THE CHEMISTRY OF THE 6β-DIACYLAMINOPENICILLINS

Ronald G. Micetich[1,2], Rajeshwar Singh[1], Chen C. Shaw[3], Samarendra N. Maiti[1], Maya P. Singh[1,2], and Paul Spevak[1]

[1]SynPhar Laboratories Inc., 4290 - 91A Street, Edmonton, Alberta, Canada T6E 5V2

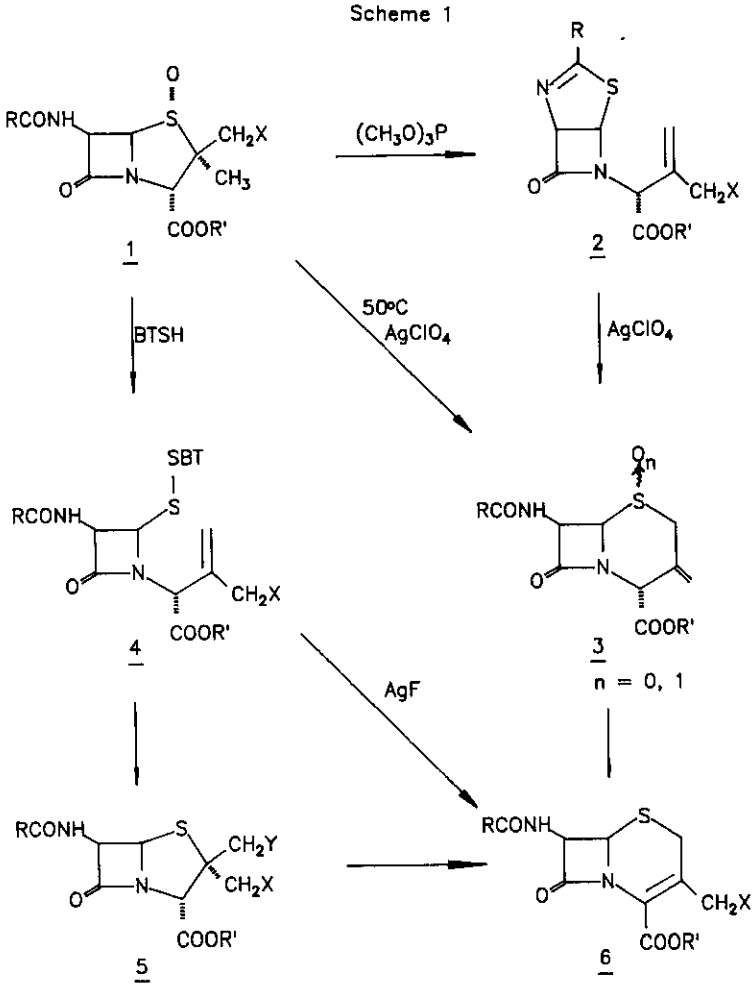
[2]Faculty of Pharmacy and Pharmaceutical Sciences University of Alberta, Edmonton, Canada

[3]Ayerst Laboratories, Montreal, Quebec, Canada

Abstract - A comparison of the chemical reactions of 6β-amidopenicillins, 6β-phthalimidopenicillins and 6β-diacylaminopenicillins with trimethyl phosphite and with benzyl and heteroaryl thiols is reported. The reaction of the unsym-azetidinone disulfides, obtained from the reaction of penicillin sulfoxides with 2-mercaptobenzothiazole, with halogenating agents is also discussed.

