with homophthalic, phthalic, maleic and succinic anhydrides formed the corresponding diesters in fair yields. Table 1 gives some illustrative examples of alkylation and esterification reactions of various substrates using lactam acetals.

Table 1. *N*-, *O*- and *S*-alkylations and esterifications of organic substrates with 2,2-dimethoxy-1-methylpyrrolidine (**15a**)

Starting material	Product	Yield
3-Formylindole	1-Methyl-3-formylindole	38.0
3-Acetylindole	1-Methyl-3-acetylindole	42.0
Isatin*	1-Methylisatin	71.5
Imidazole	1-Methylimidazole	40.0
Isatoic anhydride	Methyl *N*-methylanthranilate	61.2
Succinic anhydride	Dimethyl succinate	65.1
Maleic anhydride	Dimethyl maleate	29.7
Phthalic anhydride	Dimethyl phthalate	77.3
Homophthalic anhydride	Dimethyl homophthalate	39.0
p-Nitrophenol	*p*-Nitroanisole	66.0
Thiophenol	Thioanisole	80.0
p-Acetamidothiophenol	*p*-Acetamidothioanisole	73.2
Cyclohexane-1,3-dione	1-Methoxycyclohexen-3-one	35.6
		81.0
		61.0

* Alkylation was carried out with caprolactam acetal **15c**.

7. USE IN CONSTRUCTION OF CARBOCYCLIC AND HETEROCYCLIC SYSTEMS

7.1. *By cyclocondensation*

Lactam acetals, by providing two reactive sites of opposite polarity, condense readily with molecules/reactants incorporating suitably disposed nucleophilic and electrophilic centres 2, 3 or 4

atoms apart to form cyclic structures across the C-2 and C-3 sites and are thus of considerable utility for the synthesis of heterocyclic and carbocyclic systems. Chart 9 illustrates the types of condensations studied and the different classes of compounds thus synthesized are listed in Table 2. Reactants studied possessing condensing sites 2 atoms apart include acrylonitrile, dimethyl acetylenedicarboxylate, acetophenones, *C*-acetylheteroaromatics and indole. As discussed in Section 5.1, acrylonitrile reacts with five- and six-membered lactam acetals (**15a** and **15b**) to furnish 3-monosubstituted **103** (X = CN) and 3,3-disubstituted lactams **104** (X = CN) respectively. However, reaction of acrylonitrile with caprolactam acetal **15c** gave rise to 2-ethoxy-3-β-cyanoethyl enamine **106** and the cyclobutene adduct **107**, the latter obviously resulting from (2+2) condensation. Condensation of **15a** with dimethyl acetylenedicarboxylate resulted in the formation of 2,3-dihydroindole **109** by a [2+2+2]cyclocondensation and the 3-substituted products **110–113**. An elegant and convenient one-pot synthesis of tetrahydrobenzodipyrroles **148** was achieved[62] by [2+2+2]cyclocondensation of acetophenone or *C*-acetylheteroaromatic **146** with excess of pyrrolidone acetal **15a**; **148** could also be prepared in a stepwise sequence by reacting equimolar amounts of **15a** and acetophenone to furnish the enaminone **147** which on further condensation with lactam acetal **15a** gave rise to benzodipyrrole **148**. Cyclocondensation of lactam acetal **15a** with indole (**149**) provided a convenient one-pot synthesis[63] of tetrahydrodipyrrolocarbazole **151**, which could also be prepared from 3-pyrrolidinylideneindole **150** obtained by condensation of equimolar amounts of **15a** and indole, followed by reaction of **150** with lactam acetal. Lactam acetals **15** underwent [2+2+2]cyclocondensation with *o*-substituted araldehydes and aryl isocyanates/isothiocyanates to form dioxinopyrroles **122** and azacycloalkano[2,3-*d*]pyrimidines **121** respectively (Sections 5.3, 5.4). The only example reported of cyclocondensation with 3 atom units, is the synthesis[64] of benzofuran **153** by the cyclocondensation of lactam acetal with *p*-benzoquinone. Formation of a six-membered ring by cyclocondensation of lactam acetal with 4 atom units is well studied and the variety of heterocycles thus synthesized are listed in Table 2. Enaminone **84**, generated from amide acetal reacted with **15a** to furnish[65] 2,3-dihydroindole **154** while hydrogenated derivatives of indole, quinoline and benzazepine **156** were prepared[66] by reaction of acetals **15a–c** with enaminoester **155**. Reaction between pyrrolidone acetal **15a** and dimethyl homophthalate (**157**) led to a convenient synthesis[67] of benz(*f*)indole **158**. Building up of a pyridine ring across C-2 and C-3 of lactam acetals **15a–c** by [2+4]cyclocondensation include their reaction with β-substituted enamines **159**, **161**, **163** and methyl ester of β-alanine **165** to form azacycloalkanopyridine **160**, **164** and **166**.[32,68–74] A convenient one-pot synthesis of 7-deazapurine **168** was achieved[13] by [2+4]cyclocondensation of pyrrolidone acetal **15a** with *N*-acetylthiourea **167**.

