The Chemistry of Penicillanic Acids. Part II.[1] Some Reactions of Methyl Penicillanate and its 6α-Bromo- and 6,6-Dibromo-derivatives

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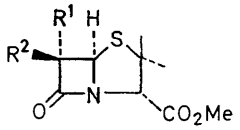
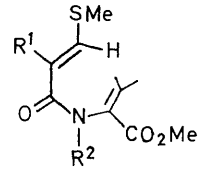
The action of methyl iodide and strong anhydrous base on methyl penicillanate or its 6α-bromo-derivative leads to *S*-methylation and cleavage of both thiazolidine and β-lactam rings, but with methyl 6,6-dibromopenicillanate the β-lactam system remains intact. Some further reactions of the resulting (4*R*)-3,3-dibromo-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-4-methylthioazetidin-2-one are described.

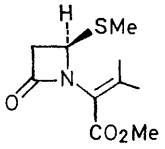
METHYL PENICILLANATE [2] (1) and its 6α-bromo- and 6,6-dibromo-derivatives [1] [(2) and (3)] are readily prepared from 6β-aminopenicillanic acid and constitute convenient model compounds for studying the chemistry of the penam system without the complications which, in penicillins, may arise from the presence of the 6β-acylamino-group. We have investigated the methylation of these compounds and some further reactions of the products.



(1) $R^1 = R^2 = H$
(2) $R^1 = Br$, $R^2 = H$
(3) $R^1 = R^2 = Br$



(4) $R^1 = R^2 = H$
(5) $R^1 = H$, $R^2 = Me$
(6) $R^1 = Br$, $R^2 = H$



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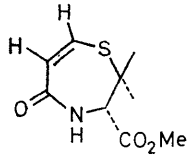

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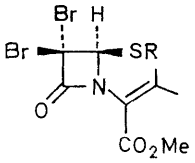
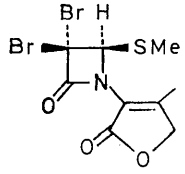


(9) R = Me
(10) R = CH_2Ph
(11) R = H
(12) R = CH_2OAc



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On treatment of methyl penicillanate (1) with equivalent amounts of methyl iodide and sodium hydride in tetrahydrofuran, no indication of methylation at either C-3 or C-6 was obtained. Instead the crystalline monomethyl derivative was shown by spectroscopic evidence to be the product of *S*-methylation and cleavage of both rings. When methyl iodide and sodium hydride were used in excess the product was a non-crystalline dimethyl derivative which lacked the exchangeable NH proton of the monomethyl compound. These two products were accordingly formulated as the unsaturated esters (4) and (5), evidently formed by two β-eliminations. No intermediate resulting from a single β-elimination was isolated, but the *trans*-configuration suggests that (4) was probably formed by way of the azetidinone (7) rather than the thiazepine derivative (8).

The action of methyl iodide and sodium hydride on methyl 6α-bromopenicillanate (2) apparently took a similar course, giving the bromo-ester (6) in low yield. Since methyl 6,6-dibromopenicillanate (3) carries no proton at C-6, only a single β-elimination is possible, and treatment with methyl iodide and sodium hydride accordingly gave the azetidinone (9). The crystalline *S*-benzyl analogue (10) was obtained when benzyl bromide was used instead of methyl iodide, but attempts to convert it into the thiol (11) by treatment with sodium in liquid ammonia [3] or with hydrogen fluoride [4] resulted in destruction of the β-lactam.

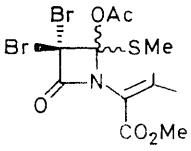
Our interest in developing procedures for converting penicillins into cephalosporins or other fused β-lactams led us to study model reactions of the azetidinone (9). Initially attempts were made to functionalise the isopropylidene group either by allylic oxidation or by addition to the double bond. Reaction with selenium dioxide in aqueous dioxan was sluggish and much azetidinone (9) was recovered after 24 h at reflux, but a small quantity of the lactone (13) was isolated.

