Synthetic Routes to β-Lactams

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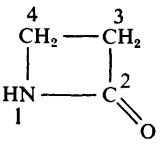
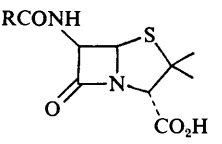
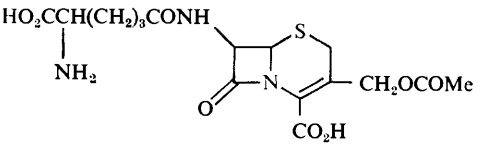
The four-membered β-lactam (2-azetidinone) ring system (1) has for many years been of great practical significance as the centre of reactivity of the penicillins (2) and cephalosporins (3). Much effort has been put into the synthesis of simpler



(1)



penicillin G (2) R = $PhCH_2$



cephalosporin c (3)

β-lactams for testing as antibiotics, antidepressants, sedatives, *etc.*,[1,2] and great interest has been aroused by their conversion into linear polymers. Numerous routes to these compounds have been devised over the years, although much of the information is to be found in the patent literature, and a wide variety of structural types is now available by rational syntheses. A review of the earlier literature by Sheehan and Corey[3a] contains representative synthetic procedures. Other aspects of synthesis have been reviewed more recently.[3b,c]

[1] E. Testa, L. Fontanella, G. F. Cristiani, and F. Fava, *Annalen*, 1958, **614**, 158; E. Testa, A. Bonati, G. Pagani, and E. Gatti, *ibid.*, 1961, **647**, 92; E. Testa, L. Fontanella, and L. Mariani, *ibid.*, 1963, **660**, 135; E. Testa, L. Fontanella, and M. Bovara, *ibid.*, 1964, **671**, 97; E. Testa and L. Fontanella, *ibid.*, 1964, **671**, 106; E. Testa, L. Fontanella, and V. Aresi, *ibid.*, 1964, **673**, 60.

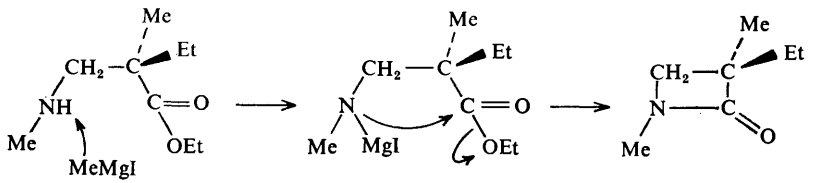
[2] E. Testa, L. Fontanella, and F. Fava, *Farmaco Ed. Sci.*, 1958, **13**, 152; E. Bellasio, A. Vigevani, G. F. Cristiani, and E. Testa, *ibid.*, 1970, **25**, 347; L. Fontanella, G. Pifferi, *ibid.*, 1972, **27**, 527; L. Fontanella, G. Pifferi, E. Testa, and P. Consonni, *ibid.*, 1973, **28**, 105.

[3] (*a*) J. C. Sheehan and E. J. Corey, in 'Organic Reactions', Wiley, New York, 1957, Vol. 9, Chap. 6; (*b*) P. G. Sammes, *Chem Rev.*, 1976, **76**, 113; (*c*) A. K. Mukerjee, and R. C. Srivastiva, *Synthesis*, 1973, 328; K. Hensler, *Helv. Chim. Acta*, 1972, **55**, 388.

1 Ring-closures of C_3N Systems

In principle, it is possible to construct the 2-azetidinone ring by cyclization at each of the four bonds, and examples of at least three of these four possibilities are known.

A. Cyclization of 3-Aminopropanoic Acid Derivatives.—The obvious synthesis of a β-lactam, dehydration of 3-aminopropanoic acid, is not readily achieved owing to the ring strain engendered on lactamization. Few examples of this method are known,[4] though heating in DMSO at 150 °C has recently been claimed[5] to yield the parent compound satisfactorily. Two versatile methods of this type have been developed and extensively used by Testa, Fontanelli, and co-workers in a long series of papers and patents recording the syntheses of hundreds of examples. The first approach, pioneered by Holley and Holley,[6] consists of treating a 3-aminopropanoate ester with a Grignard reagent, forming the β-lactam in one operation (Scheme 1). Yields were originally very low,[6]

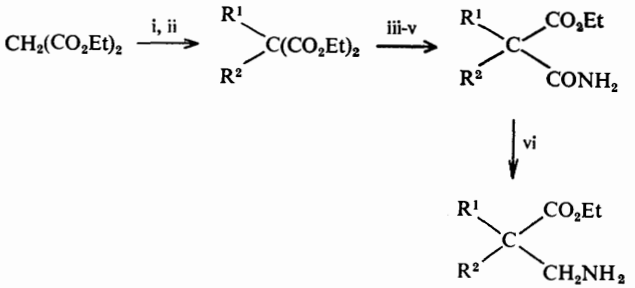


Scheme 1

but under optimum conditions 50—90% conversion may be achieved.[1,2,7,8] This method is capable of yielding a wide variety of alkyl and aryl derivatives with up to five substituents at N, C-3, and C-4. Acetic anhydride,[9] acetyl chloride–PCl_5,[10] and alanes[11] have been proposed as cyclizing agents. The second classical approach uses thionyl chloride or a similar reagent in the presence of a weak base. A β-aminopropanoyl chloride is formed which spontaneously cyclizes. Again, this approach is very versatile[9,12–14] for alkyl- and aryl-substituted β-lactams. Both these methods permit the retention of stereochemistry at the α- and β-carbons and the incorporation of chiral centres at C-3 and C-4 of the lactam ring.[12] The principal disadvantages lie in the limitations on certain functional groups, *e.g.* hydroxyl and carbonyl, which would react

[4] E. Jucker, A. Ebnoether, E. Rissi, A. Vogel, and R. Steiner, *Chem. Abs.*, 1963, **59**, P11 425*c*.
[5] T. V. Stezhko, S. Y. Skachilova, and M. G. Pleshkov, *Zhur. org. Khim.*, 1974, **10**, 1556.
[6] R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, 1949, **71**, 2124, 2129.
[7] E. Bellasio, A. Vigerani, and G. F. Cristiani, *Farmaco Ed. sci.*, 1970, **25**, 409.
[8] B. I. Kurtev, N. M. Mollov, E. M. Simova, and Y. Stefanovski, *Compt. rend. Acad. bulg. Sci.*, 1960, **13**, 167.
[9] A Dobrev and C. Ivanov, *Chem. Ber.*, 1971, **104**, 981.
[10] E. Testa and L. Fontanella, *Chem. Abs.*, 1962, **56**, P1429f.
[11] R. B. Woodward, *Chem. Abs.*, 1971, **75**, P140 833.
[12] K. D. Kampe, *Chem. Abs.*, 1970, **73**, P45 313.
[13] L. Fontanella and E. Testa, *Annalen*, 1959, **622**, 117.
[14] F. F. Blicke and W. A. Gould, *J. Org. Chem.*, 1958, **23**, 1102.

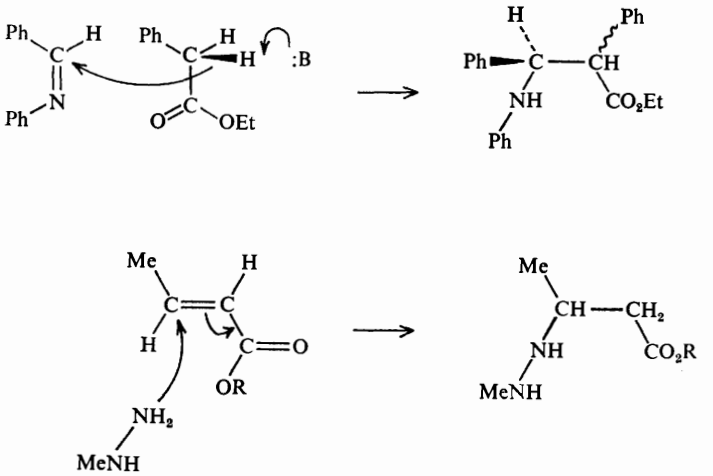
with the Grignard reagent or thionyl chloride, and also in the lengthy synthesis of the appropriate starting materials. For example, the route shown in Scheme 2



Reagents: i, OEt^-, R^1Cl; ii, OEt^-, R^2Cl; iii, OH^-; iv, $SOCl_2$; v, NH_3; vi, H_2, catalyst

Scheme 2

has been extensively used by the Italian workers. Alternatively, Michael addition of a carbanion to an imine[15] or of an amine to an acrylate[16,17] will yield the β-aminopropanoates more directly (Scheme 3).