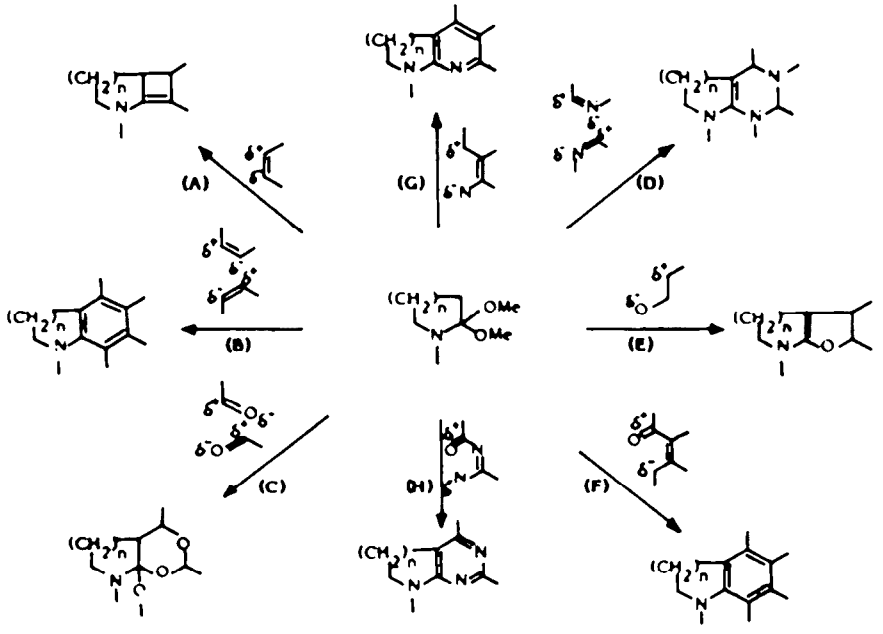
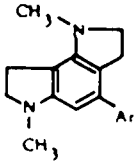
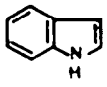
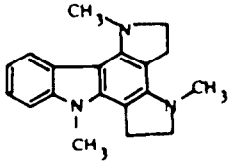
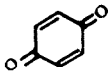
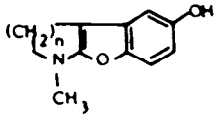
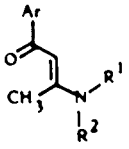
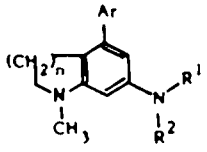
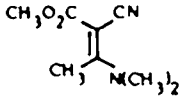
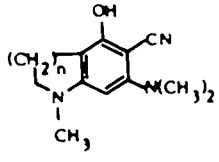
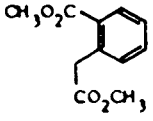
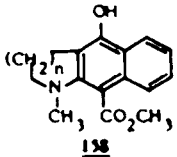
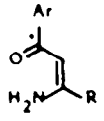
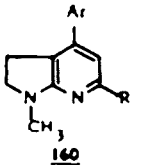
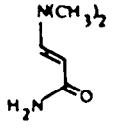
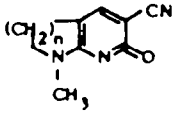


