Studies Related to Penicillins. Part IX.[1] Degradation of Penicillanic Acid Derivatives by Mercury(II) Acetate

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Mercury(II) acetate in acetic acid converts 6β-phthalimidopenicillanic acid (5) into *trans*-4-acetoxy-1-(2-methylprop-1-enyl)-3-phthalimidoazetidin-2-one (17). Potassium benzylpenicillinate (10) and phenoxymethylpenicillinic acid (11) undergo analogous reactions to yield the azetidinones (20) and (21), respectively.

Methyl 6β-phthalimidopenicillanate (6) and methyl benzylpenicillinate (12) are also degraded by mercury(II) acetate in acetic acid, to give *trans*-4-acetoxy-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-3-phthalimidoazetidin-2-one (18) and *trans*-4-acetoxy-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-3-phenylacetamidoazetidin-2-one (22), respectively.

METHODS whereby penicillanic acid derivatives can be degraded to monocyclic azetidin-2-ones are of interest in two respects. First, because of the high reactivity of the β-lactam bond of the reactants, such processes are relatively rare; secondly, the products may serve as precursors for the elaboration of penicillin and cephalosporin analogues.

Although a number of reactions involving 1,2-bond cleavages of penicillanic acid derivatives are known [2-9] only two of them have afforded monocyclic β-lactams. Thus, sulphenic acids, *e.g.* (1), which are in thermal equilibrium with penicillin ester sulphoxides, *e.g.* (3), can be trapped by activated olefins;[7] they can also be converted into *S*-acetyl derivatives by trimethyl phosphite–acetic anhydride [6] and into disulphides by 2-methylpropane-1-thiol.[8] In the presence of sodium hydride and an alkyl halide, 6β-triphenylmethylaminopenicillanic acid esters afford *S*-alkyl derivatives,[9] *e.g.* (4).

The first example involving rupture of the 3,4-bond of a penicillanic acid derivative was reported by Sheehan, who showed that Curtius degradation of 6β-phthalimidopenicillanic acid azide (7) gave the aldehyde (8).[10] Heusler [11] has extended the procedure to penicillins and, for example, has converted t-butoxypenicillinic acid (9) into the thiazolidine (13), a key intermediate in the synthesis of cephalosporins.[12]

Fission of the 1,5-bond of the thiazolidine ring is

[1] Part VIII, J. R. Jackson and R. J. Stoodley, *J.C.S. Perkin I*, 1972, 1063.

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[5] R. D. G. Cooper and F. L. José, *J. Amer. Chem. Soc.*, 1970, **92**, 2575.

[6] L. D. Hatfield, J. Fischer, F. L. José, and R. D. G. Cooper, *Tetrahedron Letters*, 1970, 4897.

[7] D. H. R. Barton, D. G. T. Greig, G. Lucente, M. V. Taylor, C. M. Cooper, G. Hewitt, and W. G. Underwood, *Chem. Comm.*, 1970, 1683.

[8] D. H. R. Barton, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, B. E. Looker, and W. G. E. Underwood, *Chem. Comm.*, 1971, 1137.

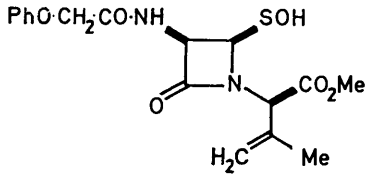
[9] J. P. Clayton, J. H. C. Nayler, R. Southgate, and P. Tolliday, *Chem. Comm.*, 1971, 590.

[10] J. C. Sheehan and K. G. Brandt, *J. Amer. Chem. Soc.*, 1965, **87**, 5468.

[11] K. Heusler, *Helv. Chim. Acta*, 1972, **55**, 388.

[12] R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, *J. Amer. Chem. Soc.*, 1966, **88**, 852; R. B. Woodward, *Science*, 1966, **153**, 487.

implicated in base-promoted rearrangements of certain penicillanic acid derivatives to 1,4-thiazepines, although the enethiolate intermediates have not been trapped.[13] Recently, however, Kukolja [14] has described an elegant



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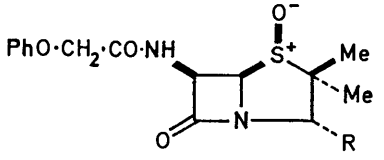
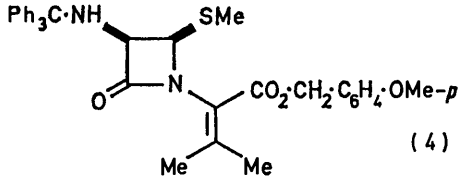


