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A CHEMICAL CONVERSION OF PENICILLIN SULFOXIDES INTO 6,7-EPI-1-OXOCEPHAMS

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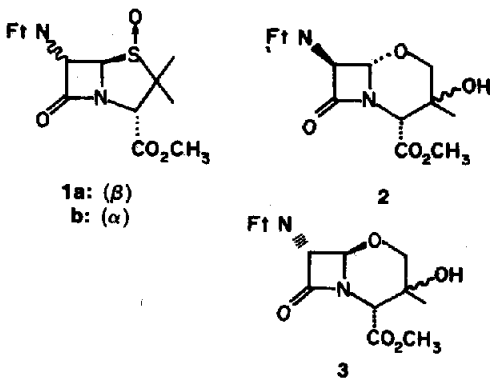
Abstract—Penicillin sulfoxides were converted into 6,7-epi-1-oxocephams by a simple and efficient method. The oxidation of 1,2-seco-Δ^2-cephem with osmium tetroxide provided 1,2 diol **5** which was then converted to the chloro-β-lactams **6**. Treatment of **6** with tin (II) chloride or silver tetrafluoroborate afforded 6,7-epi-1-oxocephams **2**, **3**. Several reactions were attempted to obtain 1-oxo-exomethylene cephalosporins **13**, **15** from the oxazoline **11** prepared from the exomethylene cephalosporin **8**.

It is well known that replacement of the S atom at position 1 of the cephalosporin nucleus with oxygen provides analogues with comparable bioactivity to their natural 1-thia-counterparts.[2,3] In spite of several efforts,[2-5] chemical synthesis of 1-oxo-cepham remains difficult, the problem being to develop a simple and efficient procedure with a maximum control of stereochemistry. We wish to report here a very simple, efficient chemical transformation of penicillin sulfoxides **1a**, **b** into 6,7-epi-1-oxocephams, **2** and **3** (Scheme 1).



1a: (β)
b: (α)

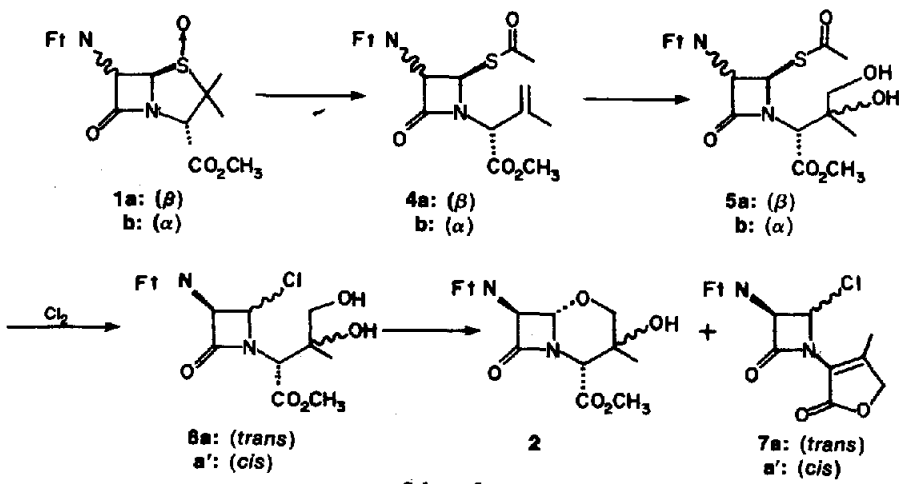
2

3

Scheme 1.