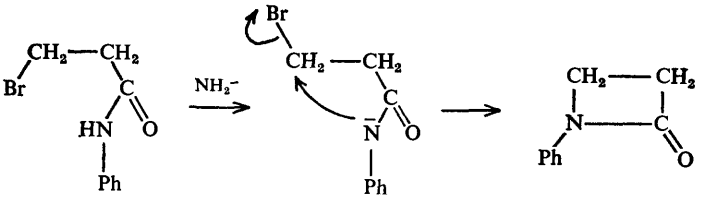
Scheme 3

Some instances are known in which the addition of a primary amine to a β-halogenopropanoyl halide leads directly to the β-lactam. One supposes that initial attack occurs at the β-carbon rather than at the carbonyl group[18] otherwise

[15] E. Simova and B. Kurtev, *Monatsh.*, 1965, **96**, 722.
[16] N. P. Zapevalova, T. A. Sokolova, N. M. Bazhenov, and A. I. Kol'tsov, *Doklady Akad. Nauk S.S.S.R.*, 1963, **150**, 551.
[17] T. A. Sokolova and L. A. Orsyannikova, *Doklady Akad. Nauk S.S.S.R.*, 1962, **143**, 140.
[18] B. J. R. Nicholaus, E. Bellasio, G. Pagani, and E. Testa, *Gazzetta*, 1963, **93**, 618.

a β-halogenoamide would result, and these are known to need strong base to effect cyclization.[19,20]

B. Cyclization of 3-Halogenopropanoamides.—Internal displacement of halide by amide nitrogen is not energetically favourable unless the amide is first converted into its conjugate base. The latter conversion requires a strong base. This type of synthesis has been developed by Knunyants[21] using alkali-metal amide as base (Scheme 4).[22,23] Other bases which may be used include lithium carbonate,[24]



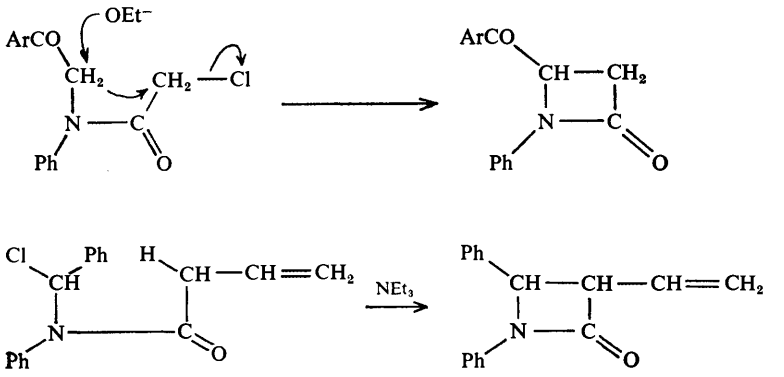
Scheme 4

sodium hydride and sodium hydroxide,[25,26] amines in dimethylformamide,[27] dimsyl sodium,[28] and weak bases at high temperatures.[24] The method is versatile for alkyl- and aryl-substituted β-lactams and no doubt involves inversion of configuration at C-4.

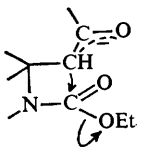
C. Ring-closure at C-3—C-4.—Bond formation between the α- and β-carbons can be accomplished if there is a nucleophilic leaving group at one and a potential carbanionic centre at the other. It is difficult to generalize, but the examples in Scheme 5 may illustrate the application of this principle.[29–32]

D. Ring-closure at C-2—C-3.—While no examples of this type of synthesis are known to the reviewer, a possible approach might be *via* the urethane (4), although the necessary basic conditions would probably induce some reaction other than cyclization.

[19] E. Bellasio, G. F. Cristiani, and E. Testa, *Ann. Chim. (Italy)*, 1969, **59**, 1122.
[20] E. Testa, L. Fontanella, and V. Aresi, *Annalen*, 1964, **673**, 60; E. Testa, B. J. R. Nicolaus, E. Bellasio, and L. Mariani, *ibid.*, p. 71.
[21] I. L. Knunyants, E. E. Rytslin, and N. P. Sambaryan, *Izvest. Akad. Nauk S.S.S.R. Odtel Khim Nauk*, 1960, 527.
[22] M. S. Manhas and S. J. Jeng, *J. Org. Chem.*, 1967, **32**, 1246.
[23] E. Testa, L. Fontanella, and V. Aresi, *Annalen*, 1964, **673**, 60.
[24] *Chem. Abs.*, 1970, **73**, 45 314.
[25] D. Greiciute, J. Kules, and L. Rosteikeine, *Zhur. org. Khim.*, 1974, **10**, 436.
[26] J. E. Baldwin, A. Au, M. Christie, S. B. Haber, and D. Hesson, *J. Amer. Chem. Soc.*, 1975, **97**, 5957; S. Nakatsuka, H. Tanino, and Y. Kishi, *ibid.*, pp. 5008, 5010.
[27] F. Merger, *Chem. Abs.*, 1972, **76**, P3683.
[28] S. D. Levine and V. L. Narayanan, *Chem. Abs.*, 1971, **74**, P87 810.
[29] R. F. Abdullah, S. K. Lataivi, T. A. Crabb, and R. Cahill, *Z. Naturforsch.*, 1971, **26**, 95
[30] A. K. Bose, G. Spiegelman, and M. S. Manhas, *Tetrahedron Letters*, 1971, 3167.
[31] E. Ziegler and G. Kleineberg, *Monatsh.*, 1965, **96**, 1296.
[32] B. G. Chattergee and P. N. Moza, *J. Medicin. Chem.*, 1966, **9**, 259.



Scheme 5



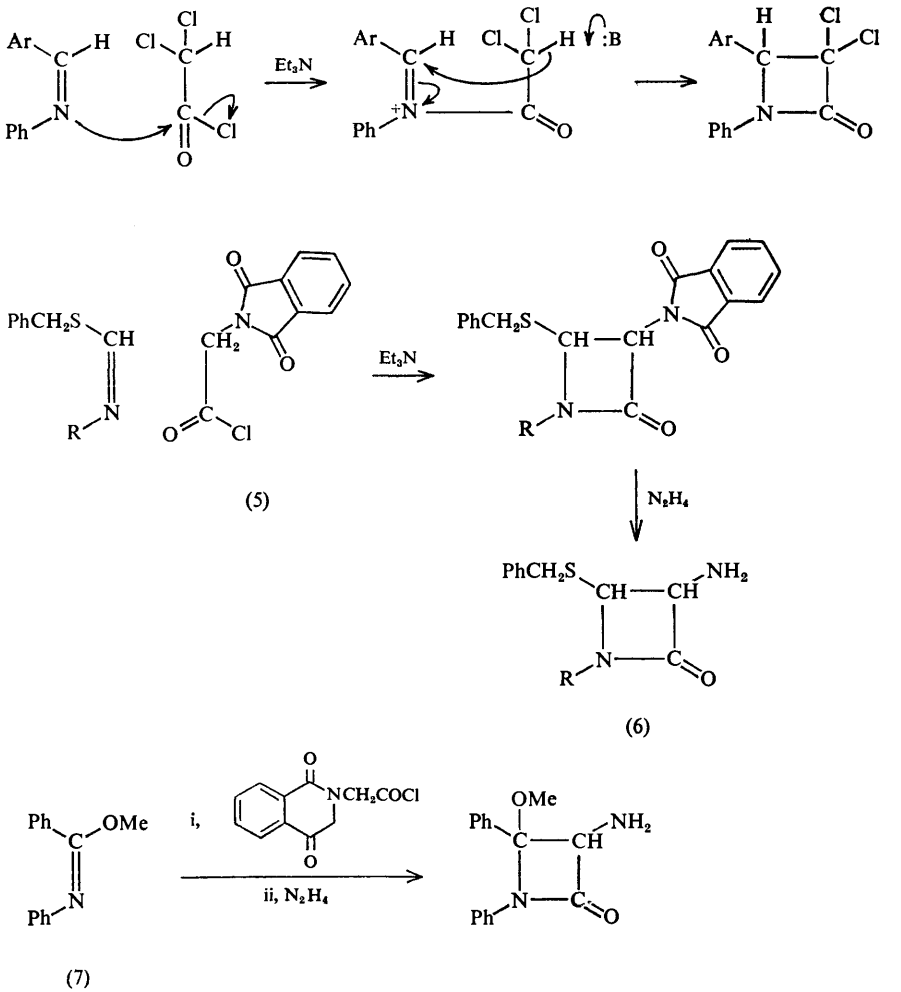
(4)

2 Non-concerted Cycloaddition Reactions

Several useful syntheses of β-lactams which have been developed consist of the addition of a C—N to a C—CO component to form the ring in a single operation with a stepwise mechanism.

