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244. Conversion of Penicillin to Cephalosporin Lactones

Preliminary Communication

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Dedicated to Professor *R. B. Woodward* on his 60th birthday

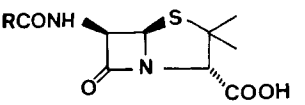
(18. VIII. 76)

Summary. Penicillin G (**1**, R = CH_2Ph) was converted to cephaloram- and 6-epicephaloram lactones **11** and **12** respectively by the initial replacement of thiazolidine part of penicillin by the mercaptan **9** followed by intramolecular cyclization and subsequent introduction of double bond at C(3).

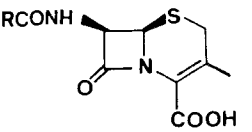
Morin et al. [1] provided a useful method for the conversion of penicillin **1** into deacetoxy cephalosporin **2** through a novel process of oxidation and ring expansion.

In 1965 *Sheehan & Brandt* [2] have demonstrated the liberation of the β-lactam nitrogen from the thiazolidine part by *Curtius* degradation of the acid azide and hydrolysis. Furthermore they have achieved the complete replacement of thiazolidine

Scheme 1



1



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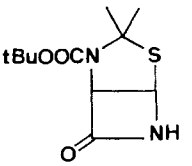

3

part of penicillin molecule by nucleophiles such as mercaptans [3] [4], keeping intact the relatively labile β-lactam ring.

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An interesting modification of the above degradation was introduced by *Woodward et al.* [5] for the conversion of penicillin to a fused thiazolidine **3** [6], which was one of the important intermediates in their classical total synthesis of cephalosporin [7].

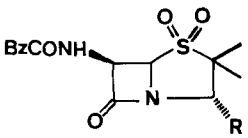
By replacing the thiazolidine part of the penicillin molecule by mercapto butenolide **9** and using our new method (see preceeding communication) we converted penicillin G (**1**, R = CH_2Ph) into cephaloram- and 6-epicephaloram lactones **11** and **12** respectively.

Penicillin G (**1**, R = CH_2Ph) was oxidized to the sulfone **4** using potassium permanganate [8] [m.p. 124°, $[\alpha]_D^{25} = +167°$ (acetone); IR. (KBr): 3345, 1805, 1745, 1635, 1550, 1520, 1320, 1115 cm^{-1}; NMR. (acetone-d_6): 8.30 (br., 1H, COOH), 7.49 (*d*, *J* = 10 Hz, 1H, NH), 7.28 (*m*, 5H, phenyl), 6.08 (*d*×*d*, $J_1 = 4$, $J_2 = 10$ Hz, 1H, H–C(6)), 5.13 (*d*, *J* = 4 Hz, 1H, H–C(5)), 4.44 (*s*, 1H, H–C(3)), 3.72 (*s*, 2H, benzyl CH_2), 1.57 (*s*, 3H, CH_3), 1.46 (*s*, 3H, CH_3)].

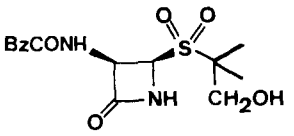
Sulfone **4** was converted to the azide **5** [IR. ($CHCl_3$): 3410, 2115, 1815, 1690, 1310 cm^{-1}] *via* the mixed anhydride using pyridine and isobutylchloroformate followed by sodium azide treatment. Thermal rearrangement of the azide **5** gave the isocyanate **6** [IR. ($CHCl_3$): 3405, 2260, 1815, 1690, 1310 cm^{-1}], which on acid hydrolysis gave 3-hydroxypenam **7** [m.p. 111–112°, $[\alpha]_D^{25} = +77°$ (acetone); IR. ($CHCl_3$): 3580, 3400, 1805, 1630, 1325 cm^{-1}; NMR. ($CDCl_3$): 7.22 (*m*, 5H, phenyl), 7.07 (*d*, *J* = 10 Hz, 1H, NH), 5.96 (*d*×*d*, $J_1 = 4$, $J_2 = 10$ Hz, 1H, H–C(6)), 5.16 (br., *s*, 2H, H–C(3) and OH, on D_2O exchange, *s*, 1H), 4.73 (*d*, *J* = 4 Hz, H–C(5)), 3.59 (*s*, 2H, benzyl CH_2), 1.38 (*s*, 6H, two CH_3)].

