beta-Lactams as Synthons.[1] Synthesis of Heterocycles via beta-Lactam Cleavage 祝古稀

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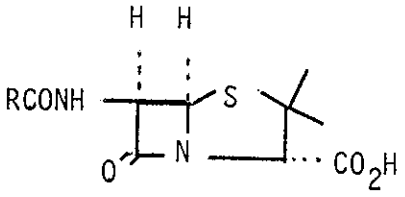
beta-Lactams show high chemical reactivity and ease of molecular rearrangement and are therefore potential synthons of value. The present communication reviews the relevant literature and describes observation made in our laboratory and elsewhere. Suitably substituted beta-Lactams can lead to multi-heteroatom cyclic compounds of various sizes including derivatives of carbostyril, coumarin, diazepin, oxazepin and thiazepin of potential interest to synthetic and medicinal chemists.

祝古稀 Dedicated to Dr. Ken'ichi Takeda on his seventieth birthday.

1. Introduction

Currently beta-lactams are receiving considerable attention from organic and medicinal chemists because of the widespread natural occurence of beta-lactam antibiotics such as penicillins (1), cephalosporins (2), cephamycins (3), bleomycins (4), *nocardicin* A (5) (2), clavulinic acid (6) (3), and thienamycin (7) (4) and the commercial success of some of them. Most of the activity at present is centered around the synthesis of variously substituted monocyclic, bicyclic - and polycyclic - beta-lactams. The fragility of the beta-lactam ring in penicillins and the ease of molecular rearrangement of this heterocyclic unit have added to the difficulty of the synthesis of penicillins and analogs (5). Recent work has demonstrated, however that although many beta-lactams undergo cleavage or rearrangement under mild conditions, a number of monocyclic as well as polycyclic beta-lactams can survive a diversity of reagents if reactions are conducted at very low temperatures or in the absence of hydroxylic and polar solvents (6).

Cleavage reactions of beta-lactams have received only cursory attention from the point of view of the synthesis of new structures. Studies during the last few years in several laboratories including our own have resulted in the development of convenient methods for preparing variously substituted beta-lactams. (7) Recently we have explored the utility of substituted monocyclic beta-lactams as a source of the -CO-C-C-N- synthon (7a) for the preparation of different heterocycles (see Scheme I). We have also studied the cleavage of the 1,4-bond of 2-azetidinones fused to another ring to obtain 8- or 9-membered ring compounds containing the -C-C-CO-N- unit (7b) as part of the ring. The present communication reviews the relevant literature and describes some of the observations made in our laboratory.



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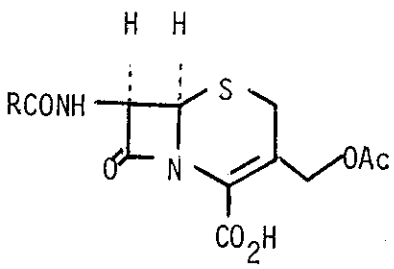

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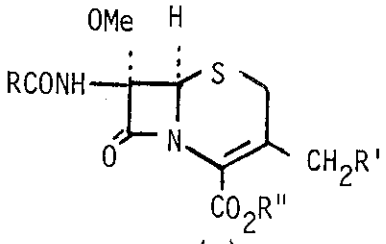

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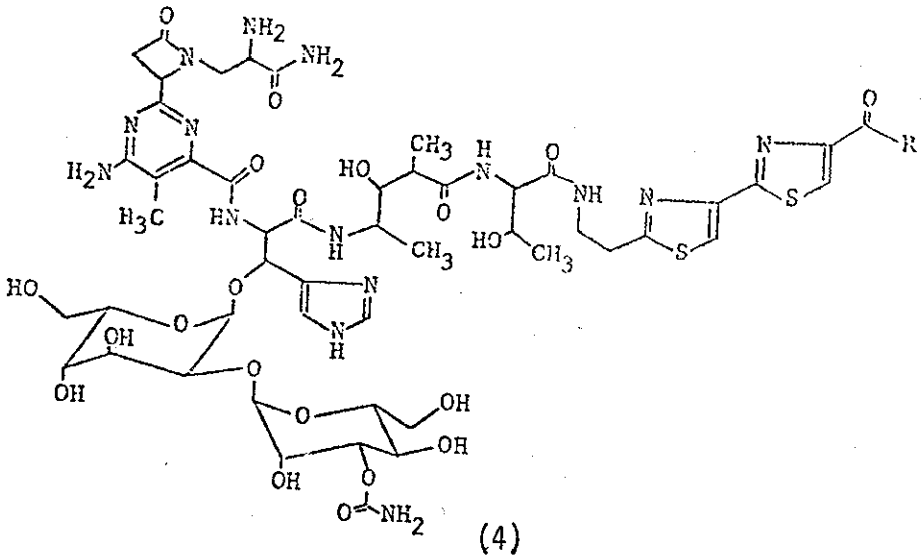

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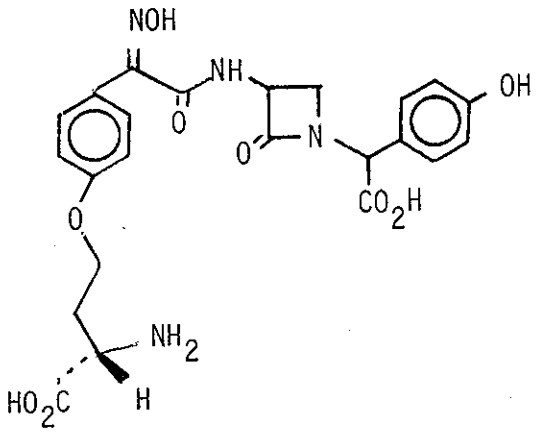

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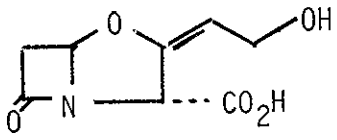