Substituted acetyl chlorides with electron-withdrawing substituents and at least one hydrogen at the α-carbon add to imines in the presence of amine bases.[33] The mechanism is probably as depicted in Scheme 6. The acyclic intermediate amide may on occasion be isolated. This method is particularly suited to the preparation of 3-X-azetidinones, where X is an acid-strengthening group such as —N_3,[34] —OR,[30,33,35,36] —hal,[33,37–39] —COCl.[30,40] This additional functionality at C-3 is valuable by virtue of the further transformations which are possible (see Section 7). Some typical examples are shown in Scheme 6. Some workers have reported stereospecificity between C-3 and C-4,[30,35,39]

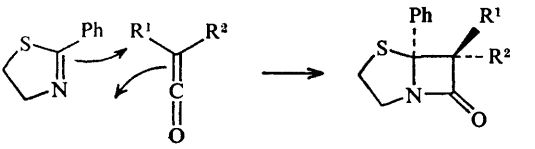
[33] R. Lattrell and G. Lohaus, *Chem. Abs.*, 1972, **77**, P48 199.
[34] A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, 1967, **23**, 4769.
[35] A. K. Bose, B. Lal, and B. Dayal, *Tetrahedron Letters*, 1974, 2633.
[36] R. Lattrell and G. Lohaus, *Annalen*, 1974, 87.
[37] D. A. Nelson, *J. Org. Chem.*, 1972, **37**, 1447.
[38] A. K. Mukerdzhi and N. N. Savarov, *Khim. geterotsikl. Soedinenii*, 1970, 1626.
[39] A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, *Tetrahedron Letters*, 1972, 2823.
[40] A. K. Bose, J. C. Kapur, B. Dayal, and M. S. Manhas, *J. Org. Chem.*, 1974, **39**, 312; *Tetrahedron Letters*, 1973, 1811, 2563.



Scheme 6

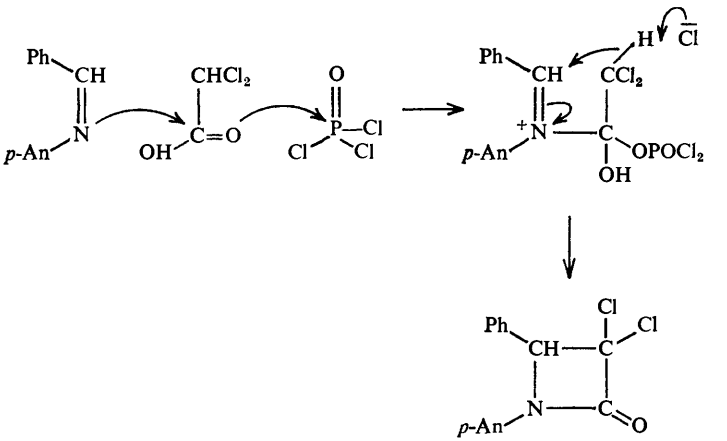
while others have obtained mixtures of *cis*- and *trans*-products.[37] The degree of stereospecificity has been shown[34] to depend upon the conditions used, mainly *trans* resulting from addition of base to the other reagents and *cis* from addition of acyl chloride to the mixture of imine and base. 3-Aminoazetidinones have been thus prepared by reduction of the azido-compounds[34] and by hydrolysis of an amidoazetidinone generated from an α-amidoacetyl chloride such as phthalyl

glycyl chloride[41] or phthalimidoacetyl chloride (5);[38,42,43] the latter eventually yields (6) on transamidation with hydrazine. If the imine component in these reactions is a Schiff base or an *N*-arylimidic acid derivative (7), then 4-alkoxyazetidinones are produced.[42] The sulphur analogues, thioimidates, give the corresponding 4-alkylthiol compounds,[43] including cyclic systems with the penam structure (8).[39,44] The reactions may be carried out in many cases by treating a



(8)

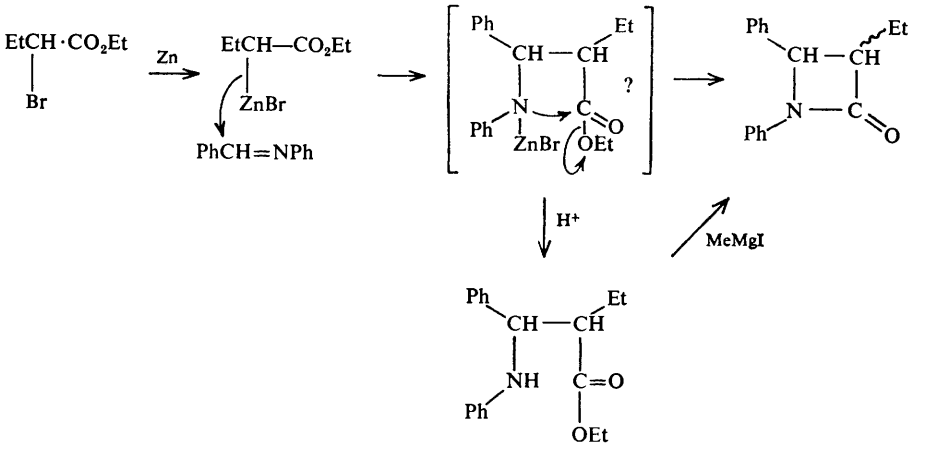
mixture of the imine and, for example, dichloroacetic acid, with $POCl_3$.[37,45] It is possible that the acid chloride is formed as an intermediate, though it has been suggested that the phosphorus halide participates as an electrophilic catalyst (Scheme 7). Anhydrides can also be used;[46] Yoshida and coworkers have extensively investigated the use of dichloroacetic anhydride in the production of 3,3-dichloroazetidinones.[47]



Scheme 7

[41] L. Paul, A. Draeger, and G. Hilgetag, *Chem. Ber.*, 1966, **99**, 1957
[42] L. Paul and K. Zieloff, *Chem. Ber.*, 1966, **99**, 1431.
[43] M. D. Bachi and O. Goldberg, *J.C.S. Chem. Comm.*, 1972, 312.
[44] R. A. Firestone, N. Maceijewicz, and B. Christensen, *J. Org. Chem.*, 1974, **39**, 3384.
[45] E. Ziegler, T. Wimmer, and A. Mittelbach, *Monatsh.*, 1968, **99**, 2128.
[46] A. K. Bose, J. C. Kapur, S. D. Sharma, and M. S. Manhas, *Tetrahedron Letters*, 1973, 2319.
[47] G. Sunagawa and N. Yoshida, *Yakugaku Zasshi*, 1962, **82**, 826, 835, 846; N. Yoshida, *Sankyo Kenkyusho Nempo*, 1966, **18**, 38.

A second method of this type is the Reformatsky reaction between imines and α-bromo-esters in the presence of zinc, which was first discovered by Gilman and Speeter.[48] The method has recently been extensively developed in France and by Bose and associates in New York.[49–54] An α-(bromozinc) ester forms and provides a nucleophilic centre for C-3—C-4 bond formation (Scheme 8). Some control of



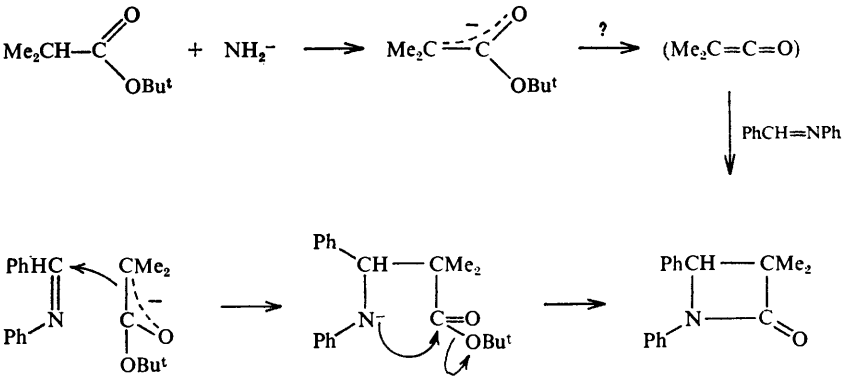
(9)

Scheme 8

the stereochemistry at these centres can be obtained as the *cis*:*trans* ratio is sensitive both to the solvent[51] and to the size of the 3-substituent.[50,55] In some instances, yields are appreciably reduced by the formation of β-amino-esters (9) which fail to cyclize because of competitive displacement of the zinc by a proton.[55,56] However, as shown above, these compounds can be converted into the β-lactam by addition of a Grignard reagent. The Reformatsky method is versatile in giving a wide range of alkyl- and aryl-azetidinones; because of their greater availability, diarylimines have been most used and consequently 1,4-diarylazetidinones are the commonest products.