RESULTS AND DISCUSSION

When the penicillin sulfoxide **1a** was treated with trimethyl phosphite in refluxing toluene containing an excess (5 eq.) of acetic anhydride, the clean 1,2 seco-Δ^2-cephem of Cooper[6] **4a** was obtained (95%). Subsequent oxidation of **4a** by osmium tetroxide provided the 1,2 diol **5a** in 85% yield. The preparation of **5a** was extremely clean and the crude material was used directly in the next step. The thioacetyl group of **5a** could be readily removed by the treatment with chlorine to give a mixture of the chloro-β-lactams **6a** and **6a'** in the ratio of 5 to 3 respectively (93%). The ring closure rules[7] predict the possibility of an endocyclic ring forming addition to an acyl immonium ion derived from the chloro-β-lactam diols **6a**, **a'**. Treatment of the mixture of **6** with anhydrous tin (II) chloride afforded a 27% yield of the 3-hydroxy-6-epi-cepham **2** (oil) and 30% of lactone-derived products such as **7a** and **7a'** (Scheme 2). As was observed by Wolfe,[8] the ring closure prefers to occur from the less sterically hindered α-face to give the epimer of 1-oxocepham. During the ring closure, if the phthalimido group is located on the α-side, SN_2 back-side attack by the alcohol of the chloro-β-lactam **6b**, **b'** could better approach C-6 from the β-side to give 7-epi-1-oxocepham **3** (Scheme 3). The *trans* isomer of 1,2 seco-Δ^2-cepham, **4b** was prepared from **1a** by epimerization[9] (**1b**, Et_3N, $CHCl_3$, r.t. 2 hr, 85%, m.p. 134°),



1a: (β)
b: (α)

4a: (β)
b: (α)

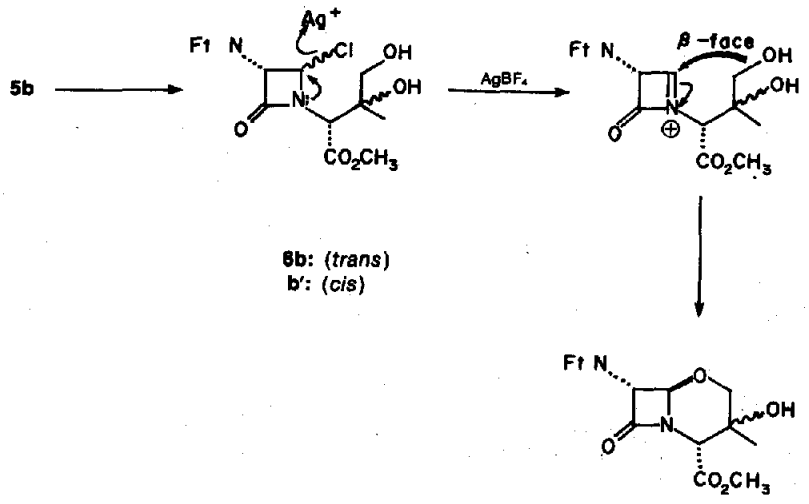
5a: (β)
b: (α)

6a: (*trans*)
a': (*cis*)