Treatment of the azetidinone (9) with lead tetra-acetate in benzene at room temperature for 7 days or at reflux for 2 h failed to result in substitution in either allylic methyl group, but three other products were separated. The major product resulted from displacement of the lone proton on the lactam ring by an acetoxy-group to give (14); a second product was the isomeric acetate (12). The remaining product was a mixture of the two isomeric sulphoxides (15). When (9) was refluxed with lead tetra-acetate in t-butyl alcohol, conditions under which cephalosporins yield 2-acetoxy-derivatives,[5] the same products were obtained but the yield of sulphoxides was lower. An alternative route to the acetoxymethylthio-compound (12) consisted of oxidising (9) to a mixture of α- and β-sulphoxides (15) followed by Pummerer rearrangement in hot acetic anhydride. In

[1] Part I, J. P. Clayton, *J. Chem. Soc.*, (*C*) 1969, 2123.
[2] E. Evrard, M. Claeson, and H. Vanderhaeghe, *Nature*, 1964, **201**, 1124.
[3] J. F. W. McOmie, *Adv. Org. Chem.*, 1963, **3**, 252.
[4] J. Lenard, *Chem. Rev.*, 1969, **69**, 625.
[5] R. D. G. Cooper, P. V. Demarco, C. F. Murphy, and L. A. Spangle, *J. Chem. Soc.* (*C*), 1970, 340.

the latter step some sulphoxide was unexpectedly reduced back to the sulphide.

Pummerer rearrangement in acetic anhydride was also applied to the β-sulphoxide [1] (16), conveniently obtained from methyl 6,6-dibromopenicillanate (3) and *m*-chloroperbenzoic acid. An inseparable mixture of the 2-acetoxymethylpenam (17) and the 3-acetoxycepham (18)



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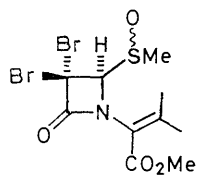

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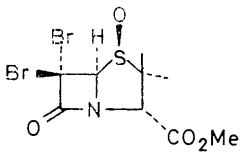

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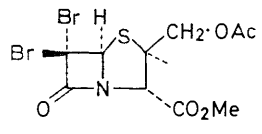

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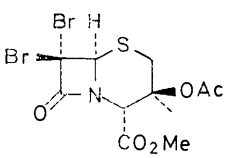

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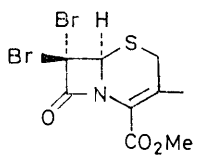

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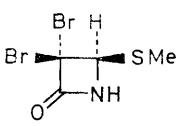

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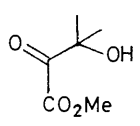

(21)

was produced, together with a larger amount of methyl 7,7-dibromo-3-methylceph-3-em-4-carboxylate (19). The cephem was the sole product when the β-sulphoxide (16) was rearranged in refluxing xylene containing a trace of toluene-*p*-sulphonic acid. These reactions parallel the behaviour of penicillin β-*S*-oxide esters,[6] and the stereochemistry of (17) and (18) is assigned by analogy.

Finally we examined oxidative addition to the double bond in the azetidinone (9). Treatment with osmium tetraoxide in benzene containing a little pyridine resulted in spontaneous breakdown of the initial adduct, giving the simple azetidinone (20) and the α-keto-ester (21).

EXPERIMENTAL

I.r. spectra were recorded for solutions in chloroform and u.v. spectra for solutions in ethanol unless stated otherwise. ^{1}H N.m.r. spectra were recorded on a Varian A60 instrument for solutions in $CDCl_3$ with tetramethylsilane as internal standard, unless stated otherwise. Mass spectra were determined with an A.E.I. MS9 machine. Merck silica gel GF_{254} was used for t.l.c. and Merck silica gel H for column chromatography, with ethyl acetate–light petroleum as eluant. Light petroleum refers to the fraction of b.p. 60—80°. M.p.s were determined with a Kofler hot-stage apparatus.