Unactivated esters will also condense with imines under the influence of strong bases (Scheme 9).[57] It is uncertain whether this reaction is a nucleophilic addition

[48] H. Gilman and H. Speeter, *J. Amer. Chem. Soc.*, 1943, **65**, 2255.
[49] E. Cuinget, D. Poulain, and M. Tarteret-Adelban, *Bull. Soc. chim. France*, 1969, 514.
[50] H. B. Kagan, J.-J. Basselier, and J.-L. Luche, *Tetrahedron Letters*, 1964, 941.
[51] J.-L. Luche and H. B. Kagan, *Bull. Soc. chim. France*, 1969, 3500.
[52] F. Dardoize, J. L. Moreau, and M. Gaudemar, *Compt. rend.*, 1969, **268**, 2228.
[53] M. S. Manhas, J. Jeng, and A. K. Bose, *Tetrahedron*, 1968, **24**, 1237.
[54] S. Mohan, P. S. Sethi, and A. L. Kaloor, *J. Indian Chem. Soc.*, 1971, **48**, 685.
[55] F. Dardoize, J. L. Moreau, and M. Gaudemar, *Bull. Soc. chim. France*, 1973, 1668.
[56] F. Dardoize, J. L. Moreau, and M. Gaudemar, *Bull. Soc. chim. France*, 1972, 3841.
[57] E. Simova, M. Mladenova, and B. I. Kurtev, *Izvest. Ost. Khim. Nauk Bulg. Akad. Nauk*, 1970, **3**, 497.



Scheme 9

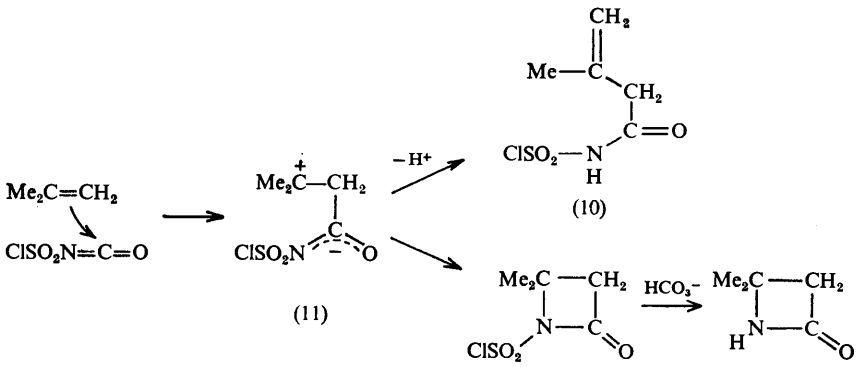
of ester enolate, or whether an intermediate keten is formed, these species being known to add to imines.

3 [2 + 2] Cycloadditions

The β-lactam ring may be synthesized in one step by the cycloaddition of component halves of the ring, each initially containing a double bond. Two well documented possibilities are an isocyanate with an olefin, and a keten with an imine. These reactions may occur by concerted processes, in which case the restrictions of orbital symmetry conservation necessitate an orthogonal approach of the reagents (a $_{\pi}2_{s} + _{\pi}2_{a}$ configuration).[58] However, in some instances at least there is strong evidence that a two-step mechanism operates *via* a zwitterionic intermediate.

A. The Addition of Isocyanate to Olefin.—Chlorosulphonyl isocyanate has been found to be very reactive towards a great variety of olefinic species, leading to β-lactams directly in moderate to high yield (Scheme 10).[59–62] The initial product, a 1-chlorosulphonylazetidinone, is thermally unstable but is readily hydrolysed to the parent β-lactam. In this way, a wide variety of C-3 and C-4 substituents may be introduced. As byproduct, a βγ-unsaturated amide (10) may be obtained, in agreement with the proposed intermediate zwitterion (11); the proportions of the two products depend upon the number and type of substituents on the olefin used.[60] This mechanism also explains the regiospecificity which invariably leads to the isomer of (11) with the most stable distribution of positive charge. One might expect some loss of stereochemical integrity in the olefinic moiety since rotation in (11) is possible. However, frequently this does not occur to any great

[58] N. S. Isaacs and P. Stanbury, *J.C.S. Perkin II*, 1973, 166.
[59] C. Ivanov and V. Dryanska, *Doklady Bolg. Akad. Nauk*, 1969, **22**, 423.
[60] R. Graf, *Annalen*, 1963, **661**, 111.
[61] H. Bestian, H. Biener, K. Clauss, and H. Heya, *Annalen*, 1968, **718**, 94.
[62] T. Haug, F. Lohse, K. Metzger, and H. Batzer, *Helv. Chim. Acta*, 1968, **51**, 2069.

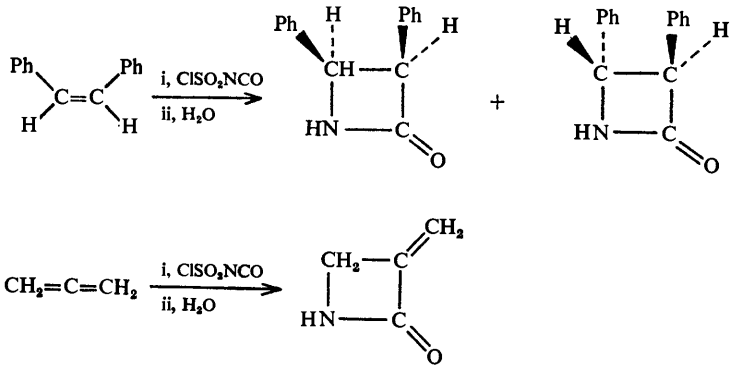


Scheme 10

extent though higher temperatures favour products of lower stereoselectivity.[63] This observation, together with the more rapid addition of *cis*- than *trans*-olefins,[58] has led to the interpretation of these reactions as concerted cycloadditions. However, the regiospecificity and the large rate-enhancing effects both of alkyl substituents on the olefin and of solvent polarity conclusively demonstate the presence of a polar intermediate. Thus 2,2-disubstituted ethylenes react *ca.* 10^4 times faster than alk-1-enes,[64] and solvent effect values such as $k_{MeNo_2}:k_{hexane} \approx 10^5$ are observed.

Conjugated dienes undergo 1,2-addition, though the 1-chlorosulphonyl-4-vinylazetidinones subsequently rearrange, even at room temperature,[65] to the 1,4-adducts[63,66–70] or to 2-pyridones.[71] As expected, nucleophilic substituents activate the olefin; vinyl ethers readily yield 4-alkoxyazetidinones[72–76] and vinyl esters the 4-acetoxy-analogues,[77] from which 4-hydroxy-β-lactams may be obtained on careful hydrolysis.[77] Enamines similarly give 4-aminoazetidinones.[76,78] Allenes also add to give 3-methylene derivatives (12).[79] Cyclopropanes

[63] H. J. Friedrich, *Tetrahedron Letters*, 1971, 2981.
[64] K. Clauss, *Annalen*, 1969, **722**, 110.
[65] R. W. Hoffmann and H. Diehr, *Tetrahedron Letters*, 1963, 1875.
[66] E. J. Moriconi and W. C. Meyer, *Tetrahedron Letters*, 1968, 3823.
[67] E. J. Moriconi and W. C. Meyer, *J. Org. Chem.*, 1971, **36**, 2841.
[68] P. Goebe and K. Clauss, *Annalen*, 1969, **722**, 122.
[69] T. Haug, F. Lohse, K. Metzger, and H. Batzer, *Helv. Chim. Acta*, 1968, **51**, 2069.
[70] M. Fischer, *Chem. Ber.*, 1968, **101**, 2669.
[71] H. Koichi, H. Matsuda, and Y. Kishida, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 1096.
[72] F. Effenberger, P. Fischer, G. Prossel, and G. Kiefer, *Chem. Ber.*, 1971, **104**, 1987.
[73] J. C. Martin, J. L. Chitwood, and P. G. Gott, *J. Org. Chem.*, 1971, **36**, 2228.
[74] R. Lattrell, *Annalen*, 1969, **722**, 132, 142.
[75] F. Effenberger and R. Gleiter, *Chem. Ber.*, 1964, **97**, 1576.
[76] F. Effenberger and R. Gleiter, *Angew. Chem.*, 1963, **75**, 450.
[77] H. Bestian and D. Grimm, *Chem. Abs.*, 1969, **73**, P98 777.
[78] G. Opitz and J. Koch, *Angew. Chem.*, 1963, **75**, 167.
[79] E. J. Moriconi and J. F. Kelly, *J. Amer. Chem. Soc.*, 1966, **88**, 3657; *J. Org. Chem.*, 1968, **33**, 3036.



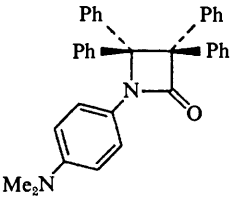
(12)

take part in the reaction, apparently following initial isomerization to the olefin caused by the electrophilic isocyanate.[80]

Chlorosulphonyl isocyanate is the most reactive, but other isocyanates have also been widely used; rates of olefin addition are greatly diminished by the presence of groups less electron-withdrawing than Cl, *e.g.* $k_{ClSO_2NCO}:k_{MeOSO_2NCO} = 1:10^{-4}$.[64] Trichloroacetyl isocyanate adds to dienes,[73,81] phenyl isocyanate to vinyl ethers,[82,83] enamines,[84] and dienes,[68] and *p*-nitrophenyl isocyanate to styrene.[70] Various aroyl and arenesulphonyl isocyanates have been shown to add to alkenes[85,86] and vinyl ethers[87,88] and even to acetylenes[89,90] (to give 2-azetinones). Alkyl isocyanates have been little examined[91] and would be expected to be somewhat unreactive.