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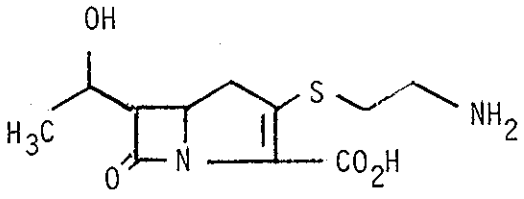
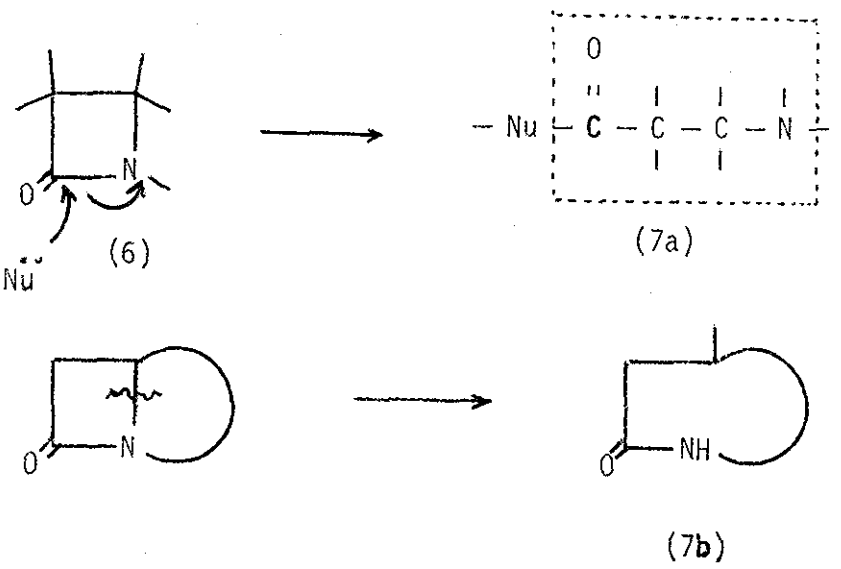


(7)

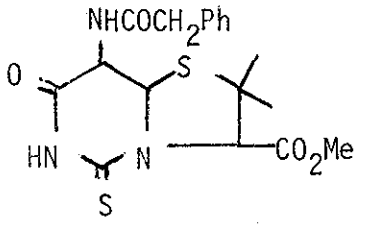
Scheme I



2. Heterocycles via Intermolecular Cleavage of the Amide Bond

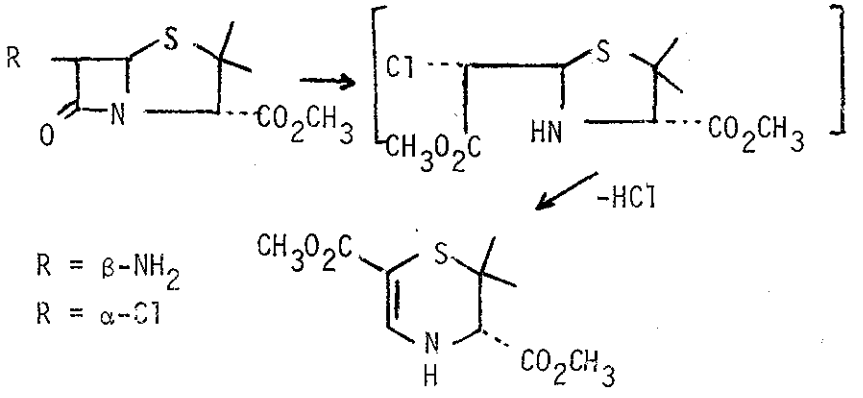
In the course of penicillin research during World War II the unusual chemical reactivity of the beta-lactam amide bond was recognized. The ready cleavage of this bond by reaction with various nucleophiles as well as diverse rearrangement reactions of the beta-lactam group have been adequately reviewed (6,7). Therefore, mention will be made here of only selected reactions that lead to interesting heterocycles.

du Vigneaud and coworkers (5) studied the reaction of ammonium thiocyanate and acetic anhydride with methyl benzylpenicillin. The isolation of the thiodihydrouracil (8) in this reaction established that the site of reaction is the amide bond in the beta-lactam part of the molecule.



(8)

More recently Stoodley **(8)** reported a deep seated rearrangement of methyl 6β-animopenicillanate (9) in the presence of sodium nitrite and hydrochloric acid in aqueous methanol solution. The formation of a 1,4-dihydrothiazine derivative (11) was assumed to involve the intermediate formation of methyl 6-chloropenicillanate (10) which undergoes beta-lactam ring cleavage under the influence of methanol and then rearranges.

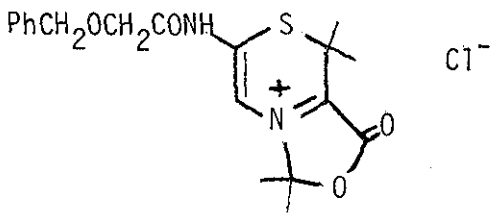


(9) R = β-NH_2

(10) R = α-Cl

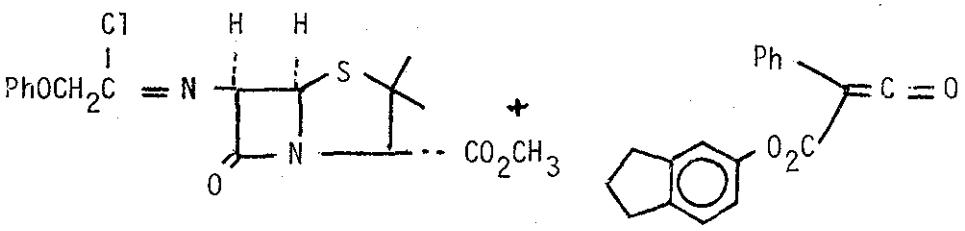
(11)

Treatment of penicillin V sulfoxide with an equivalent quantity of phenylacetylchloride in acetone solution at room temperature resulted in the formation of a 1,4-thiazine (12) the structure of which was determined by x-ray crystallography (9).

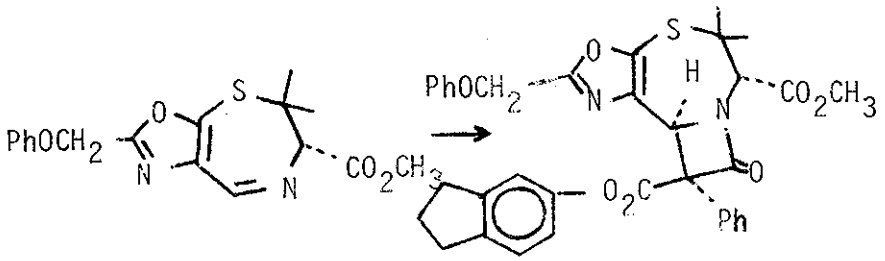


(12)

Recently a deep seated rearrangement (10,11) of penicillin V methyl ester iminochloride (13) during its reaction with phenyl - 5 - indanyloxycarbonylketene (14) has been reported in which a new tricyclic beta-lactam (16) is one of the products. The thiazepine (15) must be formed during this rearrangement to account for the formation of (16).