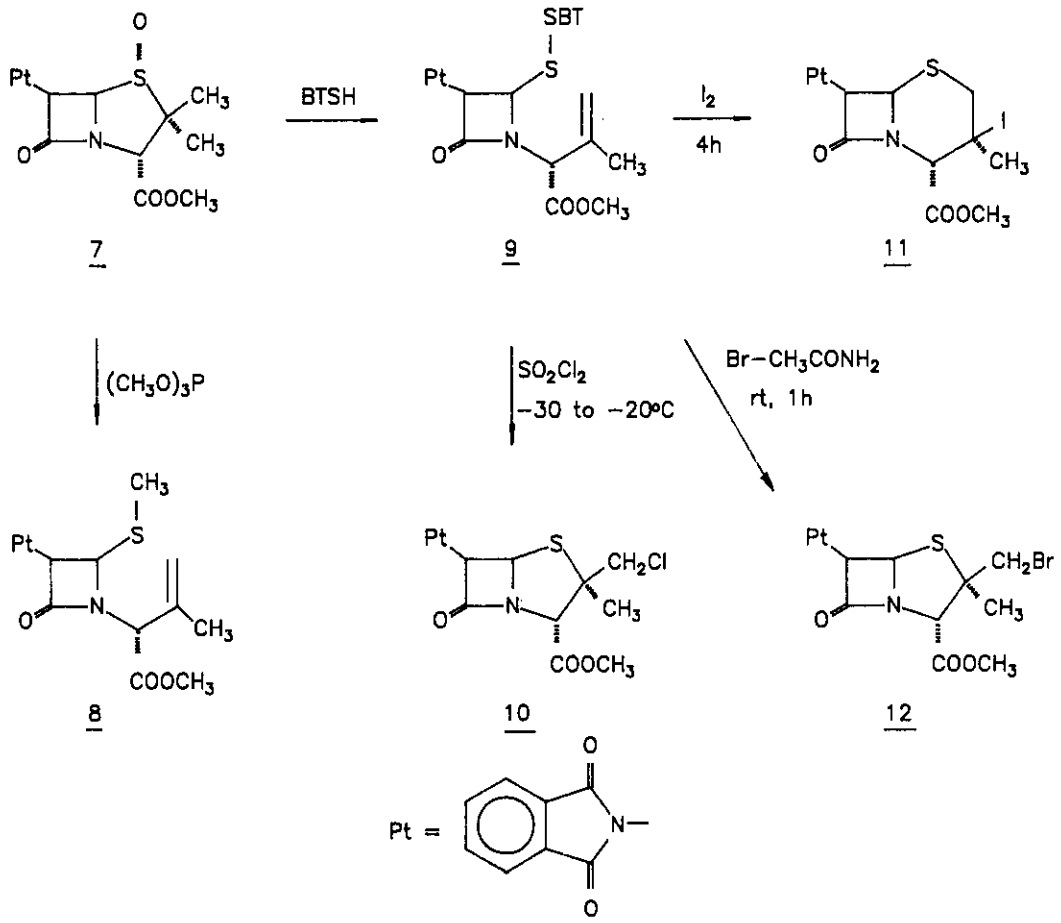
Morin's discovery of the sigmatropic rearrangement of penicillin sulfoxides to cephalosporins[1] led to the investigation of secosulfenic acids as a route to the 3-functionalised cephalosporins[2,3]. The preparation of the desired secosulfenic acids by thermolysis is dependent on the stereochemistry of the sulfoxide. The preparation and uses of 2β-substituted methyl-2α-methylpenam-1α-sulfoxides, important intermediates for the preparation of the secosulfenic acids have been reported[4-8]. This paper reports the chemistry of the 6β-diacylaminopenams 13 (Scheme 3) in comparison with that of the 6β-amidopenam-1α-sulfoxides 1 (Scheme 1) and the 6β-phthalimido-1α-sulfoxides 7 (Scheme 2). The preparation of the 6β-diacylaminopenicillins 13 and their ready conversion in almost quantitative yields to the 6β-diacylaminopenam-1α-sulfoxides 14 by oxidation with m-CPBA in benzene, has been reported by us[9]. These compounds 14 (X = H and Cl) on treatment with zinc and ammonium acetate gave the 6β-amidopenam-1α-sulfoxides, 1[9]. The 6β-amidopenam-1α-sulfoxides 1, on heating with trimethyl phosphite (one eq) in benzene or toluene, gave the thiazolineazetidinones, 2 (X = H or Cl)[10], the reaction proceeding by way of the sulfenic acid or alternatively by its S-P derivative[10,11]. The reaction of 6β-phthalimidopenicillin-1α-sulfoxide 7 with trimethyl phosphite gave the 2-methylthio-3-phthalimidoazetidinone 8[12]. The 6β-diacylaminopenam-1α-sulfoxides 14 on refluxing with trimethyl phosphite in toluene for 1 h gave the product 16,

