LITERATURVERZEICHNIS

[1] *M. Zehnder, H. Mäcke & S. Fallab*, Helv. *58*, 2306 (1975).
[2] *G. McLendon & A. E. Martell*, J. coord. Chemistry *4*, 235 (1975).
[3] *P. Paoletti, M. Ciampolini & L. Sacconi*, J. chem. Soc. *1963*, 3589.
[4] *Siemens AG*, Betriebsanleitung zum Automatischen Einkristall-Diffraktometer, EG 4 A850/2d, 1971.
[5] *U. Thewalt*, Z. anorg. allg. Chem. *374*, 259 (1970).
[6] *D. T. Cromer & J. B. Mann*, Acta crystallogr. A *24*, 321 (1968).
[7] *D. T. Cromer & D. Libermann*, J. chem. Physics *53*, 1891 (1970).
[8] *G. M. Sheldrick*, Cambridge, unveröffentlicht.
[9] *U. Thewalt & G. Struckmeier*, Z. anorg. allg. Chem. *419*, 163 (1976).

243. Synthesis of 7-Deamidocephalosporin Lactone

Preliminary Communication

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

(18. VIII. 76)

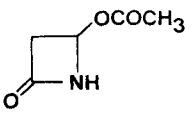
Summary. Condensation of azetidinone **1** with mercaptan **3** gave compound **5**. Bromination of **5** afforded two isomeric bromohydrins **11a** and **11b** which differ in the configuration at C(4). Acetylation and reduction with zinc and acetic acid of the above bromohydrins gave 7-deamidocephalosporin lactone (**14**).

Since a long time we were interested in the synthesis of cephalosporin derivatives. In our earlier approaches [1] [2] we used substituted butenolides [3] [4] as suitable synthetic intermediates.

In recent years a number of workers have demonstrated that β-lactams having a good leaving group at the position 4 could be successfully substituted by thiols [5] [6]. We describe now the condensation of butenolide **3** with 4-acetoxyazetidin-2-one (**1**) [5] to compound **5** and the successful transformation of **5** to cephem **14**.

Compound **3** was readily obtained in almost quantitative yield (as oil) from the 3-hydroxy-4-acetylthiomethylfuran-2(5*H*)-one [7] in two steps: (i) treatment with

Scheme 1



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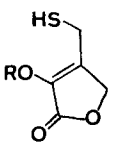
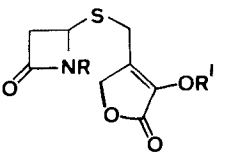


2 R = H
3 R = THP
4 R = CH_3

THP = tetrahydropyranyl



5 R = R' = H
6 R = H, R' = $COCH_3$
7 R = R' = $COCH_3$
8 R = H, R' = CH_3

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2,3-dihydropyran in presence of *p*-toluene sulfonic acid [8] and (ii) deacetylation with ammonia [9].

NMR. ($CDCl_3$): 5.80 (*m*, 1H, –O–CH–O–); 4.86 (*s*, 2H, lactone CH_2); 3.72 (*m*, 2H, THP–OCH_2); 3.52 (*d*, 2H, J = 8 Hz, on D_2O exchange collapsed into a two proton singlet, SCH_2); 2.10–1.50 (*m*, 6H, other THP-protons); 1.91 (*t*, 1H, J = 8 Hz, SH exchangeable with D_2O).

Condensation of mercaptan **3** with azetidinone **1** in presence of sodium hydroxide followed by hydrochloric acid treatment gave compound **5** in 85% yield[2]), mp. 111°. – IR. (KBr): 3310, 3010, 2960, 1755, 1725, 1625 cm^{-1}. – NMR. (DMSO–d_6): 10.42 (br., 1H, NH exchangeable with D_2O); 8.48 (br., 1H, OH exchangeable with D_2O); 4.79 (*d*×*d*, 1H, J_{cis} = 5, J_{trans} = 3 Hz, lactam CH); 4.76 (*s*, 2H, lactone CH_2); 3.64 (*s*, 2H, SCH_2); 3.34 (*d*×*d*, 1H, J_{trans} = 3, J_{gem} = 16 Hz), and 2.75 (*d*×*d*, 1H, J_{cis} = 5, J_{gem} = 16 Hz, lactam CH_2).