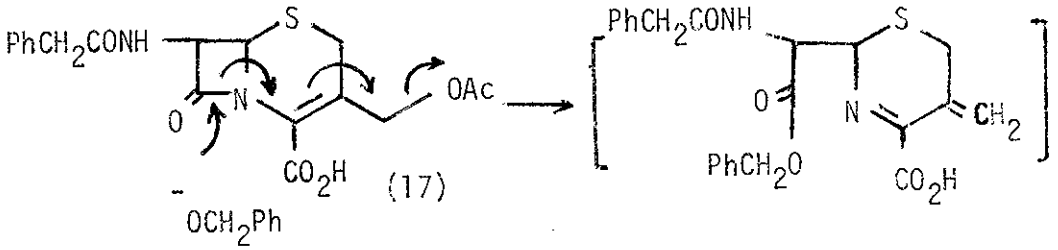


(13) (14)



(15) (16)

Not many rearrangement reactions of cephalosporins have been observed because of the relative stability of the beta-lactam ring system. A few years ago the Oxford group (12) reported beta-lactam cleavage in cephalosporins under the influence of nucleophiles. In the presence of sodium benzyl-oxide, cephaloram (17) undergoes beta-lactam amide bond scission and simultaneous elimination of the allylic acetoxy group resulting in a 1,3-thiazine derivative (18).



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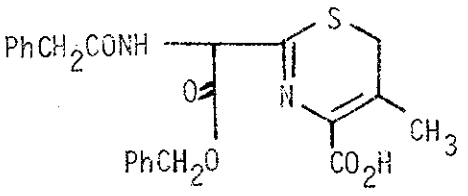
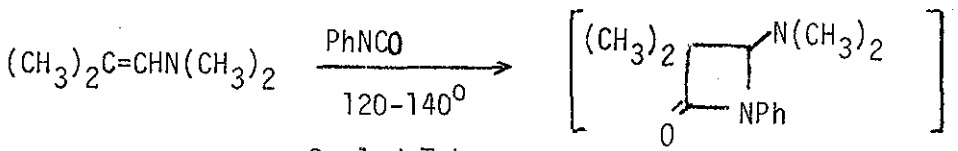


(18)

We (13) have found that enamines and isocyanates react when heated in a sealed tube at about 120° leading to the formation of dihydrouracils (20). In all probability a beta-lactam (19) is involved as an intermediate followed by ring expansion. At about this time the synthesis of some beta-amino-beta-lactams by the interaction of selected enamines and isocyanates under mild reaction conditions were reported by other laboratories (14,15). Compounds of the type (20) were readily hydrolyzed and oxidized to substituted barbiturates (21) (13).



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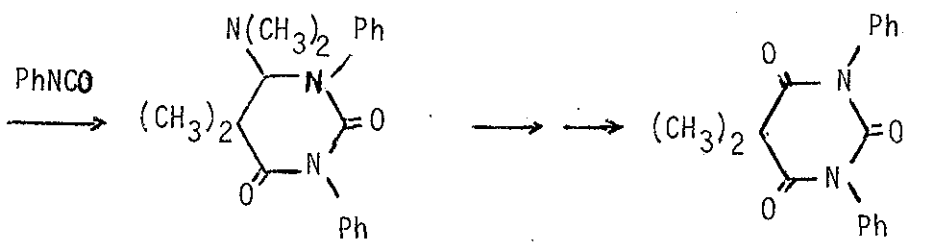
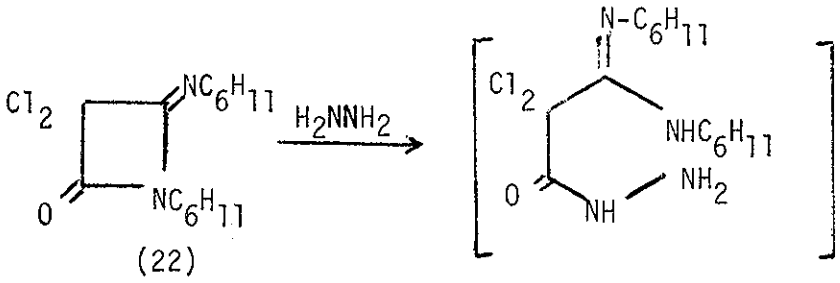


(20) (21)

The reaction of a 4-imino-2-azetidinone (22) with hydrazine (16) to give a pyrazolone (23) involves the scission of the amide bond of the beta-lactam with subsequent loss of the amino nitrogen of the -CO-C-C-N- fragment.



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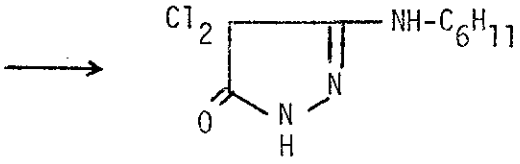
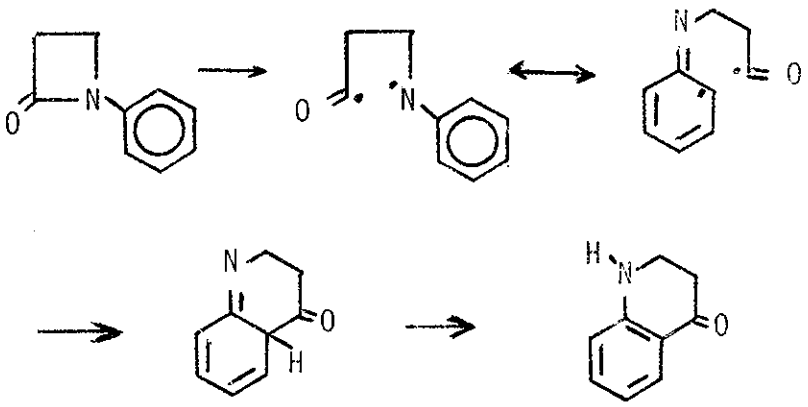


(23)

Photolytic scission of the amide bond in N-phenyl beta-lactams (17) leads to intramolecular transacylation reactions resulting in novel heterocyclic ring systems (24).