Scheme 1



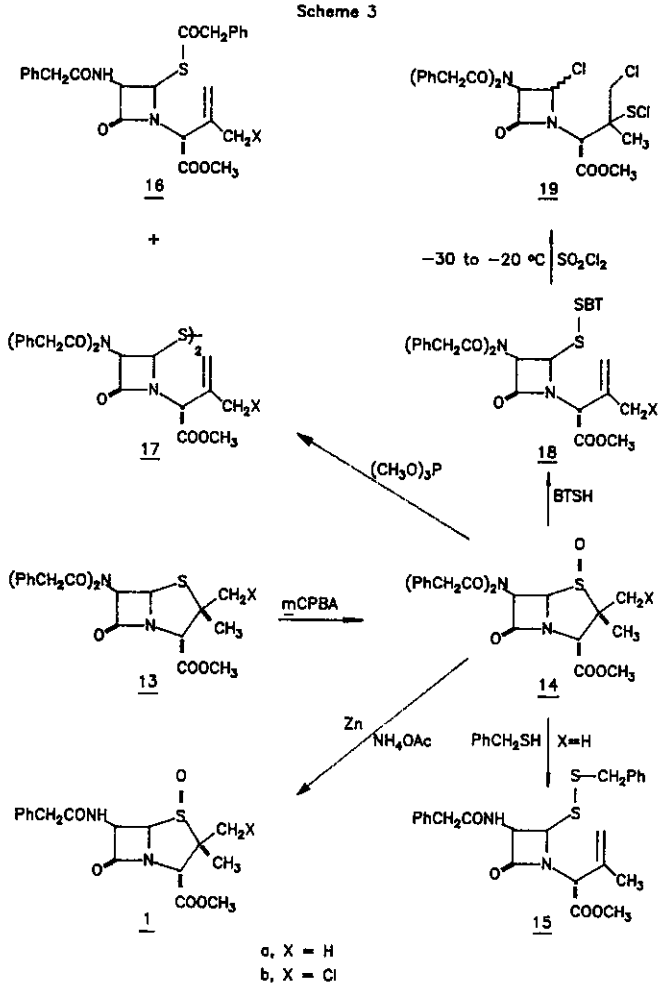
probably due to intramolecular acylation of the S-P derivative, and another product 17 showing no -SH proton signals between 2.0 - 2.2δ in its nmr spectrum. The parent ion (FAB) for 17a was 898 (930-32) and for 17b was 967 (999-32), indicating that compound 17 is a dimer of the mercapto-azetidinone. Further treatment of compound 17a with diazomethane did not afford any $-S-CH_3$ derivative as would be expected in the case of a mercaptan and this is in accordance with the structure of 17a being the dimer. That the 6-diacylaminopenicillin-1-sulfoxide 14 can acylate mercaptans was confirmed by heating 14 with benzyl mercaptan (2 eq) in toluene under reflux; 15 was obtained along with the acyl derivative of benzyl mercaptan [with 1 eq of benzyl mercaptan a complex mixture of products resulted]. The direct thermolytic conversion of the 2β-(substituted methyl) penam-1α-sulfoxides 1 to the 3-(substituted methyl) cephems 6 has not as yet been achieved. This conversion has however been brought about by the sequence 1 → 2 → 3 → 6[13] or 1 → 4 → 6[14] or 1 → 4 → 5 → 6[13,15] The reaction of the unsym-azetidinone disulfide 4 (X is not H) with halogenating agents proceeds readily to give the 2,2-di(monosubstituted methyl) penams 5[15]. In contrast the diacylamino compounds 18b undergo considerable decomposition.