(2) R = CO_2H
(3) R = CO_2Me



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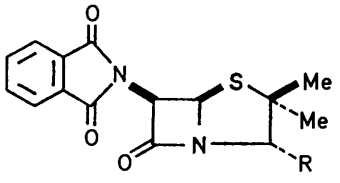
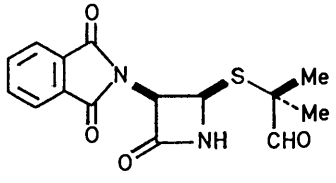
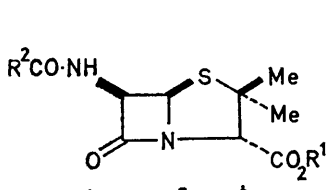


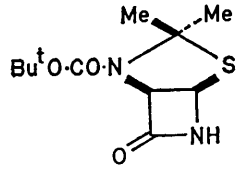
(5) R = CO_2H
(6) R = CO_2Me
(7) R = CON_3



(8)



(9) R^1 = H, R^2 = Bu^tO
(10) R^1 = K, R^2 = $PhCH_2$
(11) R^1 = H, R^2 = $PhO{\cdot}CH_2$
(12) R^1 = Me, R^2 = $PhCH_2$



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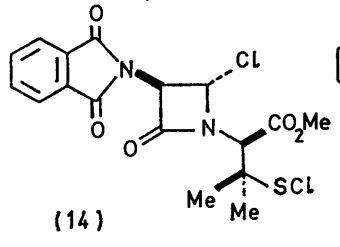

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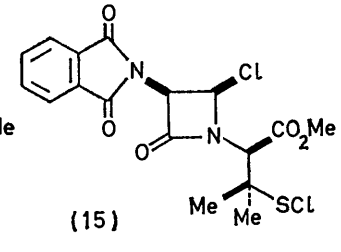


(15)

method for the selective cleavage of the 1,5-bond of methyl 6β-phthalimidopenicillanate (6). In the presence of 1 mol. equiv. of chlorine, the last derivative was transformed into a mixture of compounds (14) and (15), which afforded derivatives (16) and (19), respectively, when treated with triethylamine.

In an attempt to induce a direct oxidative decarboxylation and a concomitant cleavage of the 3,4-bond, the reactions of penicillanic acid derivatives with mercury(II) acetate have been examined. When 6β-phthalimidopenicillanic acid (5) was heated with 2 mol. equiv. of mercury(II) acetate in acetic acid, mercury(I) acetate was deposited and a neutral product (34% after silica gel chromatography) was obtained. Elemental analysis and spectroscopic evidence indicated that the substance was *trans*-4-acetoxy-1-(2-methylprop-1-enyl)-3-phthalimidoazetidin-2-one (17). When the degradation was applied to potassium benzylpenicillinate (10) and phenoxymethylpenicillinic acid (11), compounds (20) (29%) and (21) (38%) were the respective products.

A control experiment established that 6β-phthalimidopenicillanic acid (5) did not afford the acetate (17) when heated in acetic acid; consequently, mercury(II) acetate is essential for the degradation. Although, in principle, azetidin-2-one formation does not require an oxidative step, mercury(I) acetate was formed during the course of the reactions. The acetate (20), when heated with mercury(II) acetate in acetic acid was recovered unchanged and no mercury(I) acetate was formed. Consequently, either an oxidative step is involved in azetidin-2-one formation or the substrate (or a product derived from it by the action of acetic acid) reduces mercury(II) acetate in an independent reaction. The latter explanation is favoured since there is no obvious relationship between the amounts of azetidin-2-one and mercury(I) acetate formed (see Experimental section). Furthermore, the (*S*)-sulphoxide of phenoxymethylpenicillinic acid (2) did not afford the azetidin-2-one (21) under the reaction conditions.

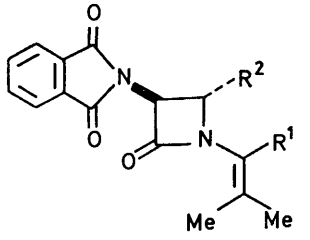
The presence of the carboxy-group at position 3 is not essential for the degradation. Thus, methyl 6β-phthalimidopenicillanate (6) afforded *trans*-4-acetoxy-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-3-phthalimidoazetidin-2-one (18) (77%) and methyl benzylpenicillinate (12) gave *trans*-4-acetoxy-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-3-phenylacetamidoazetidin-2-one (22) (41%).