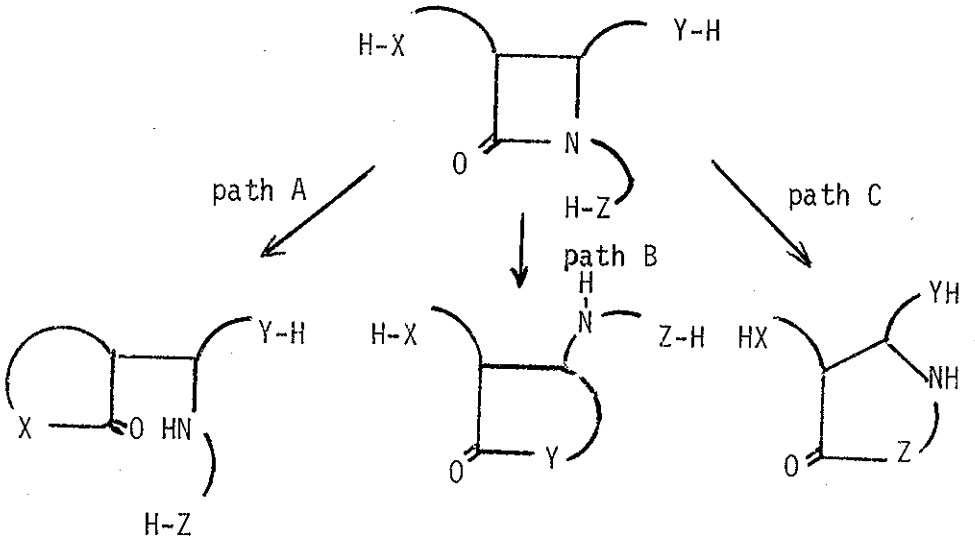


(24)

3. Heterocycles via Intramolecular Cleavage of the Amide Bond

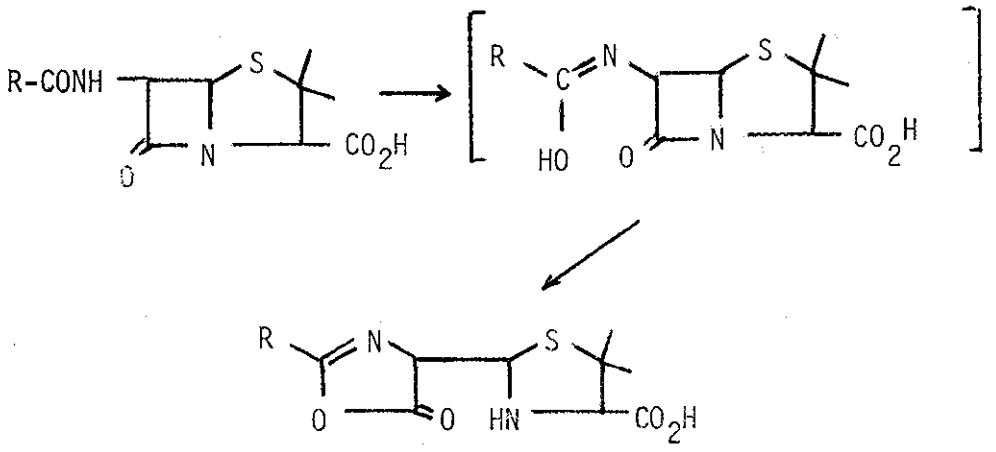
A generalized representation of intramolecular rearrangement reactions involving the scission of the beta-lactam amide bond that we have studied is given in Scheme II. Also included in the following discussion are examples from the literature that fit these categories.

Scheme II



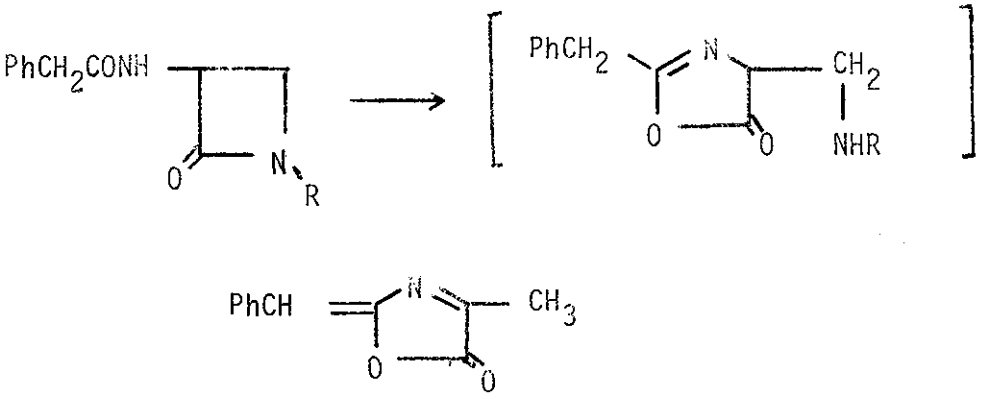
(a) *Nucleophile on the C_3 - substituent:* (path A)

The controversy (5) about the structure of penicillin in the early stages of penicillin research was largely due to the ease of scission of the beta-lactam through a nucleophilic attack by the amide side chain. The thiazolidine - oxazolidinone (25) obtained through this rearrangement was favored at one time by many as the structure for penicillin itself.



(25)

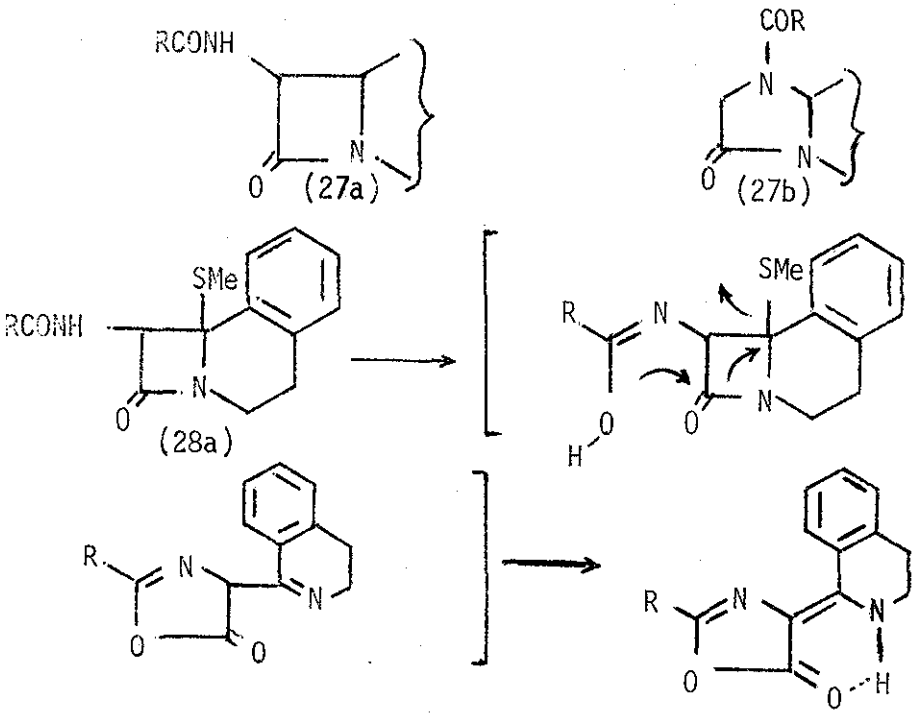
Monocyclic beta-lactams bearing an amide side chain at C_3 undergo similar ring cleavage (5) when they are refluxed in anisole. Beta-elimination accompanied by rearrangement of the product leads to oxazolones (26).