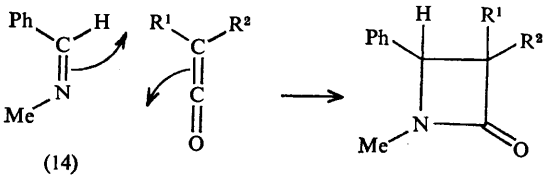
B. The Additions of Ketens to Imines.—Staudinger, investigating the chemistry of diphenylketen in 1911, added *p*-nitrosodimethylaniline and obtained the β-lactam (13). He interpreted this as an initial cycloaddition to the nitroso-group, loss of CO_2 (to give an imine), and a second cycloaddition to the imine.[92] This interpretation has been recently confirmed.[93] There are many examples of the

[80] E. J. Moriconi, J. F. Kelly, and R. A. Salomone, *J. Org. Chem.*, 1968, **33**, 3448.
[81] B. A. Arbuzov, N. N. Zabova, and E. G. Yarkova, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1969, 1114.
[82] R. W. Hoffmann, U. Bressel, G. Juergen, and H. Haeuser, *Chem. Ber.*, 1971, **104**, 873.
[83] R. W. Hoffmann, *Angew. Chem. Internat, Edn.*, 1972, **11**, 324.
[84] M. Perelman and S. A. Miszak, *J. Amer. Chem. Soc.*, 1962, **84**, 4988.
[85] F. Effenberger and W. Podszun, *Angew. Chem. Internat. Edn.*, 1969, **8**, 976; F. Effenberger and O. Gerlach, *Chem. Ber.*, 1974, **107**, 278.
[86] B. A. Arbuzov and N. N. Zobova, *Doklady Akad. Nauk S.S.S.R.*, 1967, **170**, 1317.
[87] M. Seefelder, *Chem. Abs.*, 1968, **69**, P106 257.
[88] I. Ojiwa, S. Inaba, and Y. Nagai, *Chem. Letters*, 1974, 1069.
[89] B. A. Arbuzov and N. N. Zobova, *Doklady Akad. Nauk S.S.S.R.*, 1967, **172**, 845.
[90] R. Lattrell and G. Lohaus, *Chem. Abs.*, 1971, **74**, P12 982.
[91] K. D. Kampe, *Annalen*, 1971, **752**, 142; *Chem. Abs.*, 1970, **73**, P120 136.
[92] H. Standinger and S. Jelagin, *Chem. Ber.*, 1911, **44**, 373.
[93] R. C. Kerber and M. C. Cann, *J. Org. Chem.*, 1974, **39**, 2552.



(13)

formation of a β-lactam by cycloaddition of diphenylketen to a preformed imine, *e.g.* (14) (Scheme 11).[94–96] Dimethylketen reacts analogously.[97,98] Many



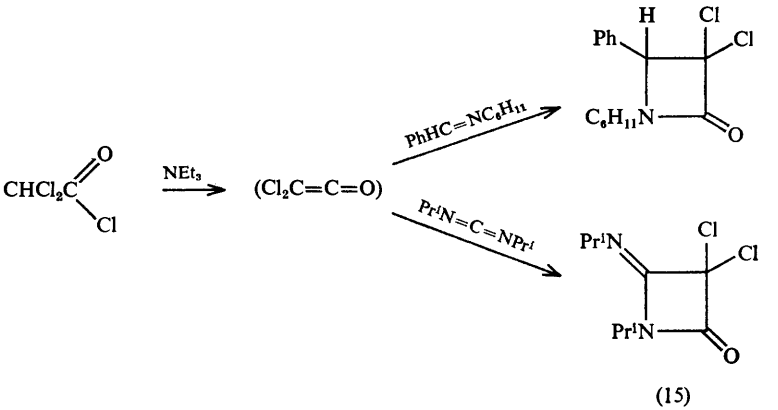
(14)

$R^1 = R^2 = Ph$

$R^1 = Me, R^2 = H$

Scheme 11

other ketens are known only as transient species and are generated *in situ* by a nitrogen base and a substituted acetyl chloride (Scheme 12). It is clear that this



(15)

Scheme 12

[94] J. M. Decazes, J.-L. Luche, and H. B. Kagan, *Tetrahedron Letters*, 1970, 3561, 3665.
[95] R. Huisgen, B. A. Davis, and M. Morikawa, *Angew. Chem. Internat. Edn.*, 1968, **7**, 826.
[96] M. Sakamoto and Y. Tomimatsu, *Yakugaku Zasshi*, 1970, **90**, 1386.
[97] J. Cuthbert, K. C. Brannock, R. D. Burpitt, G. P. Gott, and V. A. Hoyle, *J. Org. Chem.*, 1971, **36**, 2211.
[98] J. C. Martin, R. D. Burpitt, P. G. Gott, M. Harris ,and R. M. Meen, *J. Org. Chem.*, 1971, **36**, 2205.

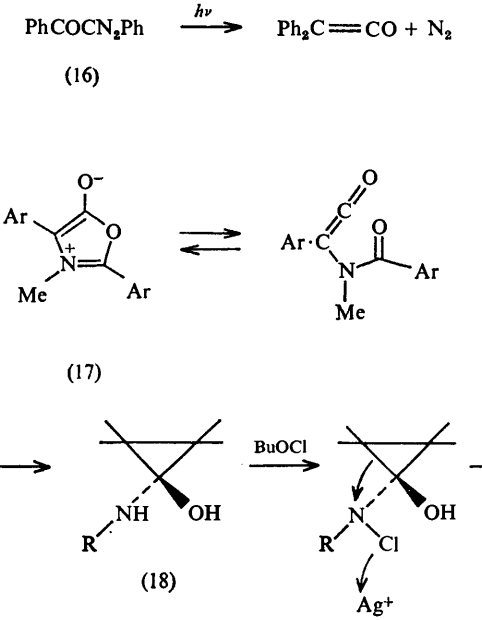
reaction is precisely that described in Section 2 as a dipolar cycloaddition initiated by attack of the imine nitrogen on the carbonyl group of the acyl chloride. The keten mechanism is frequently assumed to be the correct one for the analogous additions to alkenes,[99] since here no nucleophilic species is available to add to the carbonyl group and no reaction occurs until the addition of base. It is apparent, therefore, that there remains uncertainty as to the true nature of the additions to imines which will here be treated as occurring *via* the keten. As a preparative route to β-lactams the additions of chloro-,[100–102] fluoro-,[100] dichloro-,[102,103] bromo-,[104] azido-,[44,105] and phenyl-ketens[106] or their equivalents are easy and efficient, leading to the appropriate 3-substituted compounds (Scheme 11). The stereochemistry at C-3—C-4 is not unambigously defined, but aldoketens tend to react with monosubstituted imines to give *trans*-products,[107] though as much as 50% *cis* product has been obtained from *o*-nitrobenzaldehyde anil[101] (the *m*- and *p*-isomers giving only *trans*) for reasons which are not clear. A high *cis*:*trans* ratio was also obtained from the reaction of this anil and preformed methylketen, which tends to substantiate the keten mechanism for the former process. Few additions of keten itself have been observed, although it forms a lactam with $(CF_3)_2C{=}NPh$.[108] 4-Iminoazetidinones (15) are readily prepared from the keten and a carbodi-imide,[103,105,106,109] whereas the addition of amidines gives 4-aminoazetidinones.[110,111] Ketens can result from the photolysis of, *e.g.* diazo-ketones (16),[112] or the thermolysis of oxazolium-5-olates (17)[113] and be trapped as a β-lactam by imine.

4 Ring Expansions

Several routes to azetidinones are known which involve expansion of a three-membered ring, either a cyclopropane or an aziridine.