In consequence, two processes warrant consideration for the conversion of penicillanic acid derivatives into azetidin-2-ones. The salt, *e.g.* (23), may undergo a 1,2-bond cleavage accompanied by either a decarboxylation (when R = H) or a proton loss (when R = Me). In such an event species (24) or (25) are likely intermediates; these may afford the azetidin-2-ones (17) or (18) after replacement of the sulphur substituents by acetoxy-groups. Alternatively, the salt (23) may suffer a 1,5-bond rupture to give intermediate (26),

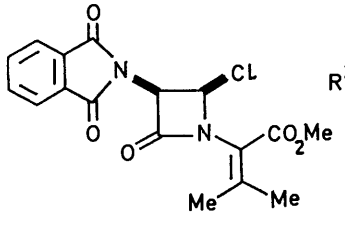
[13] O. K. Kovacs, B. Ekstrom, and B. Sjoberg, *Tetrahedron Letters*, 1969, 1863; J. R. Jackson and R. J. Stoodley, *Chem. Comm.*, 1970, 14; S. Wolfe, W. S. Lee, and R. Misra, *ibid.*, 1970, 1067; B. G. Ramsay and R. J. Stoodley, *ibid.*, 1971, 450.

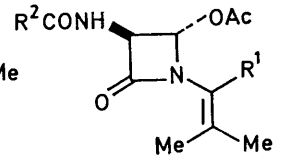
[14] S. Kukolja, *J. Amer. Chem. Soc.*, 1971, **93**, 6267.

which undergoes either a decarboxylative β-elimination to azetidin-2-one (17) (when R = H) or a β-elimination to azetidin-2-one (18) (when R = Me).



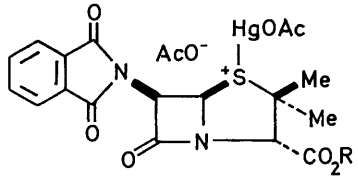
(16) $R^1 = CO_2Me$, $R^2 = Cl$
(17) $R^1 = H$, $R^2 = OAc$
(18) $R^1 = CO_2Me$, $R^2 = OAc$





(19)

(20) $R^1 = H$, $R^2 = PhCH_2$
(21) $R^1 = H$, $R^2 = PhO{\cdot}CH_2$
(22) $R^1 = CO_2Me$, $R^2 = PhCH_2$



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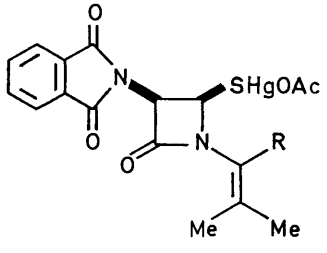
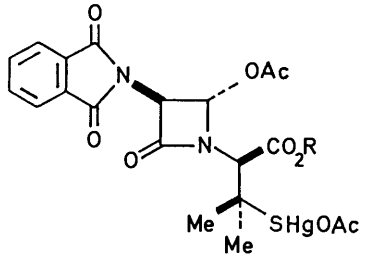


(24) R = H
(25) R = CO_2Me



(26)

EXPERIMENTAL

For general experimental details see Part I.[15]

Reaction of 6β-Phthalimidopenicillanic Acid (5) *with Mercury*(II) *Acetate.*—The acid [16] (5) (0·878 g, 2·5 mmol) and mercury(II) acetate (1·537 g, 5 mmol) were dissolved in acetic acid (30 ml) and the solution was gently heated in an oil-bath. When the bath temperature reached 85°, the mixture was allowed to cool and the precipitated mercury(I) acetate (0·547 g, 44%) was filtered off. The filtrate was diluted with water (100 ml), filtered, adjusted to *ca.* pH 5 with solid sodium hydrogen carbonate, and extracted with chloroform (3 times). The organic layer was washed with sodium hydrogen carbonate solution followed by water and dried ($MgSO_4$). Evaporation left a syrup (0·69 g) which was fractionated by silica gel chromatography (benzene–ether as eluant). The major component was trans-4-*acetoxy*-1-(2-*methylprop*-1-*enyl*)-3-*phthalimidoazetidin*-2-*one* (17) (0·282 g, 34%), m.p. 132—134° (from benzene–light petroleum), $[\alpha]_D$ 0° (0·3% in $CHCl_3$), $\nu_{max.}$ (KBr) 1780 (β-lactam C=O) and 1770 and 1725 (phthalimide C=O) cm^{-1}, τ ($CDCl_3$) 8·18 and 8·10 (each 3H, s, *gem*-Me_2), 7·82 (3H, s, MeCO), 4·62 (1H, d, *J* 1·5 Hz, β-lactam proton), 4·15br (1H, s, vinylic H), 3·52 (1H, d, *J* 1·5 Hz, β-lactam proton), and 2·06 (4H, s, aromatic protons) [Found: C, 62·0; H, 5·0; N, 8·5%; *M* (mass spectrum), 328. $C_{17}H_{16}N_2O_5$ requires C, 62·2; H, 4·9; N, 8·5%; *M*, 328].