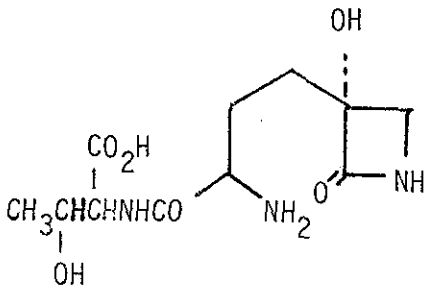
(26)

α-Amido-beta-lactams (27a) undergo ring expansion reaction when heated with a catalytic amount of iodine in xylene solution. In this reaction, 3,4- and 1,4- bonds of the beta-lactam suffer cleavage via the participation of the amide side chain to afford the rearranged imidazolidones (27b). Monocyclic beta-lactams as well as penicillins are susceptible to this reaction. The mechanism of this reaction has been the subject of some speculation (18).

When we (19) subjected the beta-lactam (28a) to this rearrangement reaction, the product lacked the characteristics of the expected imidazolidone and its mass spectrum indicated the absence of the equivalent of a CH_3SH group. On the basis of spectral data and single crystal x-ray analysis, the product was identified as the oxazolone (28b). Apparently the presence of the sulfide grouping at C_4 of the beta-lactam alters the course of the normal reaction.



(28b)



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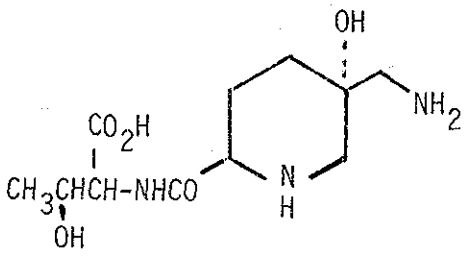
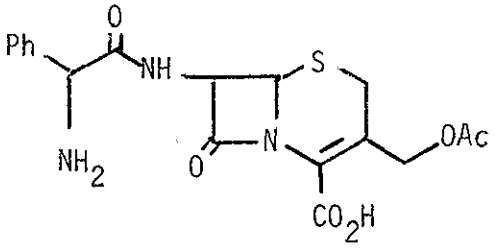


(30)

The relative instability of tabtoxin (29) at room temperature or at neutral pH has been explained as originating from the translactamization of the strained 4-membered ring to the more stable non-toxic δ-lactam isomer, isotabtoxin (30) **(20)**.

Recently it has been observed **(21)** that the 7-amino-cephalosporanic acid derivative (31) undergoes beta-lactam ring fission at pH 5-6 through the participation of the side chain amino group to form a diketopiperazine derivative (32).



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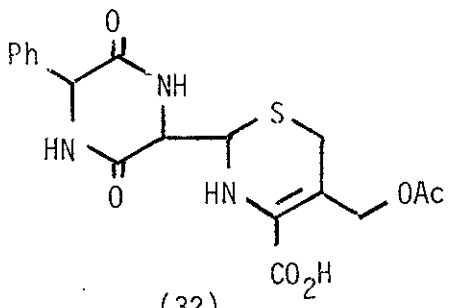
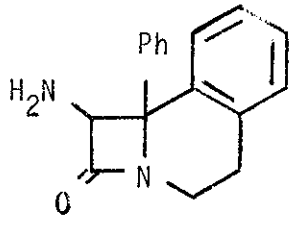


(32)

In our laboratory we **(22)** attempted to condense an α-amino-beta-lactam (33) with ethylene oxide with the aim of preparing an aminoethanol (34) but the reaction product was found to be a morpholine derivative (35). Apparently the desired product underwent facile rearrangement. Interestingly, reaction with an excess of acetyl chloride and triethylamine gave an N-mono acetylation product to which the structure (36) has been assigned on a tentative basis.



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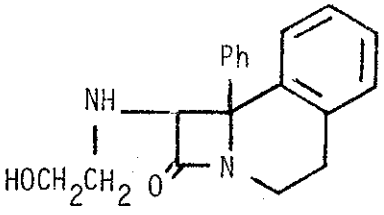

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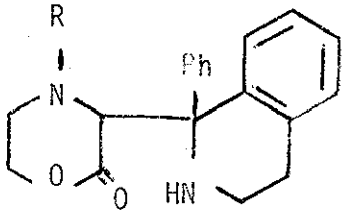
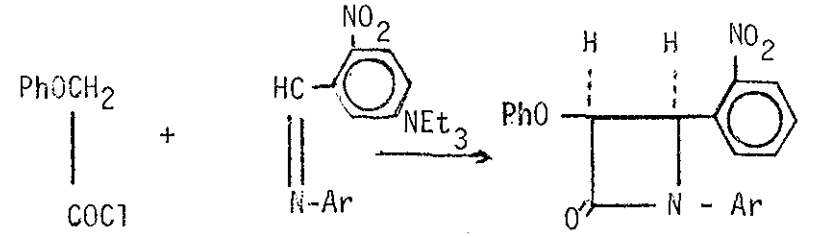


(35) R = H

(36) R = Ac

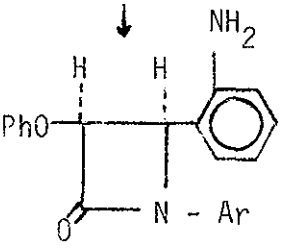
(b) *Nucleophile on the C_4 substituent:*
(path B)

Recently we **(22)** have studied several examples of this type. Condensation of o-nitrobenzaldehyde with p-toluidine gave readily the Schiff base (37) which was annelated to a **cis**-beta-lactam (38). Catalytic reduction of the nitro group produced the anilino derivative (39) which could be N-acetylated. However, on treatment with p-toluenesulfonic acid or triethylamine, rearrangement involving scisssion of the beta-lactam took place and a product was obtained which could be assigned the structure (40). As expected, the **cis** protons in (38) assumed the **trans** disposition in (40): these protons showed an AB pattern of J = 6 Hz in (40).



(37)

(38)



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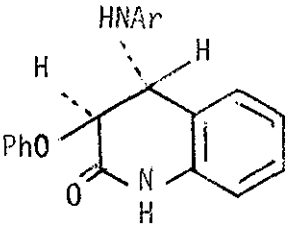
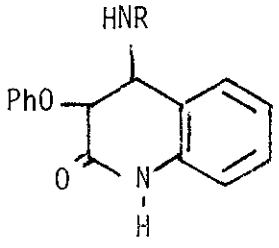


(40)

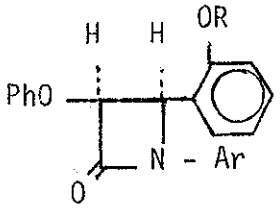
Other α-lactams prepared by this method were (41) and (42).