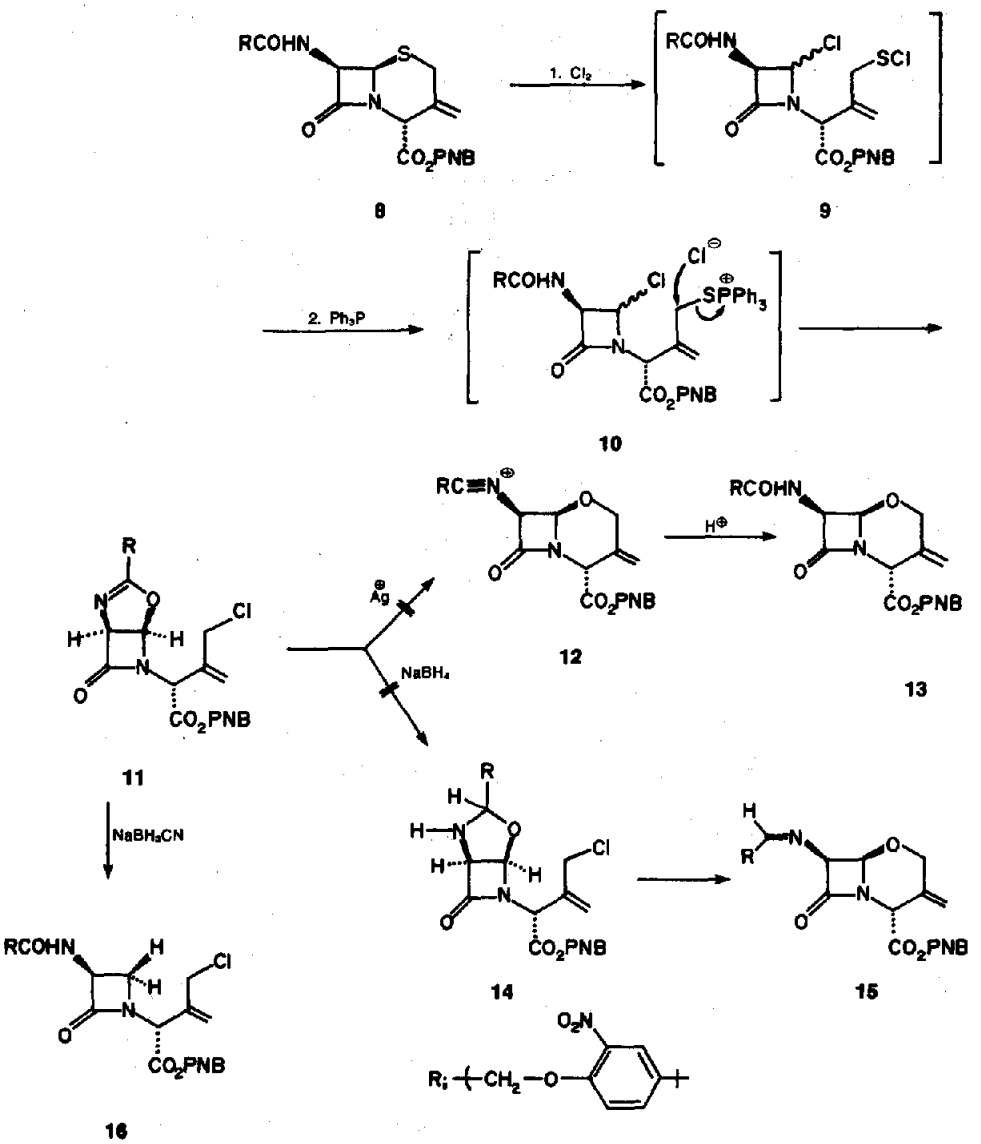
2

7a: (*trans*)
a': (*cis*)

Scheme 2.



Scheme 3.



Scheme 4.

and similar rearrangement of the penicillin sulfoxide **1b** with trimethylphosphite-acetic anhydride (reflux in toluene, 1 hr, 98%). The similar treatment of **4b** with osmium tetroxide and chlorination afforded the 7-α-phthalimido-chloro-β-lactams **6b, b'** (84%). When the mixture of **6b, b'** was treated with stannous chloride or silver tetrafluoroborate, the silver reagent afforded crystalline 7-epi-1-oxo-cepham **3** (26%, m.p. 179–181°, prep tlc two developments $CHCl_3$/EtOAc, 7/3 and CH_2Cl_2/EtOAc, 6/4). The NMR spectra showed the *trans* stereochemistry of hydrogens at C-6 and C-7 positions in the product **3** (J = 1 Hz). The mass spectrum indicated its molecular weight, 360 showing the loss of HCl from **6b, b'**.

As an alternative approach to a 1-oxo-cepham a novel direct approach was taken. The sulfenyl chloride **9** was generated at low temperature and treated with triphenyl phosphine. The intermediate thio-phosphonium **10** was formed at low temperature and upon warming followed by chromatography the desired allylic chloride **11** was formed (Scheme 4). When **11** was treated with silver ion a rapid reaction took place which caused the loss of the β-lactam. No ring closure to 1-oxa-cephams was observed. When **11** was treated with sodium borohydride in methanol a rapid isomerization of the double bond to the 1,2 - seco - Δ^3 - cephem system occurred with eventual loss of the β-lactam. Sodium cyanoborohydride was also tried as a reductant but reacted only very slowly to give what appeared to be traces of **16** (Scheme 4).

Recently Kim and McGregor[5] prepared 6-epi-1-oxocephem with the penicillin V-side chain which displayed significantly diminished antibacterial activity when compared with the normal series. However, the 7α-methoxy-1-oxocephem nucleus[10] generally provides a fourfold to eightfold increase of anti-bacterial activity.