Reaction of Potassium Benzylpenicillinate (10) *with Mercury*(II) *Acetate.*—A solution of the salt (10) (1·865 g, 5 mmol) and mercury(II) acetate (3·187 g, 10 mmol) in acetic acid (30 ml) was heated to 85° as in the previous experiment. The mixture was allowed to cool and the precipitated mercury(I) acetate (2·47 g, 95%) was collected. Work-up of the filtrate as before afforded a syrup (0·50 g), which was fractionated by silica gel chromatography (benzene–ether as eluant). The major component (0·45 g, 29%) was trans-4-*acetoxy*-1-(2-*methylprop*-1-*enyl*)-3-*phenylacetamidoazetidin*-2-*one* (20), m.p. 68—70° (from benzene–light petroleum), $[\alpha]_D$ −18° (1·3% in $CHCl_3$), $\nu_{max.}$ (KBr) 3330 (NH), 1780 (β-lactam C=O), and 1665 (amide C=O) cm^{-1}, τ ($CDCl_3$) 8·27br (6H, s, *gem*-Me_2), 7·90 (3H, s, MeCO), 6·42 (2H, s, $CH_2{\cdot}CO$), 5·30 (1H, dd, *J* 8, *J'* 1·5 Hz, 3-H), 4·32br (1H, s, vinylic H), 3·88 (1H, d, *J* 1·5 Hz, 2-H), 2·90br (1H, d, *J* 8 Hz, NH), and 2·65 (5H, s, aromatic protons) [on addition of D_2O to the solution the signal at τ 2·90 disappeared and that at 5·30 collapsed to a doublet (*J* 1·5 Hz)] [Found: C, 64·5; H, 6·5; N, 8·9%; *M* (mass spectrum), 316. $C_{17}H_{20}N_2O_4$ requires C, 64·5; H, 6·3; N, 8·9%; *M*, 316].

Reaction of Phenoxymethylpenicillinic Acid (11) *with Mercury*(II) *Acetate.*—A solution of the acid (11) (0·70 g, 2 mmol) and mercury(II) acetate (1·28 g, 4 mmol) in acetic acid (25 ml) was heated to 85° and the precipitated mercury(I) acetate (0·964 g, 92%) was removed. Work-up of the filtrate as before gave a syrup (0·496 g), which was purified by silica gel chromatography (benzene–ether as eluant) to give the syrupy trans-4-*acetoxy*-1-(2-*methylprop*-1-*enyl*)-3-*phenoxyacetamidoazetidin*-2-*one* (21) (0·253 g, 38%), $[\alpha]_D$ −12° (1·4% in $CHCl_3$), $\nu_{max.}$ (film) 3330 (NH), 1780 (β-lactam C=O), and 1680 (amide C=O) cm^{-1}, τ ($CDCl_3$) 8·22 and 8·20 (each 3H, s, *gem*-Me_2), 7·82 (3H, s, MeCO), 5·42 (2H, s, $CH_2{\cdot}CO$), 5·10 (1H, dd, *J* 9, *J'* 1·5 Hz, 3-H), 4·25br (1H, s, vinylic H), 3·72 (1H, d, *J* 1·5 Hz, 2-H), 2·80 (5H, m, aromatic protons), and 2·35br (1H, d, *J* 9 Hz, NH) [on addition of D_2O to the solution the signal at τ 2·35 disappeared and that at 5·10 collapsed to a doublet (*J* 1·5 Hz)] [Found: *M* (mass spectrum), 332·1372. $C_{17}H_{26}N_2O_5$ requires 332·1372].

Reaction of 6β-Phthalimidopenicillanic Acid (5) *with Acetic Acid.*—The acid [16] (5) (0·30 g, 0·87 mmol) was heated

[15] I. McMillan and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1968, 2533.

[16] J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, 1962, **84**, 2983.

to 85° in acetic acid (10 ml). Work-up as before gave a syrup (0·025 g) which contained no azetidin-2-one (17) on the basis of t.l.c. and n.m.r. spectroscopy.