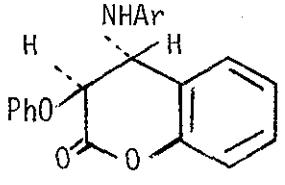


(41) R = C_6H_{11}

(42) R = $CH_2CH(OEt)_2$

The **cis** beta-lactam (43) was prepared using a silylation procedure described previously by us **(23)**. Upon removing the protective trimethylsilyl group the phenol--substituted beta-lactam (44) underwent rearrangement to a δ-lactone analog (45) of the δ-lactam (40). The two aliphatic hydrogens in (45) were **trans** to each other and showed a coupling constant of 6Hz.

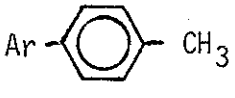




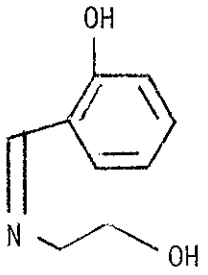
(45)

(43) R = $SiMe_3$

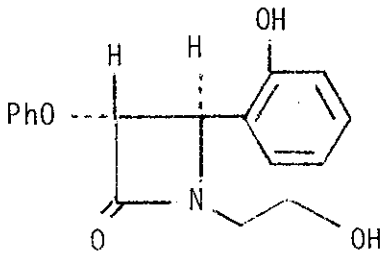
(44) R = H



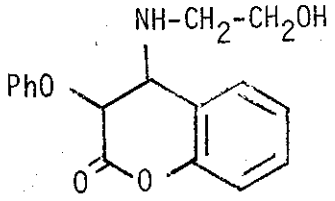
The amide ring cleavage through the intermediacy of the o-hydroxy group on the C_4 -arylsubstituent is extremely facile. The beta-lactam (47) obtained from (46), phenoxyacetyl chloride and triethylamine undergoes rearrangement to 3-phenoxy-4-(2'-hydroxyethylamino)-3,4-dihydroconmarin (48) during crystallization (24).



(46)



(47)

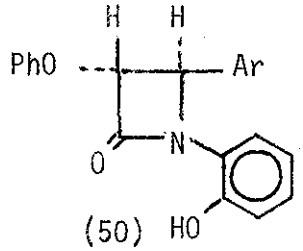


(48)

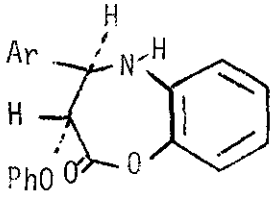
(c) *Nucleophile on the N-substituent:* (path C)

In the course of another study **(22)** we used the trimethylsilyl protective group to prepare the beta-lactam (50). Under the influence of organic acids or bases this four-membered heterocycle underwent rearrangement as well as ring enlargement to give the 7-membered heterocycle (51). The small size (2Hz) of the coupling between the adjacent protons in (50) indicated **trans** stereochemistry for the beta-lactam. This steric disposition was unaltered by ring expansion as is to be expected: the coupling (J = 6Hz) shown by the two aliphatic protons in (51) is consistent with the **trans** configuration of these two protons.

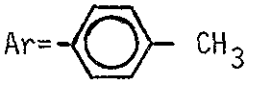
In a similar fashion the beta-lactam (52) underwent ring expansion to give the 7-membered cyclic amide (53). The coupling between the two aliphatic protons was 9Hz - an indication of their **trans** stereochemistry.

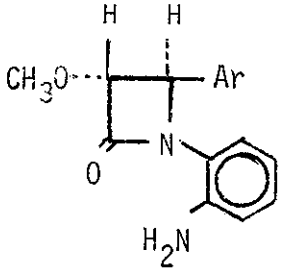


(50)

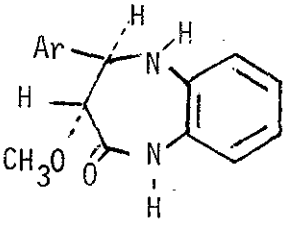


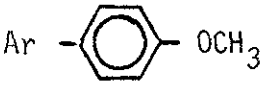
(51)





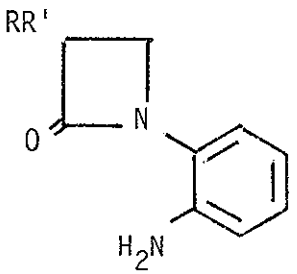
(52)





(53)

This type of beta-lactam ring cleavage to yield 1,5-benzodiazepines had been reported previously by Testa and coworkers **(25)**. Thus, refluxing beta-lactams of the general structure (54) in hydrochloric acid the 7-membered heterocycles (55) were obtained.



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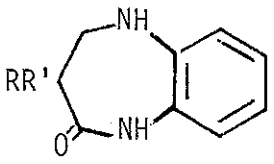
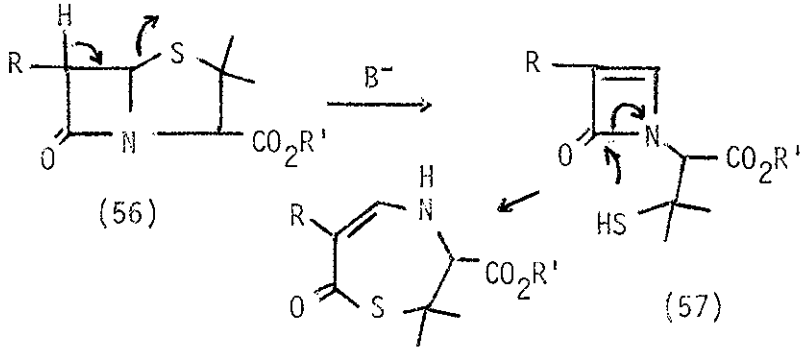


(55)

Base catalyzed epimerization of penicillin **(26)** has been extensively studied. Several laboratories have observed the formation of thiazepinones (58) from various penicillins (56) under the epimerization conditions. It has been suggested that an unsaturated beta-lactam (57) is formed as a key intermediate which undergoes the beta-lactam amide bond cleavage under intramolecular nucleophilic attack by the newly freed mercapto group in (57).