Methylation of Methyl Penicillanate (1).—(*a*) Methyl penicillanate (1) (0·43 g) in distilled tetrahydrofuran (5 ml) was treated with methyl iodide (0·32 g) and sodium hydride (0·1 g of 50% dispersion). After stirring for 1 h the mixture was diluted with ethyl acetate, washed with water, and dried. Evaporation gave a gum (0·4 g), which was dissolved in ethyl acetate and treated with light petroleum until slightly turbid. White crystals of *methyl 3-methyl-2-[trans-3-(methylthio)acrylamido]crotonate* (4) slowly separated (0·13 g); m.p. 134—136°; $\lambda_{max.}$ 233 (ε 8000) and 280 nm (21,000); $\nu_{max.}$ 3400, 1720, 1670, and 1583 cm^{-1}; δ 1·85 (3H, s), 2·15 (3H, s), 2·33 (3H, s), 3·75 (3H, s), 5·81 (1H, d, *J* 15 Hz), 7·10br (1H, exch.) and 7·67 (1H, d, *J* 15 Hz); *m/e* 229 (M^+) (Found: C, 52·4; H, 6·7; N, 5·9; S, 14·1. $C_{10}H_{15}NO_3S$ requires C, 52·4; H, 6·6; N, 6·1; S, 14·0%). Chromatography of the mother liquors gave unchanged (1) (0·12 g) and a trace of (5).

(*b*) Methyl penicillanate (1) (0·10 g) in tetrahydrofuran (2 ml) was treated with methyl iodide (0·3 g) and sodium hydride (70 mg of 50% dispersion) for 4 h. Work-up as in (*a*) gave a gum (65 mg) which was purified by chromatography to give methyl 3-methyl-2-[*N*-methyl-*trans*-3-(methylthio)acrylamido]crotonate (5), as a gum; $\lambda_{max.}$ 229 (ε 18,000) and 284 nm (28,000); $\nu_{max.}$ 1720, 1630, and 1575 cm^{-1}; δ 1·85 (3H, s), 2·27 (3H, s), 2·29 (3H, s), 3·04 (3H, s), 3·74 (3H, s), 5·80 (1H, d, *J* 15 Hz), and 7·70 (1H, d, *J* 15 Hz); *m/e* (M^+) 243 ($C_{11}H_{17}NO_3S$).

Methylation of Methyl 6α-Bromopenicillanate (2).—Methyl 6α-bromopenicillanate (2) (0·294 g) in tetrahydrofuran (3 ml) was treated with methyl iodide (0·16 g) and sodium hydride (48 mg of 50% dispersion). After 3 h the mixture was worked up as for (1) and the residue chromatographed to give unchanged (2) (0·14 g) and *methyl 2-[2-bromo-3-(methylthio)acrylamido]-3-methylcrotonate* (6) (22 mg), m.p. 125°; $\lambda_{max.}$ 227 nm (ε 7700) and 292 nm (ε 14,500); $\nu_{max.}$ 3400, 1728, 1660, and 1561 cm^{-1}; δ 1·88 (3H, s), 2·21 (3H s), 2·52 (3H, s), 3·78 (3H, s), 7·57br (1H, exch.), and 8·15 (1H, s); *m/e* (M^+) 307 (Found: C, 39·3; H, 4·6; N, 4·4. $C_{10}H_{14}BrNO_3S$ requires C, 39·3; H, 4·6; N, 4·5%).

