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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

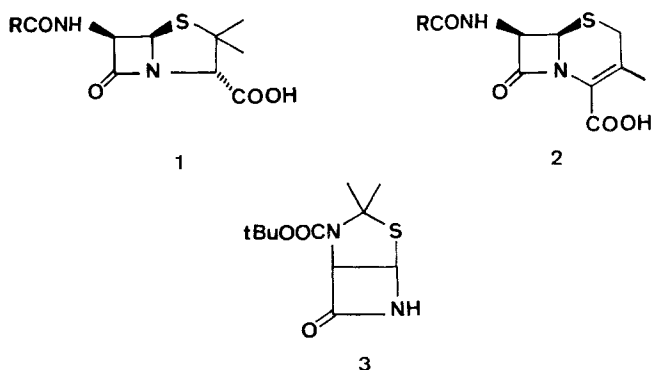
(18. VIII. 76)

Summary. Penicillin G (**1**, R = CH₂Ph) 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



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].

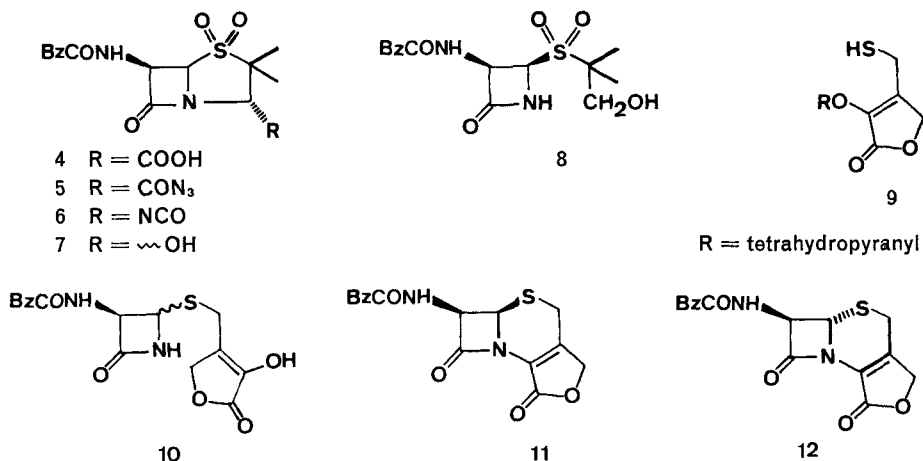
By replacing the thiazolidine part of the penicillin molecule by mercapto butenolide **9** and using our new method (see preceeding communication) we converted penicillin G (**1**, $R = \text{CH}_2\text{Ph}$) into cephaloram- and 6-epicephaloram lactones **11** and **12** respectively.

Penicillin G (**1**, $R = \text{CH}_2\text{Ph}$) was oxidized to the sulfone **4** using potassium permanganate [8] [m.p. 124° , $[\alpha]_D^{25} = +167^\circ$ (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 ($d \times d$, $J_1 = 4$, $J_2 = 10$ 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° , $[\alpha]_D^{25} = +77^\circ$ (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 ($d \times d$, $J_1 = 4$, $J_2 = 10$ 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, $[\alpha]_D^{25} = +37^\circ$ (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 ($d \times d$, $J_1 = 4$, $J_2 = 10$ 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



$J = 13$ Hz, 2H, CH₂), 2.10 (br., 1H, D₂O exchangeable, OH), 1.26 (s, 3H, CH₃), 1.23 (s, 3H, CH₃)].

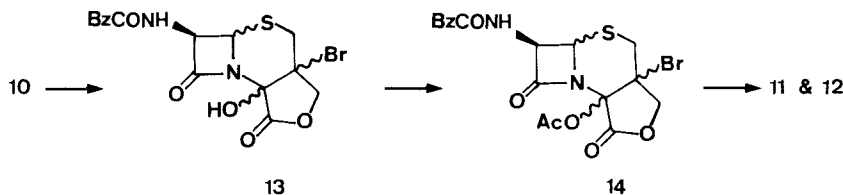
Reaction of compound **8** with mercaptan **9** in presence of triethylamine gave compound **10** as a mixture of isomers in 90% yield. This mixture on successive treatment with (i) bromine in presence of sodium hydrogencarbonate, (ii) acetyl chloride and pyridine, and (iii) zinc and acetic acid gave 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°, $[\alpha]_D^{25} = +142^\circ$ (acetone). – IR. (KBr): 3240, 1790, 1775, 1755, 1655 cm⁻¹. – NMR. (acetone-d₆): 8.06 (br., 1H, NH); 7.34 (s, 5H, phenyl); 5.97 ($d \times d$, $J_{cts} = 5$, $J_{H,NH} = 9$ Hz, 1H, H-C(7)), 5.16 (d , $J_{cts} = 5$ Hz, 1H, H-C(6)); 5.04 (s, 2H, lactone CH₂); 3.83 (q , $J_{gem} = 18$ Hz, 2H, SCH₂); 3.68 (s, 2H, benzyl CH₂). – UV. $\lambda_{max}^{EtOH}(\epsilon)$: 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°, $[\alpha]_D^{25} = -95^\circ$ (acetone). – IR. (KBr): 3370, 1785, 1745, 1670 cm⁻¹. – NMR. (Acetone-d₆): 8.18 (br., 1H, NH); 7.33 (s, 5H, phenyl); 5.03 (s, 2H, lactone CH₂); 4.91 ($d \times d$, $J_{trans} = 2.5$, $J_{H,NH} = 8$ 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, SCH₂); 3.64 (s, 2H, benzyl CH₂). – UV. $\lambda_{max}^{EtOH}(\epsilon)$: 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



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