Addition of a primary amine to cyclopropanone followed by N-chlorination of the resulting hydroxyamine (18) and treatment with silver ion produces the lactam (Scheme 13).[114] A similar synthesis may be achieved using a benzoate leaving group or tosyl hydroxylamine.[115] Oxidative ring-expansion of a cyclo-

[99] R. Montagne and L. Ghosez, *Angew. Chem. Internat. Edn.*, 1968, **7**, 221, 643.
[100] W. T. Brady and E. F. Hoff, *J. Amer. Chem. Soc.*, 1968, **90**, 6256.
[101] D. A. Nelson, *Tetrahedron Letters*, 1971, 2543.
[102] F. Duran and L. Ghosez, *Tetrahedron Letters*, 1970, 245.
[103] R. Hull, *J. Chem. Soc. (C)*, 1967, 1154.
[104] W. T. Brady, E. D. Dorsey, and F. H. Parry, *J. Org. Chem.*, 1969, **34**, 2846.
[105] M. S. Manhas, S. Jeng, and A. K. Bose, *Tetrahedron*, 1968, **24**, 1237.
[106] P. G. Bird and W. J. Irwin, *J.C.S. Perkin I*, 1973, 2664.
[107] J.-L. Luche and H. B. Kagan, *Bull. Soc. chim. France*, 1968, 2450.
[108] Y. V. Zeifman and I. L. Knunyants, *Doklady Akad. Nauk S.S.S.R.*, 1967, **173**, 354.
[109] C. Metzger and J. Kurz, *Chem. Ber.*, 1971, **104**, 50.
[110] M. Sakamoto and Y. Tomimatsu, *Yakugaku Zasshi*, 1970, **90**, 1386.
[111] A. K. Bose and I. Kugajevsky, *Tetrahedron*, 1967, **23**, 957.
[112] W. Kirmse and L. Horner, *Chem. Ber.*, 1956, **89**, 2759.
[113] E. Funke and R. Huisgen, *Chem. Ber.*, 1971, **104**, 3222.
[114] H. H. Wasserman, W. H. Adickes, and O. E. de Ochoa, *J. Amer. Chem. Soc.*, 1971, **93**, 5586.
[115] H. H. Wasserman, E. A. Glazer, and J. Hearn-Michael, *Tetrahedron Letters*, 1973, 4855.



Scheme 13

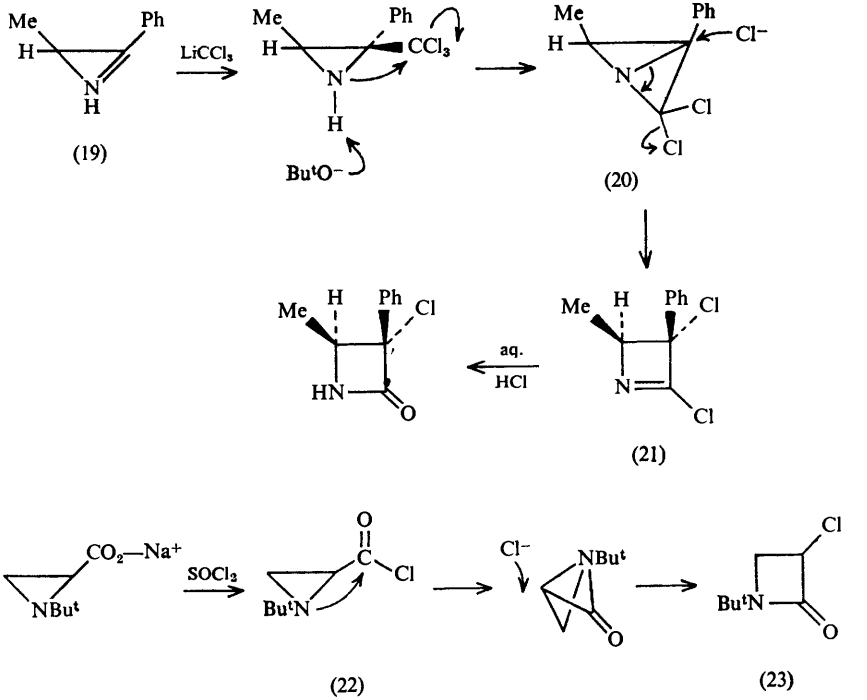
propanone tosylhydrazone by MnO_2 gives the β-lactam with retained stereochemistry at C-3—C-4.[116]

Dichlorocarbene addition to the azirine (19) leads, presumably, to the aza-bicyclobutane (20) which opens to the chloroazetine (21); this, in turn, can be readily hydrolysed to the β-lactam (Scheme 14).[117] The aziridinecarbonyl chloride (22) spontaneously rearranges to the 3-chloroazetidinone (23) (Scheme 14).[118] It has been reported that diphenylcyclopropanone reacts with ammonia in one step to give 3,4-diphenylazetidinone (*cis* + *trans*).[119]

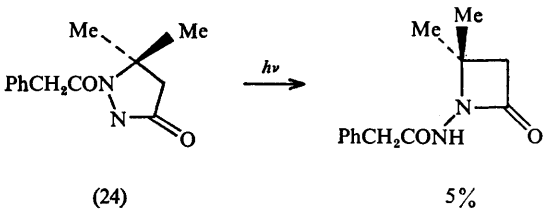
5 Ring-contraction Methods

β-Lactams can be generated by the expulsion of a carbon, oxygen, or nitrogen atom from several types of five-membered ring. Photolysis of pyrazolidones (24) brings about isomerization to 1-aminoazetidinones (Scheme 15).[120–122] Oxopyrroline oxides have also been reported to give 1-acetylazetidinones among the

[116] F. D. Greene, R. L. Camp, V. P. Abegg, and G. O. Pierson, *Tetrahedron Letters*, 1973, 4091.
[117] A. Hassner, J. O. Currie, A. S. Steinfeld, and R. F. Atkinson, *Angew. Chem. Internat. Edn.*, 1970, **9**, 731; *J. Amer. Chem. Soc.*, 1973, **95**, 2982.
[118] J. A. Deyrup and S. C. Clough, *J. Amer. Chem. Soc.*, 1969, **91**, 4590
[119] F. Toda and T. Mitote, *Bull. Chem. Soc. Japan*, 1969, **42**, 1777.
[120] J. C. Sheehan and G. D. Lambach, *J. Amer. Chem. Soc.*, 1951, **73**, 4752.
[121] S. N. Ege, *J. Chem. Soc.* (*C*), 1969, 2624.
[122] C. E. Hatch and P. Y. Johnson, *Tetrahedron Letters*, 1974, 2719.



Scheme 14

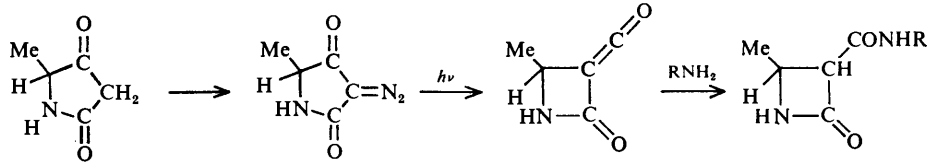


Scheme 15

products of photolysis,[123] and oxazolium salts give β-lactams on treatment with diethyl-*P*-acetylphosphite;[124] however, these methods are of limited value because the reagents are not readily available and yields are poor. Among the most useful ring-contractions is the application of the photo-Wolff rearrangement to 2-diazocyclopentane-1,5-diones (25). Starting materials are available by

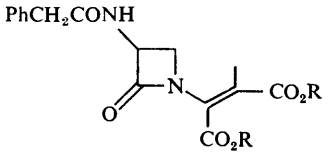
[123] D. A. Black and A. B. Boscacci, *J.C.S. Chem. Comm.*, 1974, 129.
[124] A. Takamizawa and H. Sato, *Chem. and Pharm. Bull (Japan)*, 1974, **22**, 1526.

standard routes (Scheme 16), and the method can be adapted to the synthesis of a precursor of the cepham nucleus (26).[125–127]



(25)

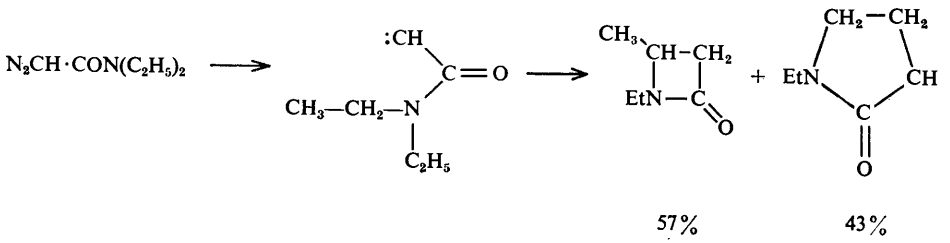
Scheme 16



(26)

6 Miscellaneous Methods

The one reported direct oxidation of an azetidine to azetidinone was catalysed by RuO_4.[128] The addition of copper phenylacetylide to diphenylnitrone leads to *cis*-1,3,4-triphenylazetidinone in good yield,[129] though nothing is known for certain of what must be a complex sequence of events. On photolysis, diazoacetic diethylamide gives cleanly a mixture of 1-ethyl-4-methylazetidinone and 1-ethylpyrrolidone;[130] presumably an intermediate carbene inserts into the methyl and methylene groups to form the two products (Scheme 17). Diazo-