Alkylation of Methyl 6,6-Dibromopenicillanate (3).—(a) *Methylation.* Methyl 6,6-dibromopenicillanate (3) (3·73 g) in tetrahydrofuran (125 ml) was treated with methyl iodide (14·2 g) and sodium hydride (0·96 g of 50% dispersion). The mixture was stirred under nitrogen for 22 h, and then worked up as for (1) to give a crude gum (4·15 g). Chromatography gave unchanged (3) (1·23 g) and (4R)-3,3-*dibromo*-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylthioazetidin*-2-*one* (9) (1·81 g) as an oil, b.p. 140° at 0·01 mmHg; $\lambda_{max.}$ 222 nm (ε 11,700); $\nu_{max.}$ 1793, 1730, and 1630 cm^{-1}; δ 2·02 (3H, s), 2·24 (3H, s), 2·31 (3H, s), 3·81 (3H, s), and 5·51 (1H, s); *m/e* (M^+) 385 (Found: C, 31·3; H, 3·5; Br, 41·1; N, 3·4; S, 8·3. $C_{10}H_{13}Br_2NO_3S$ requires C, 31·0; H, 3·4; Br, 41·3; N, 3·6; S, 8·3%).

(b) *Benzylation* (we thank Miss P. M. Tolliday for this

[6] R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1969, **91**, 1401; D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc.* (*C*), 1971, 3540.

preparation). The dibromo-ester (3) (2 g) was treated with benzyl bromide (1·38 g) and sodium hydride (0·52 g of 50% dispersion) in tetrahydrofuran (50 ml). After stirring under nitrogen for 60 h the mixture was worked up as previously described and the dark oil chromatographed. After removal of the excess of benzyl bromide and unchanged (3) (0·73 g), (4R)-4-*benzylthio*-3,3-*dibromo*-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)*azetidin*-2-*one* (10) (0·72 g) was obtained as a crystalline solid, m.p. 93—94° (from chloroform–light petroleum), $\nu_{max.}$ 1790, 1725, and 1625 cm^{-1}; δ 1·92 (3H, s), 2·22 (3H, s), 3·64 (3H, s), 3·83 (2H, s), 5·42 (1H, s), and 7·3 (5H, s) (Found: C, 41·5; H, 3·7; Br, 34·6; N, 3·0; S, 6·5. $C_{16}H_{17}Br_2NO_3S$ requires C, 41·5; H, 3·7; Br, 34·5; N, 3·0; S, 6·9%).

2-[(4R)-3,3-*Dibromo*-4-*methylthio*-2-*oxoazetidin*-1-*yl*]-3-*methylcrotonolactone* (13).—The lactam (9) (195 mg) was dissolved in dioxan (5 ml) and selenium dioxide (244 mg, 4 equiv.) was added, followed by sufficient water to give a homogeneous solution. After 24 h at reflux the cooled solution was poured into chloroform and the mixture washed with water. The organic layer was separated, dried (Na_2SO_4), and evaporated. Chromatography afforded starting material (9) (95 mg) and the lactone (13) (24 mg); $\nu_{max.}$ 1793, 1768, and 1680 cm^{-1}; δ 2·23 (3H, d, *J* 1 Hz), 2·33 (3H, s), 4·80 (2H, d, *J* 1 Hz), and 6·17 (1H, s); *m/e* (M^+) 369 ($C_9H_9Br_2NO_3S$).

Reaction of the Lactam (9) *with Lead Tetra-acetate.*—The lactam (9) (200 mg) was dissolved in dry benzene (10 ml) and lead tetra-acetate (1 g) was added. The mixture was refluxed for 2 h, cooled, and treated with ethylene glycol (1 ml) to remove unchanged lead tetra-acetate. The mixture was washed with dilute aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4), and evaporated to give an oil (210 mg). Chromatography afforded (4*R*)-4-acetoxymethylthio-3,3-dibromo-1-(1-methoxycarbonyl-2-methylprop-1-enyl)azetidin-2-one (12) (46 mg) as a gum; $\nu_{max.}$ 1790, 1750, 1730, and 1630 cm^{-1}; δ 1·97 (3H, s), 2·31 (3H, s), 2·07 (3H, s), 3·80 (3H, s), 5·18 (2H, centre of ABq, *J* 12 Hz), and 5·78 (1H, s); *m/e* (M^+) 433 ($C_{12}H_{15}Br_2NO_5S$). Acetoxylation of the *S*-methyl group was confirmed by the following fragmentation: (12) *m/e* 443 ⟶ $(Br_2C{=}CH{\cdot}S{\cdot}CH_2{\cdot}OAc)^+$ *m/e* 288.