Compound **7** was reduced to azetidinone alcohol **8** with sodium borohydride [oil, $[\alpha]_D^{25} = +37°$ (acetone); IR. ($CHCl_3$): 3400, 1780, 1670, 1300 cm^{-1}; NMR. ($CDCl_3$): 7.51 (*s*, 1H, H–C(1)), 7.26 (*s*, 5H, phenyl), 7.13 (*d*, *J* = 10 Hz, 1H, C(3) NH), 5.78 (*d*×*d*, $J_1 = 4$, $J_2 = 10$ Hz, H–C(3)), 5.06 (*d*, *J* = 4 Hz, 1H, H–C(4)), 3.58 (*s*, 2H, benzyl CH_2), 3.94–3.28 (br., 2H, on D_2O exchange collapsed into a clean *AB*-quartet,

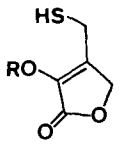
Scheme 2



4 R = COOH
5 R = CON_3
6 R = NCO
7 R = ⁓OH

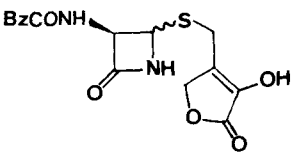


8

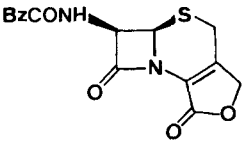


9

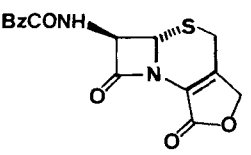
R = tetrahydropyranyl



10



11



12

J = 13 Hz, 2H, CH_2), 2.10 (br., 1H, D_2O exchangeable, OH), 1.26 (*s*, 3H, CH_3), 1.23 (*s*, 3H, CH_3)].

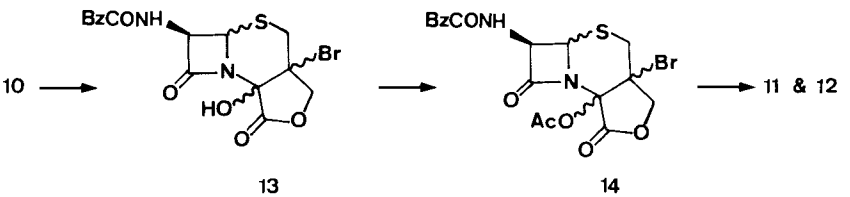
Reaction of compound **8** with mercaptan **9** in presence of triethylamine gave compound **10** as a mixture of isomeres in 90% yield. This mixture on successive treatment with (i) bromine in presence of sodium hydrogencarbonate, (ii) acetyl chloride and pyridine, and (iii) zinc and acetic acid gave cephaloram lactone (**11**) and 6-epicephaloram lactone (**12**) in the ratio of 1:1 in 30% yield starting from the azetidinone **8**.

Cephaloram lactone **11**: m.p. 210°, $[\alpha]_D^{25} = +142°$ (acetone). – IR. (KBr): 3240, 1790, 1775, 1755, 1655 cm^{-1}. – NMR. (acetone-d_6): 8.06 (br., 1H, NH); 7.34 (*s*, 5H, phenyl); 5.97 (*d*×*d*, $J_{cis} = 5$, $J_{H,NH} = 9$ Hz, 1H, H–C(7)), 5.16 (*d*, $J_{cis} = 5$ Hz, 1H, H–C(6)); 5.04 (*s*, 2H, lactone CH_2); 3.83 (*q*, $J_{gem} = 18$ Hz, 2H, SCH_2); 3.68 (*s*, 2H, benzyl CH_2). – UV. $\lambda_{max}^{EtOH}(\varepsilon)$: 259 (9940) nm. All these Data were found to be identical in all respects with the authentic sample obtained from the phenacetylation of 7-aminocephalosporin lactone.

6-Epicephaloram lactone **12**: m.p. 176–177°, $[\alpha]_D^{25} = -95°$ (acetone). – IR. (KBr): 3370, 1785, 1745, 1670 cm^{-1}. – NMR. (Acetone-d_6): 8.18 (br., 1H, NH); 7.33 (*s*, 5H, phenyl); 5.03 (*s*, 2H, lactone CH_2); 4.91 (*d*×*d*, $J_{trans} = 2.5$, $J_{H,NH} = 8$ Hz, 1H, H–C(7)); 4.83 (*d*, $J_{trans} = 2.5$ Hz, 1H, H–C(6)); 3.81 (*q*, $J_{gem} = 18$ Hz, 2H, SCH_2); 3.64 (*s*, 2H, benzyl CH_2). – UV. $\lambda_{max}^{EtOH}(\varepsilon)$: 262 (9730) nm.

In analogy with our results on a related cyclization (see preceeding communication) we assume the formation of intermediates **13** and **14** involving the mixture of stereoisomers in the transformation of **10** to compounds **11** and **12** (*Scheme 3*).

Scheme 3



The authors thank Dr. *J. Gosteli*, Woodward Research Institute, Basel, for the generous gift of Penicillin G.

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