Scheme 2



The reaction of the unsym-3β-amidoazetidinone disulfides 4 (X=H) with various halogenation agents as a route to the 2β-halomethylpenams is now well known[16,17], and we have found that the heterogeneous reaction with $CuCl_2$ and $CuBr_2$ is an excellent route to the 2-chloro-(and bromo-) methylpenams. In contrast, the unsym-3β-phthalimidoazetidinone disulfide, 9, and the unsym-3β-diacylaminoazetidinone disulfides 18 do not react with $CuCl_2$ or $CuBr_2$. The phthalimido compound, 9, reacts with SO_2Cl_2 at -20 to -30°C to give the 2β-chloromethylpenam, 10; with Br_2 and acetamide at ambient temperature to give the 2β-bromomethylpenam, 12; and with iodine over 4 h to give the 3β-iodocepham, 11. The unsym-3β-diacylaminoazetidinone disulfide 18 (X = H), reacted with SO_2Cl_2 at -20 to -30° to give a mixture of starting material 18a, the 6β-diacylamino-2β-chloromethylpenam 13b, along with chlorinolysis product 19[18]. With Br_2-acetamide at room temperature a mixture of the desired 6β-diacylamino-2β-bromomethylpenam and the 7β-diacylamino-3β-bromocepham is obtained (the reaction was incomplete at 0°C); and with iodine (4 h at room temperature) there is no reaction. The data hence shows that there is a considerable difference in reactivity and in the course of reactions between the 6β-amidopenams, the 6βphthalimidopenams and the 6β-diacylamidopenams.

Scheme 3



EXPERIMENTAL

Ir spectra were recorded on a Nicolet DX-FT Ir spectrophotometer. Nmr spectra were recorded on a Varian EM-390A and a Brucker AM-300 spectrometer, using tetramethylsilane as internal standard.

Methyl 6β-(Diphenylacetyl)aminopenicillanate 1α-sulfoxide (14a):

m-Chloroperbenzoic acid (540 mg, 80%, 2.5 mmole) was added to a well stirred solution of the pure 6β-diacylaminopenam 13a (1.16 g, 2.5 mmole) in benzene (50 ml) at room temperature. After 30 min, the reaction mixture was washed successively with aqueous 5% $NaHSO_3$, $NaHCO_3$ and brine solution. The organic layer was dried over Na_2SO_4, filtered and concentrated to give a product which was purified on silica gel using ethyl acetate-hexane as gradient eluant: Yield 808 mg (67%), ir (KBr) cm^{-1}: 2992, 1797, 1741, 1694; nmr ($CDCl_3$)δ: 1.20 (s, 3H), 1.72 (s, 3H), 3.82 (s, 3H), 4.08 and 4.14 (ABq, J = 17.24 Hz, 4H), 4.30 (d, J = 4.30 Hz, 1H), 4.52 (s, 1H), 5.38 (d,J = 4.30 Hz, 1H), 7.18 (m,4H), 7.34 (m,6H). EIMS: $M^+(-C_8H_8O_2)$ 366.0988 for $C_{17}H_{18}N_2O_4S$ calcd 346.1020.

Methyl 6β-(Diphenylacetyl)amino-2β-chloromethylpenicillanate 1α-sulfoxide (14b):

Prepared in 66% yield by the same was as described above. Ir (KBr)cm^{-1}: 2992, 1799, 1744, 1693; nmr ($CDCl_3$)δ: 1.36 (s,3H), 3.83 (s,3H), 4.05 and 4.13 (ABq, J = 11.9 Hz, 2H), 4.14 (s, 4H), 4.40 (d, J = 4.75 Hz, 1H), 4.72 (s, 1H), 5.46 (d, J = 4.75 Hz, 1H), 7.16 (m, 4H), 7.36 (m, 6H). EIMS: M^+ ($-C_8H_8O_2$) 380.0598 for $C_{17}H_{17}N_2O_4SCl$ calcd 380.0630.