Further elution of the column produced 4-*acetoxy*-3,3-*dibromo*-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylthioazetidin*-2-*one* (14) (100 mg), which solidified; m.p. 87—89°; $\nu_{max.}$ 1805, 1785, 1725, and 1635 cm^{-1}; δ 2·00 (3H, s), 2·17 (3H, s), 2·20 (3H, s), 2·23 (3H, s), and 3·75 (3H, s) (Found: C, 32·3; H, 3·4; Br, 36·1; N, 3·2; S, 7·4. $C_{12}H_{15}Br_2NO_5S$ requires C, 32·4; H, 3·4; Br, 35·9; N, 3·2; S, 7·2%). The final product was a 1 : 1 mixture of the two possible sulphoxides (15) (37 mg), $\nu_{max.}$ 1807, 1732, 1710, 1630, and 1060 cm^{-1}. The ratio of isomers was deduced by comparison of the n.m.r. spectrum of the mixture with that of the product obtained by treatment of the lactam (9) with *m*-chloroperbenzoic acid (1 mol. equiv.).

(4R)-3,3-*Dibromo*-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylsulphinylazetidin*-2-*one* (15).—The lactam (9) (293 mg) was dissolved in dry chloroform (12 ml) and the solution cooled to about 5° in an ice-bath. *m*-Chloroperbenzoic acid (137 mg) was added in portions over 5 min and the solution was stirred for a further 20 min. The mixture was extracted with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated to give an oil, which crystallised on trituration with light petroleum. The crude product (303 mg) was recrystallised from benzene–light petroleum to give white crystals (250 mg), m.p. 104—106°; $\nu_{max.}$ (Nujol) 1799, 1720, 1630, and 1070 cm^{-1}. The n.m.r. spectrum indicated that the product was a 3 : 1 mixture of the two sulphoxides (15), the least polar (t.l.c.) being the major isomer: *major isomer* (deduced from n.m.r. of mixture) δ 2·13 (3H, s), 2·30 (3H, s), 2·78 (3H, s), 3·81 (3H, s), and 5·12 (1H, s); *minor isomer* δ 1·98 (3H, s), 2·30 (3H, s), 2·61 (3H, s), 3·80 (3H, s), and 5·08 (1H, s) [Found (mixture): C, 29·9; H, 3·3; N, 3·4; S, 7·9. $C_{10}H_{13}Br_2NO_4S$ requires C, 29·8; H, 3·3; N, 3·5; S, 7·9%].

Pummerer Rearrangement of the Sulphoxides (15).—The crystalline mixture of sulphoxides (15) (343 mg; m.p. 104—106°) was dissolved in acetic anhydride (25 ml; redistilled from anhydrous sodium acetate); the solution was refluxed for 4 h, then evaporated *in vacuo*. The residue (350 mg) was chromatographed to give the methyl sulphide (9) (130 mg) and the acetoxymethyl sulphide (12) (105 mg), identical with authentic specimens.

Methyl 6,6-*Dibromopenicillanate* 1β-*Oxide* (16).—Methyl 6,6-dibromopenicillanate (3) (4·03 g) dissolved in dry chloroform (100 ml) was cooled to about 10° in an ice-bath. *m*-Chloroperbenzoic acid (1·88 g) in dry chloroform (20 ml) was added over 5 min. The solution was allowed to warm to room temperature (30 min) and was then washed with dilute aqueous sodium hydrogen carbonate and brine. The organic layer was separated, dried ($MgSO_4$), and evaporated to a white solid (4·06 g). Recrystallisation from benzene–light petroleum afforded white crystals of the β-sulphoxide (16) (3·33 g), m.p. 133—135° (lit.,[1] 133—135°).