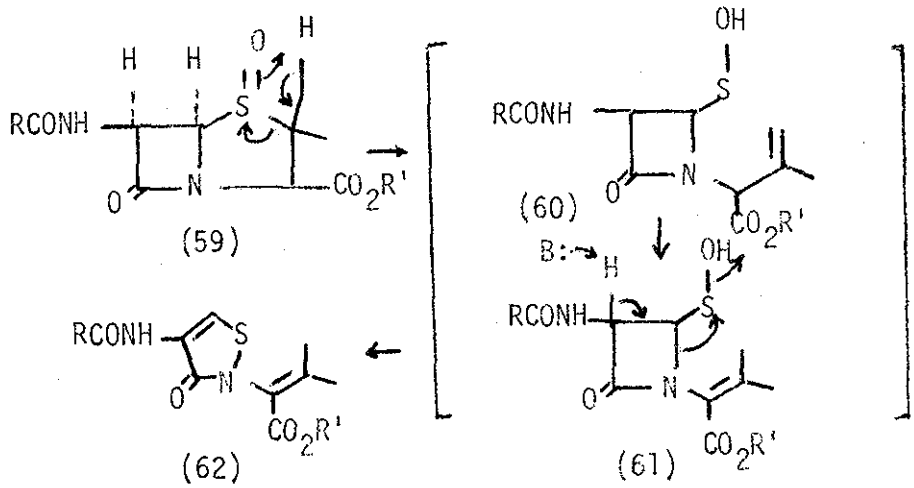
(56)

(57)

(58)

Base catalyzed epimerization of penicillin sulfoxides can take a different course as regards the formation of byproducts. In our laboratory (27) 1,5-diazabicyclo 4.3.0 non-5-ene(DBN) was discovered to be a convenient base for the epimerization of beta-lactams. When we used this reagent on methyl benzylpenicillanate sulfoxide (59,R=$PhCH_2$,R'=CH_3) in chloroform solution (28), epimerization at C_6 occurred and a mixture of cis and trans (1:2) isomers was obtained in 10 minutes. The addition of a drop of dimethyl sulfoxide to a fresh chloroform solution of the penicillin sulfoxide containing DBN resulted in complete isomeriaztion to the 6α-epimer almost instantaneously. Several laboratories have reported the successful use of DBN for the epimerization of the amide side chain of penicillin derivatives (29).

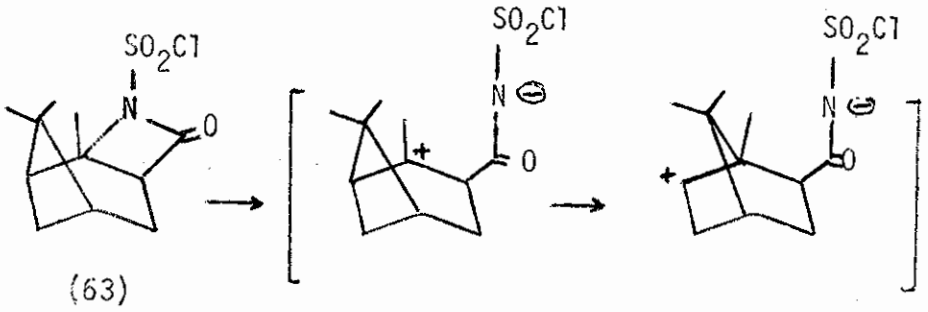
We observed (28) that when a chloroform solution of the sulfoxide (59) and DBN were allowed to stand for a few hours, considerable decomposition of the penicillins occurred. The by-product isolated in about 15% yield corresponded to the sulfoxide (59) less a molecule of water. In the light of a recent publication (30) this by-product is identified as the isothiazolone (62,R=$PhCH_2$,R'=CH_3). This type of compound had been obtained as a by-product in about 1% yield by Morin et al (31) in the course of the rearrangement of penicillin sulfoxides to cephalosporin structures. Fukumara and coworkers (30) have shown that the yield of the isothiazolone (61) is increased when the acidity of the 6-H and 3-H are increased by using appropriate side chain and ester groups. A plausible intermediate is the 1,2-secopenicillin (60) which could undergo a ring enlargement reaction initiated by loss of the proton adjacent to the beta-lactam carbonyl.



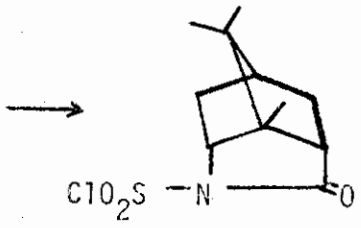
4. Heterocycles via the Cleavage of 1,4-Bond.

The intramolecular cleavage of 1,4-bond in beta-lactams is not a very common reaction. Isolated cases have been reported in the literature in which this type of cleavage results in rearranged products with enlarged rings. There does not appear to be a common mechanistic pathway that can account for all the known reactions. Obviously the relief of the ring strain in the fused beta-lactam structures leading to thermodynamically more stable heterocyclic systems appears to be the driving force in such reactions. Such cleavage reactions may take place spontaneously or under the influence of chemical reagents. Studies related to the 4-5 bond cleavage in penicillin series have recently been reviewed by Stoodley (7a).

Furst and coworkers (32) noticed that the beta-lactam (63) obtained through the reaction of chlorosulfonyl isocyanate with beta-pinene spontaneously rearranges to the γ-lactam (64).

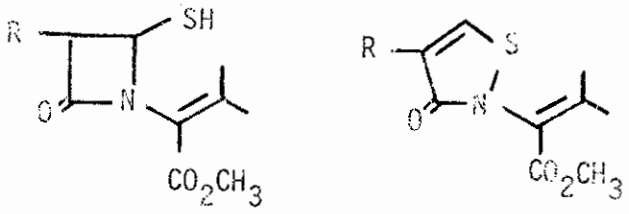


(63)



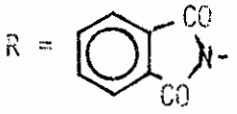
(64)

The 1,4-bond cleavage in beta-lactams leading to rearranged products has also been observed by Bachi and Goldberg **(33)**. Thus, the monocyclic beta-lactam (65) in dimethyl sulfoxide rearranges to (66) through oxidative ring cleavage. These findings are in full accord with the mechanism suggested earlier for the conversion of (59) to (62) under the influence of DBN.