Chart 9.

Table 2. Heterocyclic systems synthesized from lactam acetals

Acetal	Reactant	Product	References
15a			62
	146	148	
15a			63
	149	151	
15a-c			64
	152	153	
15a			65
	84	154	
15a-c			66
	155	156	
15a			67
	157	158	
15a			68
	159	160	
15a-c			69
	161	162	

continued

Table 2—*continued*

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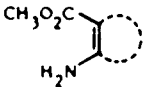
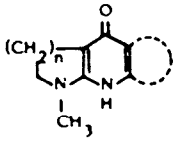
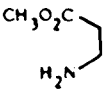
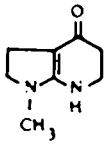
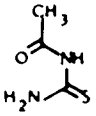
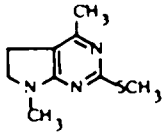
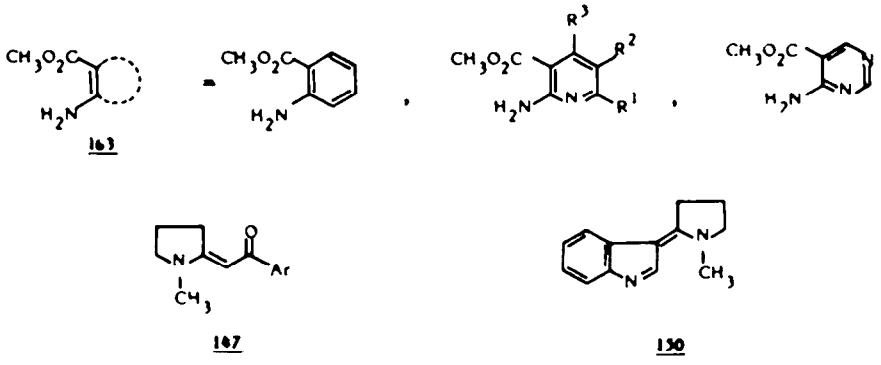
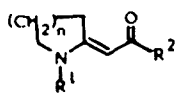
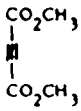
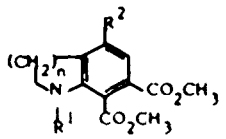
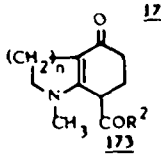
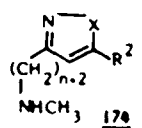
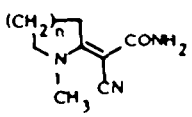
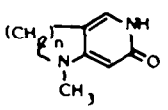
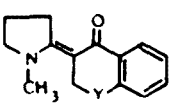
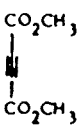
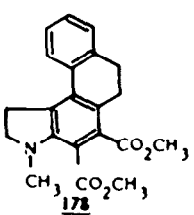
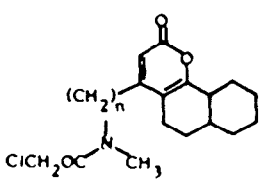
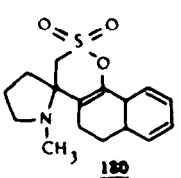
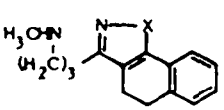
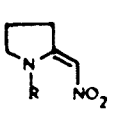
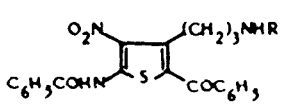
15a–c	 163	 164	70–74
15a	 165	 166	32
15a	 167	 168	13