EXPERIMENTAL

NMR spectra (60 MHz) were obtained on a Varian T-60 or Perkin–Elmer R-20. IR spectra were recorded on a Perkin–Elmer 700 and calibrated vs a polystyrene film. Mass spectra were obtained on a Hitachi Perkin–Elmer RMU-6E or a Varian Associates MAT-44. For silica gel for column chromatography, Merck silica gel 60, No. 7734 was used and preparative tlc was made on Merck silica gel 60 GF 254 No. 7730. M.ps were obtained on Thomas-Hoover capillary or a Kofler Micro block and are uncorrected. Solvents were purified and dried in advance.

6 - Epi - phthalimido penicillin sulfoxide, **1b**. Compound **1a** (2g, 5.32 mmol) was dissolved in 30 ml of dry CH_2Cl_2. Et_3N (30 ml, 216 mmol) was added dropwise. The mixture was stirred under N_2 for 2 hr. The soln was washed with water and dried. Evaporation and recrystallization from toluene gave **1b** (1.74 g, 84.5%) m.p. 134°; IR ($CHCl_3$), 1780 and 1718 cm^{-1}; NMR ($CDCl_3$) δ 1.44 (s, 3H), 1.50 (s, 3H), 3.88 (s, 3H), 4.67 (s, 1H), 5.21 (d, J = 2Hz, 1H), 5.73 (d, J = 2Hz, 1H) 7.90 (m, 4H): $[\alpha]_D^{20} = +140°$ (c; 0.67, $CHCl_3$); MS (70 eV), *m/e* 376 (M^+), 104 (100). (Found: C, 54.59; H, 4.14; N, 7.36; S, 8.58. Calcd. for $C_{17}H_{16}N_2SO_6$: C, 54.26; H, 4.26; N, 7.45; S, 8.51%).

6 - Epi - phthalimido - 1,2 - seco - Δ^2 - cephem, **4b**. A mixture of **1b** (1.5 g, 4.0 mmol), trimethyl phosphite (0.495 g, 4.0 mmol) and Ac_2O (0.24 g, 20 mmol) was dissolved in dry toluene (100 ml) and was heated under reflux at 115° for 1 hr. The mixture was cooled to r.t. and then washed with saturated brine, dried and evaporated *in vacuo* to give 1.468 g (98%) of a foam **4b**; IR (CCl_4) 2950, 1780, 1725 and 1390 cm^{-1}; NMR ($CDCl_3$) δ 1.97 (s, 3H), 2.33 (s, 3H), 3.82 (s, 3H), 4.60 (s, 1H), 5.10–5.25 (m, 2H), 5.38 (d, J = 2Hz, 1H), 5.82 (d, J = 2Hz, 1H), 7.70 (m, 4H): $[\alpha]_D^{20} = -18°$ (*c*; 0.67, $CHCl_3$); MS (70 eV), *m/e* 403 (0.1) 402 (M^+), 205 (100), 104 (95). (Found: C, 56.99; H, 4.56; N, 6.84; S, 7.60. Calcd. for $C_{19}H_{18}N_2SO_6$: C, 56.72; H, 4.48; N, 6.97; S, 7.96%).

Compound **4a** was prepared from **1a** by the procedure of Cooper[6] described above (95%).