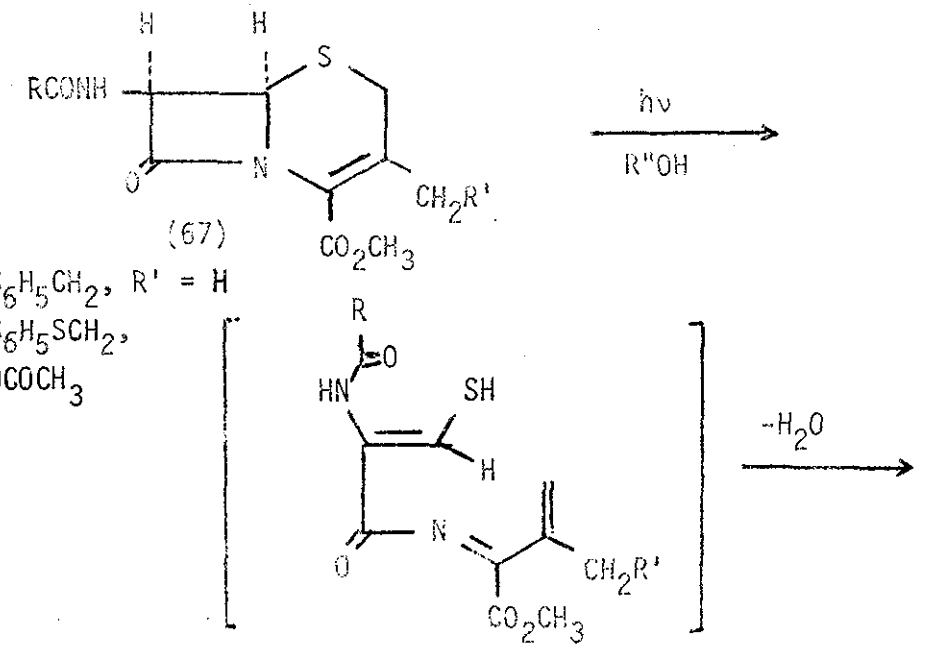


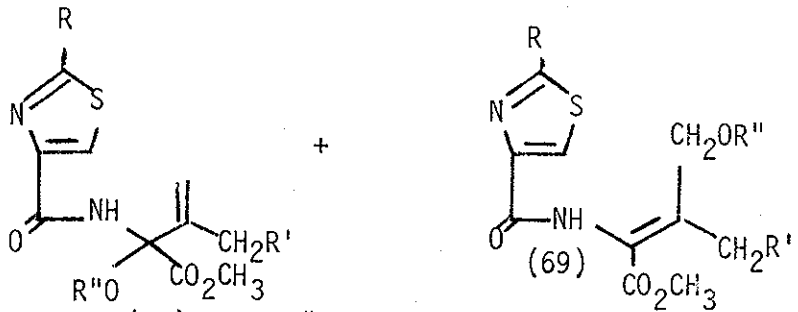
(65)

(66)



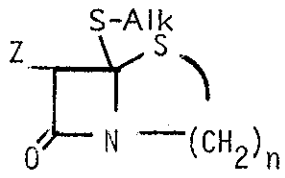
Maki and Sako (34) have recently reported profound structural change when 7-acylamido-3-cephem derivatives were subjected to ultraviolet irradiation of their alcoholic solutions. Thus, when (67) was photolyzed using a high-pressure mercury arc lamp, novel rearrangement products (68) and (69) were isolated. Evidently, a key step in this rearrangement is the scission of the N-C_6 bond of the cepham system with subsequent incorporation of the solvent.



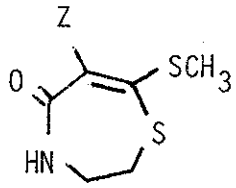


(68) R" = CH_3 or C_2H_5

Synthetic work in our laboratory has led to a convenient method for preparing bicyclic beta-lactams of type (70). These beta-lactams are fairly stable under most conditions but they undergo ready rearrangement in presence of trifluoroacetic acid; the products are 1,4-thiazepines (71) formed through an N-C bond cleavage **(35)**. Under similar conditions penicillin G methyl ester is degraded to thiazoline-4-carboxylate (72) **(36)**.



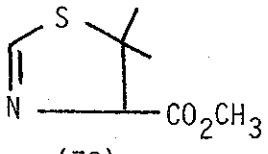
(70)



(71)

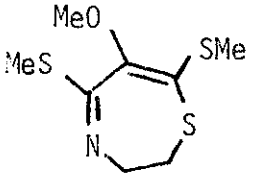
Z = OR, N_3, NHCOR

n = 2 or 3

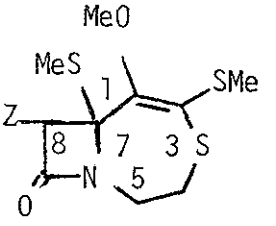


(72)

The 1,4-thiazepine derivative (71) is a convenient intermediate for the synthesis of fused beta-lactams. Following methods developed earlier (37) in our laboratory, (71) was thioamidated and then alkylated to produce a cyclic thiomidate (73). Annelation of this heterocycle with substituted acetyl chlorides and triethylamine let to the 3-thia-1-nonem (1b)(74). Obviously, acid catalyzed rearrangement of (74) would lead to a 9-membered heterocycle which could give a 3-thia-1-undecam (1b) through annelation to a fused beta-lactam.



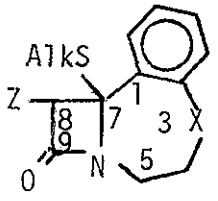
(73)

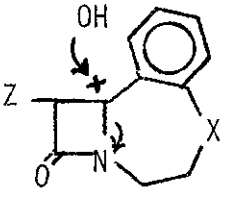


(74)

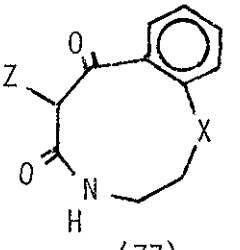
Z = OMe, OPh or N_3

3-Oxa- and 3-thiaoctam derivatives of type (75) are conveniently prepared by synthetic approaches developed in our laboratory (24). These beta-lactams undergo an interesting rearrangement in the course of attempted oxidation with sodium periodate in aqueous isopropanol; some medium-sized polyhetero rings of type (77) were obtained in high yield (24).





(76)



(77)

(75) X = S or O, Z = OCH_3 or N_3

This rearrangement could arise through the intermediate formation of a sulfoxide which under acidic conditions gave the carbonium ion (76). Nucleophilic attack of the hydroxyl ions followed by ring opening results in the rearranged product. Interestingly enough the ring sulfur in (75,X=S) is not affected under these conditions. This ring expansion reaction provides an easy access to some medium-sized polyhetero rings which are not readily accessible by other methods.

5. Conclusion

The beta-lactam has been shown here to be a versatile synthon for the preparation of medium sized heterocycles with one or more heteroatoms in the ring. Some of the rearrangement products of strategically substituted beta-lactams lead to medium size lactams which can be the starting point of bicyclic beta-lactams using methods developed in our laboratory. The rearrangement of these beta-lactams in turn can provide access to polyheteroatom ring systems not readily prepared by other methods. Many of the heterocycles obtained from beta-lactams are of interest to synthetic and medicinal chemists.

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