7.2. *By use of reactive intermediates prepared from lactam acetals*

As discussed in the reactions with nucleophiles (Section 4.1–4.3), lactam acetals offer an easy access to β-functionalized enamines such as enaminones, β-nitroenamines and *N*-substituted amidines which by themselves possess suitably positioned reactive centres and synthetic utility. The reactions of enaminones prepared from lactam acetals with second molecule of lactam acetals to form various 2,3-annulated heterocycles and carbocycles has been discussed in Section 7.1. The enaminones **169** also react[75] readily with dimethyl acetylenedicarboxylate to form 4-substituted 6,7-dicarbomethoxy-2,3-dihydro-1-methylindole **170** presumably via the intermediates **171** and **172** (Table 3). Similar reaction of the cyclic enaminone **177** with dimethyleneacetylene dicarboxylate led[76] to the formation of pyrrolophenanthrene **178**. Acryloyl chloride reacted with enaminone **169** to furnish[77] hydrogenated derivatives **173** of indoles, quinolines and benzazepines, while reaction between β-substituted enamine **175** with DMF-acetal **1** formed[78,79] 1-azacycloalkanopyridones **176**. Bifunctional nucleophiles such as hydrazine hydrate and hydroxylamine hydrochloride reacted with enaminones **169** and **177** to form pyrazole and isooxazole derivatives **174** and **181** resulting from ring cleavage of the lactam ring. The ring cleavage of the lactam ring has also been observed[41] in the reaction of the cyclic enaminone **177** with chloroketene which resulted in the formation of naphthopyranone **179**, while spiro derivative **180** was formed in its reaction with sulphene. The adduct **183** formed by the reaction of β-nitroenamine **182** with benzoyl isothiocyanate furnished[80] the thiophene derivative **184** when reacted with phenacyl bromide. Phenacyl bromide also reacted with mono- and bis-amidines **75** and **74** to form the thiazole derivatives **187** and **186** respectively. The nitroenamine **182** possessing *N*-ethoxycarbonylmethyl group furnished[81] 1,4-diazabicyclo[4.3.0]nonan-3-one **185** on hydrogenation. *N*-Benzoylamidine **188** reacted with pyrroli-

Table 3. Some representative products obtained by use of reactive intermediates prepared from lactam acetals

Intermediate	Reagent	Product	Reference
 169		 170	75
	$H_2C{=}CHCOCl$	 173	77
	$NH_2{-}XH$ X = O, NH	 174	40
 175	DMF-acetal (1)	 176	78,79
 177		 178	76
	ClCH : C : O	 179	61
	$CH_2 + SO_2$	 180	61
	NH_2-XH X = O,NH	 181	61
 182	(i) C_6H_5CONCS (ii) $C_6H_5COCH_2Br$	 184	80

continued

Table 3—*continued*

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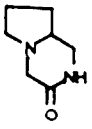
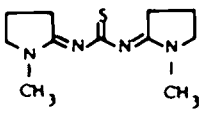
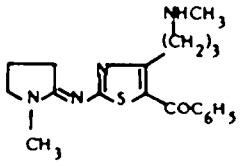
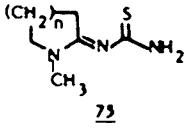
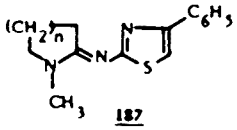
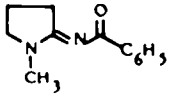
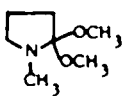
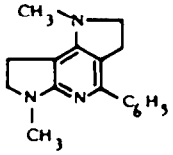
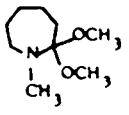
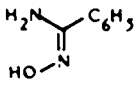
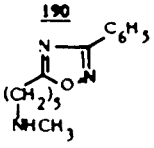
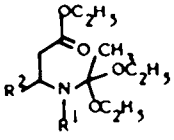
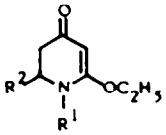
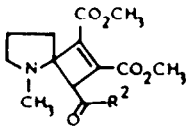
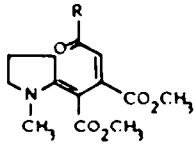
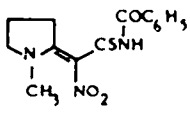
	H_2/Raney Ni R = $CH_2CO_2C_2H_5$	 185	81
 74	$C_6H_5COCH_2Br$	 186	80
 75	$C_6H_5COCH_2Br$	 187	80
 188	1.  2. $POCl_3$	 190	82
	 191	 192	83
 193	t-BuOH	 194	84