Methyl 6β-Phenylacetamidopenicillanate 1α-sulfoxide (1a):

Zinc (2.0 g) was added to a solution of the 6β-diacylaminopenam-1α-sulfoxide (14a, 1.0 g) in THF (15 ml), followed by 1 M aqueous ammonium acetate (5 ml) under stirring at room temperature. After 2 h, the reaction mixture was filtered through Celite, washed with ethylacetate and the filtrate was washed with water, dil HCl and brine solution successively. The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified over silica gel using ethyl acetate-dichloromethane as gradient eluant. Yield 435 mg (60%), ir (KBr)cm^{-1}: 3279, 3000, 1796, 1753, 1672; nmr ($CDCl_3$)δ: 1.28 (s,3H), 1.64 (s,3H), 3.60 (s,2H), 3.80 (s,3H), 4.40 (s,1H), 4.68 (d, J = 4.0 Hz,1H), 5.12 (q, J_1 = 7.8 Hz, J_2 = 4 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 7.30 (m,5H).

Methyl 6β-Phenylacetamido-2βchloromethylpenicillanate 1α-sulfoxide (1b):

Prepared in 43% yield by the same way as described above. Ir (KBr)cm^{-1}: 3312, 2984, 1794, 1748, 1667; nmr ($CDCl_3$)δ: 1.40 (s,3H), 3.60 (s,2H), 3.84 (s,3H), 4.08 and 4.12 (ABq, J = 12.5 Hz, 2H), 4.76 (d, J = 4.30 Hz, 1H), 4.78 (s,1H), 5.12 (q, J_1 = 7.30 Hz, J_2 = 4.30 Hz, 1H), 7.30 (m,6H).

Reaction of Methyl 6β-(Diphenylacetyl)aminopenicillanate 1α-sulfoxide (14a) with Trimethyl Phosphite:

Trimethyl phosphite (0.4 ml) in excess was added to a solution of 14a (482 mg, 1 mmole) in toluene (10 ml) and heated under reflux for 1 h. The reaction mixture was concentrated and the residue dissolved in ethyl acetate. The organic phase was washed with water and brine solution successively, dried over Na_2SO_4 and concentrated. The residue was heated under vacuum at 60°C for 1 h to remove residual trimethyl phosphite and then purified by preparative thin layer chromatography on silica gel using ethyl acetate - hexane as developing solvent and gave two pure fractions.

Fraction A: 70 mg (20%) is assigned structure 17a from the following spectroscopic data. Ir (KBr)cm^{-1}: 2951, 1786, 1746, 1704, 1499; nmr ($CDCl_3$)δ: 1.78 (s,3H), 3.70 (m,5H), 4.20 (bs, 2H), 4.84 (m,3H), 5.34 (d, J = 5.66 Hz, 1H), 6.12 (d, J = 5.66 Hz, 1H), 7.04 (bs,1H), 7.28 (m, 10H); MS(FAB): M^+ 898 (930 - 32) for $C_{50}H_{50}N_4O_{10}S_2$ calcd 930, Anal.: found S, 6.45 for $C_{50}H_{50}N_4O_{10}S_2$ (930) calcd S, 6.88%.

Fraction B: 112 mg (24%) is assigned structure 16a from the following spectroscopic data. Ir (KBr)cm^{-1}: 2919, 1774, 1746, 1670, 1529; nmr ($CDCl_3$)δ: 1.74 (s, 3H), 3.56 (s, 2H), 3.72 (m, 5H), 4.72 (s,1H), 4.80 (m,2H), 5.28 (q, J_1 = 7.93 Hz, J_2 = 4.75 Hz, 1H), 5.94 (d, J = 4.75 Hz, 1H), 6.48 (d, J = 7.93 Hz, 1H), 7.30 (m,10H); Anal.: found S, 6.58 for $C_{25}H_{26}N_2O_5S$ (466),

calcd S, 6.88%. Similarly methyl 6β-(diphenylacetyl)amino-2β-chloromethylpenicillanate-1α-sulfoxide (14b) on refluxing with trimethyl phosphite in toluene gave compounds 17b in 18% and 16b in 25% yields.