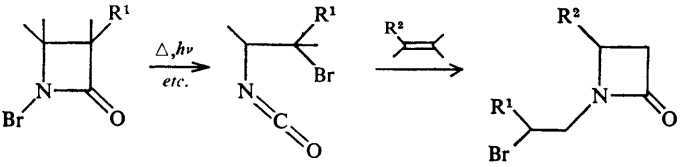


57% 43%

Scheme 17

[125] G. Lowe and D. D. Ridley, *J.C.S. Chem. Comm.*, 1973, 328.
[126] G. Lowe and D. D. Ridley, *J.C.S. Perkin I*, 1973, 2024.
[127] G. Lowe and H. Wing Yeung, *J.C.S. Perkin I*, 1973, 2907.
[128] J. C. Sheehan and R. W. Turley, *J. Org. Chem.*, 1974, **39**, 2264.
[129] M. Kinugasa and S. Hashimoto, *J.C.S. Chem. Comm.*, 1972, 466.
[130] R. R. Rando, *J. Amer. Chem. Soc.*, 1970, **92**, 6706.

methane reacts over a prolonged period with phenyl isocyanate giving a 20% yield of 1-phenylazetidinone. It is to be supposed that a double methylene insertion occurs forming an intermediate aziridinone.[131] Radical decomposition or photolysis of *N*-bromoaziridinones can give alkyl isocyanates which react ***in situ*** with an olefin to give a more complex aziridinone (Scheme 18).[91]



Scheme 18

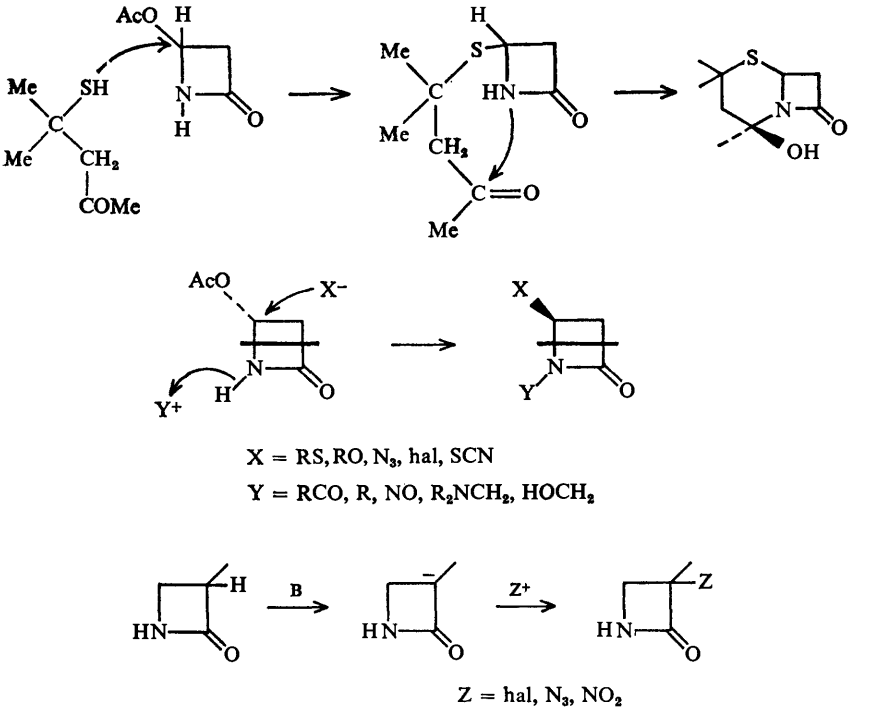
7 Modification of the β-Lactam Ring

The synthetic scope of the preceding methods is considerably widened by the transformations which may be carried out upon substituent groups while leaving the lactam ring intact. The amide link in monocyclic β-lactams appears to be little more reactive than in acyclic analogues[132,133] so that even hydrolytic procedures may be carried out, *e.g.* hydrolysis of 1-chlorosulphonyl derivatives (see Section 3A, Scheme 10).

N-Acylation,[134] alkylation (by NH_2^- followed by alkyl halide)[23,135] aminomethylation and hydroxymethylation (Mannich reaction),[134,136] and nitrosation[137] have been widely reported, and all appear to be easier with β-lactams than with acyclic amides. Possibly the lactam nitrogen is more basic than its acyclic counterpart, though no quantitative information is available. The protonated lactam appears to be stable in acetic–sulphuric acid.[138] Other reactions at nitrogen include halogenation[91] and Michael addition to form lactim ethers.[139]

Nucleophilic substitution at C-4 is possible. Acetate may be displaced by a wide variety of oxygen, nitrogen, and sulphur nucleophiles.[140–142] Inversion of configuration results following displacement of sulphonate, and this may be used to build up fused ring systems (Scheme 19).[143,144] Low-temperature

[131] J. C. Sheehan and P. T. Izzo, *J. Amer. Chem. Soc.*, 1948, **70**, 1985.
[132] R. J. Washkuhn and J. R. Robinson, *J. Pharm. Soc.*, 1971, **60**, 1168.
[133] G. M. Blackburn and J. D. Plackett, *J.C.S. Perkin II*, 1972, 1366; 1973, 981.
[134] E. Testa, G. Pifferi, L. Fontanella, and V. Aresi, *Annalen*, 1966, **696**, 108.
[135] D. Bormann, *Annalen*, 1969, **725**, 124.
[136] C. Cignarelli, G. F. Cristiani, and E. Testa, *Annalen*, 1963, **661**, 181.
[137] G. Pifferi, P. Consonni, and E. Testa, *Gazzetta*, 1967, **97**, 1719.
[138] P. A. Petyunin and G. P. Petyunin, *Zhur. org. Khim.*, 1972, **8**, 373; (*Chem. Abs.*, 1972, **77**, 153 448).
[139] D. Bormann, *Chem. Ber.*, 1970, **103**, 1797.
[140] K. Clauss and D. Grimm, *Chem. Abs.*, 1971, **74**, P141 500.
[141] R. Lattrell and G. Lohaus, *Chem. Abs.*, 1972, **77**, 48 201.
[142] R. Lattrell and G. Lohaus, *Annalen*, 1974, 901.
[143] H. W. Schnabel, D. Grimm, and H. Jensen, *Annalen*, 1974, 477.
[144] D. Bormann, *Annalen*, 1974, 1391; *Chem. Abs.*, 1975, **82**, P171 004, P171 005.



Scheme 19

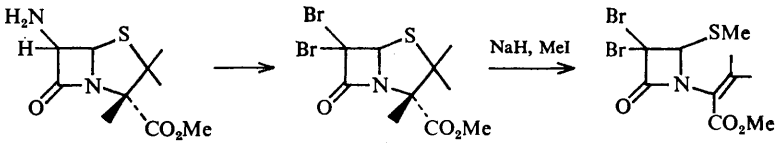
bromination of the 4-thiolate leads to the 4-alkoxy-derivative with retention of configuration.[145]

3-Substitution may be accomplished by electrophilic displacement, taking advantage of the acidic α-hydrogen. 3-Nitroazetidinones are formed by the action of strong base followed by alkyl nitrite on the azetidinone.[146] Acylation,[147,148] alkylation,[148,149] and halogenation may be carried out at the 3-position, and 3-azidoazetidinones generated by reaction of the enolate ion with tosyl azide.[150] If a suitable leaving group is present nucleophilic substitutions may also be carried out at C-3.[147,151] Oxidative cleavage of a wide variety of alkyl and aryl substituents on nitrogen may be accomplished by ozonolysis[152] and de-*S*-

[145] A. K. Bose, J. C. Kapur, S. G. Amin, and M. S. Manhas, *Tetrahedron Letters*, 1974, 1917
[146] H. Jensen and P. Wegener, *Chem. Abs.*, 1971, **75**, P63 589.
[147] K. Kuehein and H. Jensen, *Annalen*, 1974, 369.
[148] T. Durst and M. J. Labelle, *Canad. J. Chem.*, 1972, **50**, 3196.
[149] T. Durst, R. Van den Elzen and R. Legoult, *Canad. J. Chem.*, 1974, **52**, 3206.
[150] *Chem. Abs.*, 1975, **82**, P171 001—P171 005.
[151] K. R. Henery-Logan and V. V. Rodricks, *J. Amer. Chem. Soc.*, 1963, **85**, 3521, 3524.
[152] R. B. Woodward, *Chem. Abs.*, 1967, **70**, P28 911; R. Lattrell and G. Lohaus, *Chem. Abs.*, 1971, **74**, P12 982.

alkylation by silver[153] and mercury[154] compounds. 3,4-Elimination produces the $\alpha\beta$-unsaturated lactam.[151]

Modification of naturally occurring β-lactams can be the most economical route to certain azetidinones. The penicillins and cephalosporins are the most accessible natural products of this type, and several methods have been devised whereby the thiazolidine or dihydrothiazine rings may be cleaved leaving the β-lactam system intact.[155] 6β-Aminopenicillanic acid (27) may be readily converted into the 6,6-dibromo-derivative (28). Treatment of (28) with sodium hydride and methyl iodide (Scheme 20) gives the lactam (29).[156] This type of

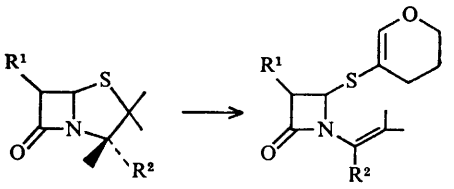


(27) (28) (29)