done acetal **15a** to form 2-benzoylimino-1-methyl-3-(1-methyl-2-pyrrolidinylidene)pyrrolidine **189** which furnished[82] tetrahydrodipyrrolo [2,3-*b*: 2′3′-*d*]-pyridine **190**, on intramolecular cyclization with phosphorus oxychloride. A facile and convenient synthesis[83] of oxodiazole **192** was achieved by the reaction of caprolactam acetal **15c** with *N*-hydroxyamidine **191**, while intramol-


171


172


183

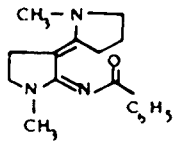
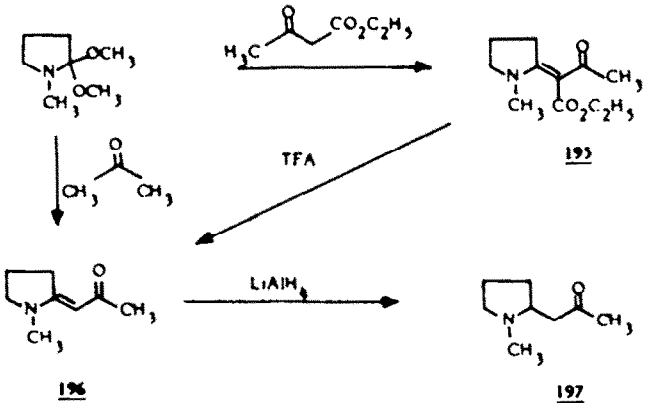

189

Chart 9a.

ecular cyclization of the acetal **193** when heated in *t*-BuOH led[84] to the formation of the dihydropyrridone **194**.

7.3. *Use for natural product synthesis*

Facile substitution of position 2 and/or 3 of lactams through acetal formation provides good scope for the synthesis of various natural products such as pyrrolidine, piperidine, indole and quinoline alkaloids. A convenient and short synthesis of a pyrrolidine alkaloid hygrine **197** has, in fact, been achieved[85] by selective reduction of the enamine **196** generated either by the reaction of the pyrrolidone acetal **15a** with acetone or decarboethoxylation of the condensation product (**195**) of **15a** and ethyl acetoacetate (Scheme 26). Earlier synthesis of hygrine[86] (**197**) involved multisteps starting from α-pyrrylmagnesium bromide.



Scheme 26.

8. CONCLUSION

The foregoing review describes that in lactams and amides greatly enhanced reactivity towards nucleophiles and electrophiles at positions 2 and 3 respectively can be achieved through acetal formation, which provides vast scope for preparation of 2 and/or 3-substituted heterocycles and for building 2,3- and 1,2-annulated carbocyclic and heterocyclic rings on them. These acetals are also useful reagents for *N,S,O*-alkylation reactions and for diesterification of anhydrides under almost neutral conditions.

Acknowledgement—We express our grateful thanks to BASF India Limited for the liberal gift of many chemicals used in this investigation.

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