Compound 17b: Ir (KBr)cm^{-1}: 3410, 3033, 2951, 1786, 1745, 1712, 1494; nmr ($CDCl_3$)δ: 3.66 and 3.72 (ABq, J = 14.06 Hz, 2H), 3.76 (s, 3H), 3.86 and 4.14 (ABq, J = 12.09 Hz, 2H) 4.24 (bs, 2H), 4.98 (d, J = 10.81 Hz, 2H), 5.16 (s, 1H), 5.36 (d, J = 5.24 Hz, 1H), 6.00 (d, J = 5.24 Hz, 1H), 7.00 (bs, 1H), 7.30 (m, 10H); MS(FAB): M^+ 967(999-32) for $C_{50}H_{48}N_4O_{10}S_2Cl_2$ calcd 999.

Compound 16b: Ir (KBr)cm^{-1}: 3297, 3026, 2959, 1785, 1747, 1697, 1537; nmr ($CDCl_3$)δ: 3.58 (s, 2H), 3.76 (m, 5H), 3.86 and 4.13 (ABq, J = 12.03 Hz, 2H), 5.04 (d, J = 5.85 Hz, 2H), 5.10 (s, 1H), 5.20 (q, J_1 = 8.09 Hz, J_2 = 4.49 Hz, 1H), 6.00 (d, J = 4.49 Hz, 1H), 6.35 (d, J = 8.09 Hz, 1H), 7.30 (m, 10H).

Reaction of Methyl 6β-(Diphenylacetyl)aminopenicillanate-1α-sulfoxide (14a) with Benzyl Mercaptan:

Benzyl mercaptan (248 mg, 2 mmole) was added to a solution of 14a (482 mg, 1 mmole) in toluene (10 ml) and heated under reflux for 2 h. The reaction mixture was concentrated to approximately half the volume and diluted with hexane. The semisolid residue that separated was dissolved in methylene chloride and concentrated. The residue was purified by thin layer chromatography over silica gel using ethyl acetate - hexane as developing solvent to give 15 (120 mg, 25%). The structure was assigned on the basis of the following spectroscopic data. Ir ($CHCl_3$)cm^{-1}: 3361, 3016, 1779, 1745, 1680, 1517; nmr ($CDCl_3$)δ: 1.83 (s, 3H), 3.65 (s, 2H), 3.76 (s, 3H), 3.82 (S, 2H), 4.74 (s, 1H), 4.90 (d, J = 4.3 Hz, 1H), 5.06 (d, J = 49 Hz, 2H), 5.30 (q, J_1 = 8.6 Hz, 1H), 7.30 (m, 10H). MS(FAB): MH^+ 471 for $C_{24}H_{26}N_2O_4S_2$ calcd 470.

Methyl 2-[2-Oxo-3β(diphenylacetyl)amino-4-(benzothiazol-2-yl-dithio)azetidin-1-yl]-2-prop-2 en-2-yl-acetate (18a):