(3S) - Phthalimido - 1 - [(1R) - methoxycarbonyl - 2 - methyl - 2,3 - di - hydroxypropyl] - (4R) - thioacetyl - 2 - azetidinone, **5a**. Compound **4a** (1.5 g; 3.7 mmol) and osmium tetroxide (1.0 g, 3.9 mmol) was dissolved in 20 ml dry CH_2Cl_2 and stirred at r.t. for 12 hr under N_2. The CH_2Cl_2 was removed at reduced pressure, the black residue dissolved in 25 ml dioxane and H_2S bubbled through the soln for 15 min. The mixture was diluted with 70 ml CH_2Cl_2 and filtered through celite. The filtrate was washed with water, dried with $MgSO_4$ and evaporated to a white foam **5a** (1.23 g, 78%); IR ($CHCl_3$), 3200 (broad, OH), 1782 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 1.43 (s, Me), 2.29 (s, AcS), 3.72 (s, H-2), 3.93 (s, OMe), 4.51 (s, H-4), 5.88 (d, J = 5, H-7), 6.20 (d, J = 5, H-6), 7.81 (m, Ft). Compound **5b** was prepared from **4b** using the procedure described above. Compound **5b** (73%); IR ($CHCl_3$) 3500, and 1780 cm^{-1}; NMR ($CDCl_2$) δ 1.45 (s, 3H), 3.77 (s, 3H), 4.05 (s, 1H), 4.57–4.20 (m, 2H), 5.37 (d, J = 2Hz, 1H), 5.70 (d, J = 2Hz, 1H), 7.72 (m, 4H). (Found: C, 52.33; H, 4.29; N, 6.63; S, 7.98. Calcd. for $C_{19}H_{20}N_2SO_8$: C, 52.29; H, 4.59; N, 6.42; S, 7.34%).

(3S) - Phthalimido - 1 - [(1R) - methoxycarbonyl - 2 - methyl - 2,3 - di - hydroxypropyl] - 4 - chloro - 2 - azetidinone, **6a, a'**. Compound **5a** (47 mg; 0.11 mmol) was dissolved in 8 ml dry CH_2Cl_2 and Cl_2 gas was bubbled through the soln for 3 min. The reaction was then poured onto 20 g ice and stirred for 10 min, then diluted with 30 ml CH_2Cl_2 and separated. The organic layer was washed twice with sat. $NaHCO_3$aq and once with brine. It was dried with $MgSO_4$ and evaporated to an oil to give a 5 to 3 mixture of **6a** and **6a'** respectively (40 mg, 93%); IR ($CHCl_3$) 3500 (OH), 1780 cm^{-1} β-lactam). Compound **6a**; NMR ($CDCl_3$) δ 1.41 (s, Me), 3.69 (s, H-2), 3.76 (s, OMe), 4.51 (s, H-4), 5.49 (s, J = 1, H-7), 6.00 (d, J = 1, H-6), 7.73 (m, Ft). Compound **6a'**; NMR ($CDCl_3$) δ 1.38 (s, Me), 3.61 (s, H-2), 3.76 (s, OMe), 4.70 (s, H-4). 5.60 (d, J = 4, H-7), 6.35 (d, J = 4, H-6), 7.73 (m, Ft). Compounds **6b, b'** were prepared from **5b** using the procedure described above. Compound **6b** (91%); IR ($CHCl_3$), 3500 (OH) and 1700 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 1.31 (s, 3H), 3.20–2.85 (br.s, 2H), 3.87 (s, 3H), 4.14 (s, 1H), 4.45–4.05 (m, 2H), 5.08 (d, J = 1 Hz, 1H), 5.97 (d, J = 1 Hz, 1H), 7.82 (m, 4H).

Methyl - 7 - phthalimido - 3 - hydroxy - 6 - epi - 1 - oxocephalosporanate 2—(3S) - phthalimodo - 1 - [2 - (3 - methyl - 2 - butene - 4 - olidyl] - 4 - chloro - 2 - azetidinone **7**. Compounds **6a, a'** (0.464 g; 1.17 mmol) and anhyd tin (II) chloride (0.222 g; 1.17 mmol) were dissolved in 25 ml dry dimethoxyethane and stirred under a drying tube at r.t. for 12 hr. The reaction was then diluted with 75 ml $CHCl_3$ and washed with 5% $NaHCO_3$aq, dried with $MgSO_4$ and evaporated to 282 mg of oil. The oil was chromatographed on silica-gel (benzene-EtOAc) to give 102 mg (27%) of **2** and 137 mg (31%) of **7**. Compound **2**; IR ($CHCl_3$), 3300 (broad, OH), and 1785 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 1.32 (s, Me), 3.66 (m, H-2), 3.78 (s, OMe), 4.08 (s, H-4), 5.30 (d, J = 1, H-6), 5.55 (d, J = 1, H-7), 7.76 (m, Ft), MS (70 eV) *m/e* 360 (M^+). Compounds **7a** and **7a'**; IR ($CHCl_3$) 1770 cm^{-1} (β-lactam); **7a**; NMR ($CDCl_3$) δ 2.30 (s, Me), 4.81 (s, CH_2), 5.62 (d, J = 1, H-6), 6.64 (d, J = 1, H-6), 7.81 (m, Ft): **7a'**; NMR ($CDCl_3$) δ 2.21 (s, Me), 4.81 (s, CH_2), 5.72 (d, J = 4, H-6), 6.65 (d, J = 4, H-6), 7.81 (m, Ft).