Reaction of the Azetidin-2-one (20) *with Mercury*(II) *Acetate*.—The azetidin-2-one (20) (0·316 g, 1 mmol) was dissolved in acetic acid (5 ml) containing mercury(II) acetate (0·636 g, 2 mmol) and the solution was heated to 85°; no mercury(I) acetate was deposited. Work-up as before gave a material (0·268 g, 85%) which, on the basis of t.l.c. and n.m.r. spectroscopy, was the starting azetidin-2-one (20).

Reaction of Phenoxymethylpenicillinic Acid (S)-*Sulphoxide* (2) *with Mercury*(II) *Acetate*.—The sulphoxide [17] (2) (0·366 g, 1 mmol) was heated to 100° with mercury(II) acetate (0·637 g, 2 mmol) in acetic acid (30 ml). The mixture was allowed to cool and the precipitated mercury(I) acetate (0·26 g, 50%) was collected. Work-up as before gave a syrup (0·025 g) which, on the basis of i.r. and n.m.r. spectroscopy, contained no azetidin-2-one (21).

Reaction of Methyl 6β-*Phthalimidopenicillanate* (6) *with Mercury*(II) *Acetate*.—The ester [16] (6) (0·832 g, 2·3 mmol) was heated to 85° with mercury(II) acetate (1·47 g, 4·6 mmol) in acetic acid (35 ml). The cooled mixture was filtered to remove mercury(I) acetate (0·71 g, 67%) and the filtrate was worked up in the usual manner. The derived syrup (1·06 g) was fractionated by silica gel chromatography (benzene–ether as eluant) to give trans-4-*acetoxy*-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*phthalimidoazetidin*-2-*one* (18) (0·685 g, 77%), m.p. 110—112° (from benzene–light petroleum), $[\alpha]_D$ −81° (0·6% in $CHCl_3$), $\nu_{max.}$ (KBr) 1775 (β-lactam C=O), 1755 and 1720 (phthalimide C=O) cm^{-1}, τ ($CDCl_3$) 7·92 and 7·90 (3H, s, *gem*-Me_2), 7·70 (3H, s, MeCO), 6·15 (3H, s, OMe), 4·00 (2H, ABq, *J* 1·5 Hz, β-lactam protons), and 2·15 (4H, s, aromatic protons) [Found: C, 59·1; H, 4·5; N, 7·2%; *M* (mass spectrum), 386. $C_{19}H_{18}N_2O_7$ requires C, 59·1; H, 4·7; N, 7·2%; *M*, 386].

Reaction of Methyl Benzylpenicillinate (12) *with Mercury*(II) *Acetate*.—The ester (12) (0·70 g, 2 mmol) was heated to 95° with mercury(II) acetate (1·27 g, 4 mmol) in acetic acid (30 ml). The cooled mixture was filtered to remove mercury(I) acetate (0·71 g, 55%) and the filtrate was worked up in the usual manner. The syrupy product (0·638 g) was fractionated by silica gel chromatography (benzene–ether as eluant) to afford trans-4-*acetoxy*-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*phenylacetamidoazetidin*-2-*one* (22) (0·305 g, 41%), m.p. 105—107° (from benzene–light petroleum), $[\alpha]_D$ −38° (0·4% in $CHCl_3$), $\nu_{max.}$ (KBr) 3250 (NH), 1785 (β-lactam C=O), and 1665 (amide C=O) cm^{-1}, τ ($CDCl_3$) 8·08 and 7·96 (each 3H, s, *gem*-Me_2), 7·80 (3H, s, MeCO), 6·42 (2H, s, CH_2·CO), 6·27 (3H, s, OMe), 5·02 (1H, dd, *J* 8, *J′* 1·5 Hz, 3-H), 3·86 (1H, d, *J* 1·5 Hz, 2-H), and 2·68 (5H, s, aromatic protons) [the NH signal was not visible but on addition of D_2O to the solution the signal at τ 5·02 collapsed to a doublet (*J* 1·5 Hz)] [Found: C, 60·7; H, 5·9; N, 7·5%, *M* (mass spectrum), 374. $C_{19}H_{22}N_2O_6$ requires C, 60·9; H, 5·9; N, 7·5%; *M*, 374].

We thank the Beecham Research Laboratories for gifts of penicillins and the S.R.C. for financial support.

[2/1503 *Received*, 27*th June*, 1972]

[17] R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 1408.