A solution of 705 mg (1.46 mmole) of 14a was heated under reflux in toluene or benzene (50 ml) with 0.244 g (1.46 mmole) of 2-mercaptobenzothiazole for 1.5 to 2 h. Approximately half of the solvent was distilled off and the rest was diluted with hexane. The semisolid residue which separated was dissolved in dichloromethane and concentrated to give a light yellow foamy compound which was purified by flash chromatography on silica gel using ethyl acetate - hexane as eluant. Yield 640 mg (69%), Ir (KBr)cm^{-1}: 3386, 3050, 2951, 1780, 1742, 1700 (w), 1678 (w), 1428; nmr ($CDCl_3$)δ: 2.04 (s, 3H), 3.78 (m, 5H), 4.40 (bs, 2H), 5.04 (d, J = 11.2 Hz, 2H), 5.22 (s, 1H), 5.22 (s, 1H), 5.48 (d, J = 4.63 Hz, 1H), 5.78 (d, J = 4.63 Hz, 1H), 6.90 (bs, 2H), 7.30 (m, 10H), 7.78 (d, J = 6 Hz, 1H), 7.90 (d, J = 6 Hz, 1H). MS(FAB): MH^+ 632 for $C_{32}H_{29}N_3O_5S_3$ calcd 631. Similarly methyl 6β-(diphenylacetyl)amino-2β-chloromethylpenicillanate-1α-sulfoxide (14b, 2.56 g, 4.95 mmole) on refluxing with mercapto benzothiazole (844 mg, 5.05 mmole) in benzene or toluene gave 18b in 75% (2.46 g) yield. Ir (KBr)cm^{-1}: 3443, 2984, 1783, 1741, 1700 (w), 1430; nmr ($CDCl_3$)δ: 3.80 (m, 5H), 4.40 (bs, 2H), 4.24 and 4.44 (ABq, J = 12.12

Hz, 2H), 5.50 (d, J = 4.70 Hz, 1H), 5.61 (s, 1H), 5.78 (d, J = 4.70 Hz, 1H), 6.94 (bs, 2H), 7.34 (m, 10H), 7.74 (d, J = 6 Hz, 1H), 7.90 (d, J = 6 Hz, 1H). MS (FAB): M^+ 663 for $C_{32}H_{28}N_3O_5S_3Cl$ calcd 665.6.

ACKNOWLEDGEMENT

M.P.S. and R.S. thank the Alberta Heritage Foundation for Medical Research, Alberta, Canada, for the award of Postdoctoral Fellowships.

REFERENCES

1. R.B. Morin, B.G. Jackson, R.A. Mueller, E.R. Lavagnino, W.B. Scanlon, and S.L. Andrews. J. Am. Chem. Soc., 1963, 85, 1896; Idem, Ibid., 1969, 91, 1401.
2. Recent Advances in the Chemistry of β-Lactam Antibiotics, J. Elks, Ed. The Chem. Soc., London, 1977, p. 101 and 181.
3. G.A. Koppel and L.J. McShane, J. Am. Chem. Soc., 1978, 100, 288.
4. S. Uyeo, T. Aoki and W. Nagata; Heterocycles, 1978, 11, 305.
5. D.O. Spry; J. Org. Chem., 1972, 37, 793.
6. A.J. Vlietinck, E. Roets, H. Vanderhaeghe and S. Toppet; J. Org. Chem., 1974, 39, 441.
7. 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.
8. C.R. Harrison and P. Hodge, J. Chem. Soc. Perkin Trans. 1, 1976, 1772.
9. R.G. Micetich, R. Singh, and C.C. Shaw, J. Org. Chem., 1986, 51, 1811.
10. R.D.G. Cooper and F.L. Jose, J. Am. Chem. Soc., 1970, 92, 2575.
11. L.D. Hatfield, J.W. Fisher, F.L. Jose, and R.D.G. Cooper, Tetra. Lett., 1970, 4897.
12. Cephalosporins and Penicillins, Chemistry and Biology, Editor E.H. Flynn, Academic Press, New York, 1972, 201.
13. S. Uyeo, T. Aoki, H. Itani, T. Tsuji, and W. Nagata, Heterocycles, 1978, 10, 99.
14. T. Kamiya, Japan Kokai Patent, 49-75592.
15. Shionogi and Co. Ltd., U.K. Patent 1978, No. 1529 662.
16. T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, Tetra. Lett., 1973, 3001.
17. T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi, and T. Oku, U.S. Patent 1976, No. 3954 732.
18. R.G. Micetich, R. Singh, W.O. Merlo, D.M. Tetteh, C.C. Shaw, and R.B. Morin, Heterocycles, 1984, 22, 2757.

Received, 24th February, 1986