Methyl - 7 - epi - phthalimido - 3 - hydroxy - 1 - oxocephalosporanate, **3**. 7-Epimer **3** was prepared from **6b, b'** (1g, 2.5 mmol) with silver tetrafluoroborate (0.5 g, 2.6 mmol) using the procedure described above in 26% yield (0.24 g, prep tlc—two developments, chloroform—EtOAc, 7/3 and CH_2Cl_2–EtOAc, 6/4), m.p. 179–181°; IR ($CHCl_3$), 3450, 3000, 1775, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (s, 3H), 2.83 (br.s, 1H), 3.62 (m, 2H), 3.76 (s, 3H), 4.21 (s, 1H), 5.17 (d, J = 1 Hz, 1H), 5.52 (d, J = 1 Hz, 1H), 7.74 (m, 4H); MS (70 eV) *m/e* 360 (M^+), 104 (71), 43 (100).

(4S, 7S) - 2 - (2 - Nitro - 4 - t - butylphenoxymethyl) - 5 - [(1R) - (p - nitro - benzyloxycarbonyl) - 2 - chloromethyl - 2 - propenyl] - 1,5 - diaza - 3 - oxa - bicyclo - [3.2.0] - 1 - heptene - 6 - one, **11**. Compound **8** (0.276 g; 0.438 mmol) was dissolved in 10 ml dry CH_2Cl_2 and cooled to −30° under N_2. Cl_2 (34.2 mg; 0.482 mmol) was added and stirred for 2 hr at −30°, then N_2 was bubbled through the soln for 5 min. Triphenylphosphine (115 mg; 0.438 mmol) was added and stirred at ambient temp for 3 hr. The solvent was evaporated to give a yellow oil which was chromatographed on florisil (100% $CHCl_3$ to 25% EtOAc—75% $CHCl_3$), to give (62 mg, 21%) of white oil **11**; IR ($CHCl_3$) 1780 cm^{-1} (β-lactam), 1740 cm^{-1} (ester); NMR ($CDCl_3$) δ 1.39 (s, t-butyl), 4.09 (s, H-2), 4.89 (s, CH_2), 5.3 (m, 5H), 5.53 (s, H-3), 6.31 (d, J = 3, H-6), 7.0–8.3 (m, 7H).

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REFERENCES

[1]All correspondence should be sent to the Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, England.
[2]L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.* **96** 7582 (1974).
[3]S. Wolfe, J. B. Ducep, K. C. Tin and S. L. Lee, *Can. J. Chem.* **52**, 3996 (1974).
[4]R. A. Firestone, J. L. Fahey, N. S. Maciejewicz, C. S. Patel and B. G. Christensen, *J. Med. Chem.* **20**, 551 (1977).
[5]C. U. Kim and D. N. McGregor, *Tetrahedron Letters* 409 (1978).
[6]L. D. Hatfield, J. Fisher, F. L. Jose and R. D. G. Cooper, *Ibid.* 4897 (1970).
[7]J. E. Baldwin, *J. Chem. Soc. Chem. Comm.* 734 (1976).
[8]S. Wolfe, J. B. Ducep, W. S. Lee and G. Kannengiessier, *Can. J. Chem.* **50**, 2898 (1972).
[9]S. Wolfe and W. S. Lee, *J. Chem. Soc. Chem. Comm.* 242 (1968).
[10]W. Nagata and T. Yoshida, *Penicillin 50 Years after Fleming.* The Royal Society, London, 2–3 May (1979).