Reaction of the Sulphoxide (16) *with Acetic Anhydride.*—The β-sulphoxide (16) (500 mg) was dissolved in acetic anhydride (35 ml; redistilled from anhydrous sodium acetate) and the solution was refluxed for 30 min. The solvent was removed under vacuum at 40° to give an oily residue which was taken up in ethyl acetate. The solution was washed successively with cold dilute aqueous sodium hydrogen carbonate, water, and saturated brine, dried (Na_2SO_4), and evaporated. The crude product (510 mg) was chromatographed to afford *methyl* 7,7-*dibromo*-3-*methylceph*-3-*em*-4-*carboxylate* (19) (165 mg), m.p. 128° (from ethyl acetate–light petroleum), $\nu_{max.}$ (Nujol) 1785, 1725, and 1642 cm^{-1}; δ 2·3 (3H, s), 3·25 (2H, s), 3·85 (3H, s), and 5·26 (1H, s) (Found: C, 29·0; H, 2·5; N, 3·8; S, 9·8. $C_9H_9Br_2NO_3S$ requires C, 29·1; H, 2·5; N, 3·8; S, 8·6%).

The second product (200 mg) was a 2 : 1 mixture of the penam (17) and the cepham (18), inseparable by t.l.c.; $\nu_{max.}$ 1800 and 1747 cm^{-1}. The n.m.r. spectrum of each compound was deduced from that of the mixture: (17) δ 1·43 (3H, s), 2·12 (3H, s), 3·82 (3H, s), 4·08 (2H, centre of ABq, *J* 12 Hz), 4·86 (1H, s), and 5·8 (1H, s); (18) δ 1·58 (3H, s), 2·07 (3H, s), 3·48 (2H, centre of ABq, *J* 12 Hz), 3·82 (3H, s), 4·73 (1H, s), and 5·57 (1H, s).

Methyl 7,7-*Dibromo*-3-*methylceph*-3-*em*-4-*carboxylate* (19).—Methyl 6,6-dibromopenicillanate 1β-oxide (16) (500 mg) was dissolved in dry xylene and anhydrous toluene-*p*-sulphonic acid (15 mg) was added. The solution was refluxed for 1 h, and the solvent removed at 40° under vacuum to give an oil. The latter was dissolved in ethyl acetate and the solution was washed with dilute aqueous sodium hydrogen carbonate and brine. The dried organic layer was evaporated and the crude product (480 mg) chromatographed to afford the cepham (19) (275 mg), m.p. 128° (from ethyl acetate–light petroleum).

Osmium Tetraoxide Oxidation of the Lactam (9).—The lactam (9) (152 mg) in dry benzene (3 ml) containing dry

pyridine (0·4 ml) was treated with osmium tetraoxide (100 mg) in dry benzene (2 ml), and the mixture was left in the dark at room temperature for 15 h. Ethyl acetate (15 ml) was added and hydrogen sulphide was bubbled through the mixture for 20 min. The black precipitate was filtered off and the washings were evaporated to dryness at room temperature to yield a dark oil (150 mg). Chromatography afforded (4R)-3,3-*dibromo*-4-*methylthioazetidin*-2-*one* (20) (60 mg), m.p. 84° (from benzene–light petroleum); $\nu_{max.}$ 3375 and 1804 cm^{-1}; δ 2·27 (3H, s), 5·18 (1H, s), and 6·67br (1H, s, exchanged with D_2O) (Found: C, 17·8; H, 1·8; N, 5·2; S, 11·7. $C_4H_5Br_2NOS$ requires C, 17·5; H, 1·8; N, 5·1; S, 11·6%).

Further elution of the column gave methyl 3-hydroxy-3-methyl-2-oxobutyrate (21) (20 mg) as a liquid, $\nu_{max.}$ 3520, 1740sh, and 1728 cm^{-1}; δ 1·5 (6H, s), 4·37br (1H, s, D_2O exchanged), and 3·9 (3H, s).

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