Scheme 20

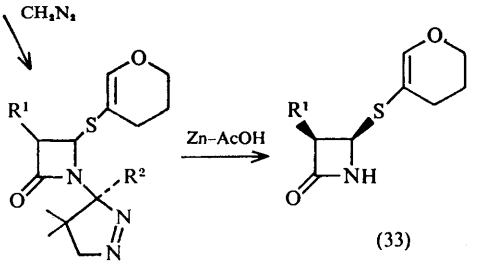
cleavage appears to be restricted to penam derivatives with no 6-hydrogen, or at least a non-acidic 6-hydrogen, in which case elimination leading to lactam ring-opening occurs. 6-Tritylamino- or 6-amido-derivatives will undergo alkylation and elimination in an analogous fashion.[157] The 'secopenicillins' thus obtained can be used to build up the cepham ring system. From the penicillin derivative (30), Barton and co-workers obtained[158] the corresponding sulphoxide which on pyrolysis to a sulphinic acid was trapped as the dihydropyranyl derivative (31) (Scheme 21). Furthermore, a method for the removal of the isopentene residue on the nitrogen was found; 1,3-dipolar cycloaddition of diazomethane to the double bond yielded the pyrazoline (32) which, on cleavage by zinc and acetic acid, gave the *cis*-3-amino-4-thioalkylazetidinone (33), a most promising intermediate for the elaboration of novel penicillins and cephalosporins.[159] Cleavage of the thiazolidine ring may also be accomplished using diazoalkanes, and it has been reported[160] that the remaining nitrogen side-chain may be removed using

[153] R. Lattrell, *Annalen*, 1974, 1361.
[154] A. K. Bose, B. Dayal, J. C. Kapur, and M. S. Manhas, *Tetrahedron Letters*, 1974, 3135.
[155] M. S. Manhas and A. K. Bose, 'Synthesis of Penicillin, Cephalosporin C, and Analogs', Marcel Dekker, New York, 1969; 'Cephalosporins and Penicillins', ed. E. H. Flynn, Academic Press, New York, 1972.
[156] J. P. Clayton, J. H. Naylor, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1974, 22.
[157] J. P. Clayton, J. H. Naylor, M. J. Pearson, and R. Southgate, *Chem. Abs.*, 1971, **74**, P141 499; *Chem. Abs.*, 1964, **61**, P105 255; *Chem. Abs.*, 1973, **78**, 111 335; E. G. Brain and N. F. Osborne, *Chem. Abs.*, 1974, **81**, P120 654.
[158] D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, and W. G. E. Underwood; *J.C.S. Chem. Comm.*, 1970, 1683; R. D. G. Cooper and F. L. Jose, *J. Amer. Chem. Soc.*, 1970, **92**, 2575.
[159] D. H. R. Barton, D. G. T. Greig, P. G. Sammes, and M. V. Taylor, *J.C.S. Chem. Comm.*, 1971, 845.
[160] N. Soma, M. Yoshimoto S. Ishihara, and E. Nakayama, *Chem. Abs.*, 1975, **82**, P43 164.



(30) $R^1 = PhCH_2CONH$
$R^2 = CO_2CH_2CCl_3$

(31)

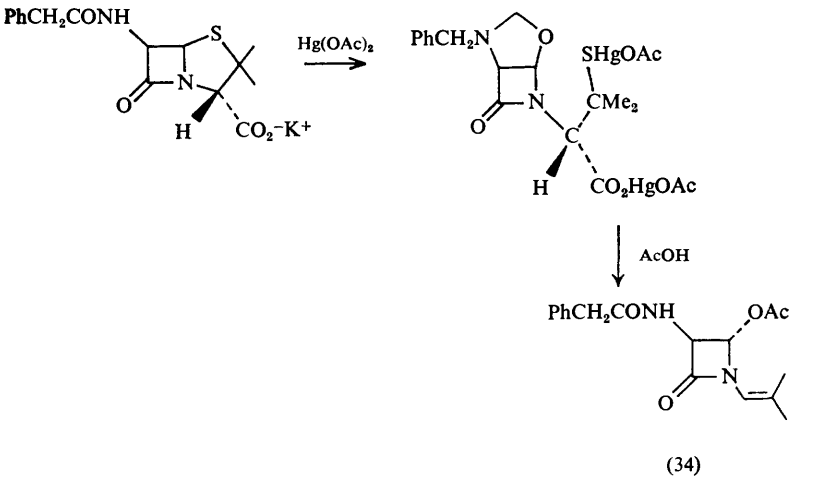


(32)

(33)

Scheme 21

zinc and acetic acid. Ring-opening with desulphurization can be brought about by the action of Raney nickel[161a] or mercuric acetate (Scheme 22).[161b] The



(34)

Scheme 22

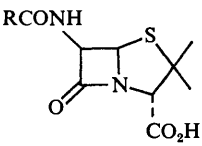
[161] (*a*) A. K. Bose, M. S. Manhas, J. S. Chib, H. P. S. Chawla, and B. Dayal, *J. Org. Chem.*, 1974, **39**, 2877; (*b*) R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1974, 181

trans-3-amino-4-acetoxylactam (34) is potentially capable of yielding the correct *cis*-relationship of a penicillin upon displacement with a sulphur nucleophile. New routes to such potential antibiotic precursors are still being sought.[162]

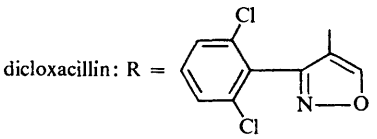
8 Uses of β-Lactams

The most important uses of compounds containing a β-lactam ring are undoubtedly as antibiotics related to penicillin (2) or cephalosporin (3). Innumerable modifications of the 6-side-chain have been carried out with the objects of increasing the range of organisms susceptible, *e.g.* to include Gram-negative bacteria, increasing the potency of the drug, and countering the resistance developed by certain organisms which can mobilize a lactamase system. Structures (35) illustrate some of the useful semi-synthetic derivatives of (2) prepared by chemical or microbiological acylation methods.[163]

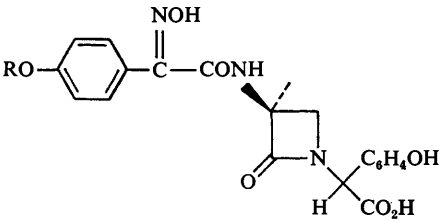
With the ability to remove and replace the thiazolidine ring, new prospects open for the synthesis of an even greater variety of structures. Recently, some monocyclic β-lactams have been shown to have bactericidal activity, including the naturally occurring norcardicin (36) and some 1,4-diaryl-3-methoxyazeti-



ampicillin: R = $PhCHNH_2$
carbenicillin: R = $PhCHCO_2H$
methicillin: R = $o,o\text{-}(MeO)_2C_6H_3$



(35)



(36) R = $(CH_2)_2CHCO_2H$ (NH$_2$)

dinones which have been claimed to be active against both Gram-positive and Gram-negative organisms.[164] Other biological activity which may be associated with simple β-lactams includes inhibition of aspartate oxidase[165] and other enzymes[166] and antidepressant activity.

[162] T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi, and T. Okei, *J. Amer. Chem. Soc.*, 1975, **97**, 5020; P. W. Wojkowski, *ibid.*, p. 5628; S. Kukolja and S. R. Lammert, *ibid.*, p. 5582.
[163] K. E. Price, *Adv. Appl. Microbiol.*, 1969, **11**, 17.
[164] A. K. Bose, M. S. Manhas, J. C. Kapur, S. D. Sharma, and S. G. Amin, *J. Medicin. Chem.*, 1974, **17**, 541.
[165] A. Guidetta and G. Di Prisco, *Biochem. Biophys. Acta*, 1963, **77**, 394.
[166] L. Gasola, A. Guidetta, and E. Rocca, *Arch. Biochem. Biophys*, 1964, **107**, 57.

Linear polyamide formation from simple alkyl azetidinones has attracted a lot of attention.[167,168] The conversion is effected by strong base and useful polymers can be obtained. These may be chiral,[169] and vinyl substition may give rise to mixed vinyl and polyamide materials which are highly cross-linked.[170] The potential of the β-lactam ring to react with a nucleophilic entity and yield a free amine function makes these species likely to be of use in a variety of industrial situations if economic considerations prove favourable.

[167] T. Kodaira, H. Mikake, K. Hayashi, and S. Okamura, *Bull. Chem. Soc. Japan*, 1965, **38**, 1788.
[168] *Chem. Abs.*, 1966, **65**, P7347; 1969, **71**, P4427.
[169] E. Schmidt, *Angew. Makromol. Chem.*, 1970, **14**, 185.
[170] J. Walter and C. Beermann, *Chem. Abs.*, 1967, **66**, P76 541.