Compound **5** gave an O-acetyl derivative (**6**) with pyridine and acetyl chloride, m.p. 114°. – IR. (KBr): 3270, 1780, 1760, 1730, 1685 cm^{-1}. – NMR. ($CDCl_3$): 6.66 (br., 1H, NH exchangeable with D_2O); 4.96 (*s*, 2H, lactone CH_2); 4.79 (*d*×*d*, 1H, J_{cis} = 5, J_{trans} = 3 Hz, lactam CH); 3.56 (*s*, 2H, SCH_2); 3.46 (*d*×*q*, 1H, J_{cis} = 5, J_{gem} = 16, $J_{H,NH}$ = 2.5 Hz)[3]) and 2.93 (*d*×*d*, 1H, J_{trans} = 3, J_{gem} = 16 Hz, lactam CH_2); 2.36 (*s*, 3H, acetyl). – MS.: M^+ = 257.

Treatment of **5** with acetic anhydride at 80° for 12 h gave a diacetyl derivative (**7**), oil. – IR. ($CHCl_3$): 1790, 1710 cm^{-1}. – NMR. ($CDCl_3$): 5.12 (*d*×*d*, 1H, J_{cis} = 6, J_{trans} = 4 Hz, lactam CH); 5.10 and 4.84 (2*d*, 2H, J_{gem} = 16 Hz, lactone CH_2); 4.51 and 3.43 (2*d*, 2H, J_{gem} = 14 Hz, SCH_2); 3.52 (*d*×*d*, 1H, J_{cis} = 6, J_{gem} = 16 Hz) and 2.88 (*d*×*d*, 1H, J_{trans} = 4, J_{gem} = 16 Hz, lactam CH_2); 2.39 (*s*, 3H, acetyl); 2.31 (*s*, 3H, acetyl).

Compound **5** gave a monomethyl ether (**8**) with diazomethane, m.p. 103°. – IR. ($CHCl_3$): 3410, 1770, 1680 cm^{-1}. – NMR. ($CDCl_3$): 6.82 (br., 1H, NH); 4.80 (*m*, 3H, lactone CH_2 and lactam CH); 4.07 (*s*, 3H, OCH_3); 3.56 (*d*×*d*, 2H, J_{gem} = 14 Hz, SCH_2); 3.38 and 2.92 (*m*, 2H, lactam CH_2). This compound was also obtained by the condensation of mercaptan **4** with azetidinone **1**.

Based on the spectral characteristics, it was concluded that compound **5** exists in the acyclic form and not in the corresponding cyclic form **9**, in contrast with the analog α-keto acid derivatives **16** which were known to exist in the corresponding cyclic form **17** only [5].

Attempts to cyclize compound **5** to the cephem **14** under a variety of dehydrating conditions were not successful. The only experiment worth mentioning was the treatment of **5** in trifluoroacetic acid, which gave the dihydrothiazine **10** [m.p. 199°.– IR. (KBr): 3440, 3320, 1745, 1690, 1660 cm^{-1}. – NMR. (DMSO–d_6): 7.52 (br., 1H, NH or COOH, exchangeable with D_2O), 7.05 (br., 1H, NH or COOH, exchangeable with D_2O), 5.53 (*d*×*d*, 1H, J_1 = 6, J_2 = 7 Hz, H–C(6)), 4.88 (*s*, 2H, lactone CH_2), 3.85 and 3.50 (2*d*, 2H, J_{gem} = 18 Hz, SCH_2), 2.77 (*d*×*d*, 2H, J_1 = 6, J_2 = 7 Hz, CH_2COOH)], in which the desired cyclization did take place, but with opening of the β-lactam ring.

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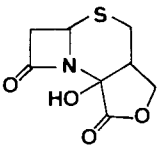
[2]) Compound **5** could be obtained in poor yield by the condensation of mercaptan **2** with azetidinone **1**.

[3]) Such long range couplings are reported in [10].

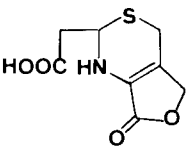
However, we were successful in forcing compound **5** to the corresponding cepham form by brominating the enolic function [11] [4]. Treatment of **5** with bromine resulted in the formation of two isomeric cepham bromohydrins **11a** and **11b** in 85% yield, in the ratio of 1:1, obviously through the intermediacy of the corresponding bromo ketone **13**. The two isomers were separated by careful fractional crystallization in methanol in which only compound **11b** crystallized and **11a** was obtained from the mother liquor.

Bromohydrin **11a**: m.p. 111° (recrystallized from methylene chloride). – IR. (KBr): 3440, 1805, 1730 cm^{-1}. – NMR. (DMSO-d_6): 8.86 (br., 1H, OH, exchangeable with D_2O); 4.67 ($d \times d$, 1H, $J_{cis} = 5$, $J_{trans} = 2$ Hz, H–C(6)); 4.63 (q, 2H, $J_{gem} = 9$ Hz,

Scheme 2



9



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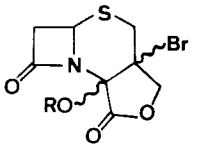
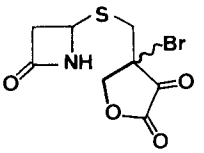


11 a,b R=H

12 a,b R=COCH$_3$



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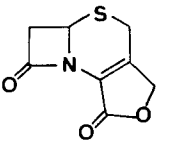


14

lactone CH_2); 3.43 ($d \times d$, 1H, $J_{cis} = 5$, $J_{gem} = 14$ Hz, H–C(7)); 3.44 (s, 2H, SCH_2); 2.92 ($d \times d$, 1H, $J_{trans} = 2$, $J_{gem} = 14$ Hz, H–C(7)). – MS.: $M^+ = 293/295$.

Bromohydrin **11b**: m.p. 147° (recrystallised from methanol). – IR. (KBr): 3460, 1805, 1745 cm^{-1}. – NMR. (DMSO-d_6): 8.20 (s, 1H, OH, exchangeable with D_2O); 5.19 and 4.58 (2d, 2H, $J_{gem} = 12$ Hz, lactone CH_2); 4.87 ($d \times d$, 1H, $J_{cis} = 5$, $J_{trans} = 2$ Hz, H–C(6)); 3.75 and 3.50 (2d, 2H, $J_{gem} = 14$ Hz, SCH_2); 4.49 ($d \times d$, 1H, $J_{cis} = 5$, $J_{gem} = 15$ Hz, H–C(7)); 2.88 ($d \times d$, 1H, $J_{trans} = 2$, $J_{gem} = 15$ Hz, H–C(7)). – MS.: $M^+ = 293/295$.

The isomeric bromohydrins were stable in neutral conditions and they were interconvertible in presence of catalytic amounts of bases such as pyridine or triethylamine showing that they differ in the configuration at C(4).

Both **11a** and **11b** gave the corresponding acetyl derivatives **12a** and **12b** respectively, by treating with pyridine/acetyl chloride in the case of the former and triethylamine/acetyl chloride in the latter case.

Compound **12a**: m.p. 84°. – IR. ($CHCl_3$): 1820, 1785 cm^{-1}. – NMR. (DMSO-d_6): 4.85 and 4.70 (2d, 2H, $J_{gem} = 10$ Hz, lactone CH_2); 4.81 ($d \times d$, 1H, $J_{cis} = 5$, $J_{trans} = 2$ Hz, H–C(6)); 3.63 ($d \times d$, 1H, $J_{cis} = 5$, $J_{gem} = 15$ Hz, H–C(7)); 3.55 (s, 2H, SCH_2); 3.18 ($d \times d$, 1H, $J_{trans} = 2$, $J_{gem} = 15$ Hz, H–C(7)); 2.20 (s, 3H, acetyl). – MS.: $M^+ = 355/357$.

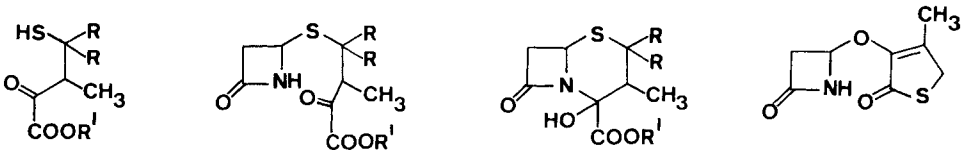
Compound **12b**: m.p. 141°. – IR. (KBr): 1820, 1785 cm^{-1}. – NMR. (DMSO-d_6): 5.32 and 4.62 (2*d*, 2H, J_{gem} = 12 Hz, lactone CH_2); 5.01 (*d*×*d*, 1H, J_{cis} = 5, J_{trans} = 2 Hz, H–C(6)); 4.08 and 3.58 (2*d*, 2H, J_{gem} = 14 Hz, SCH_2); 3.54 (*d*×*d*, 1H, J_{cis} = 5, J_{gem} = 15 Hz, H–C(7)); 2.95 (*d*×*d*, 1H, J_{trans} = 2, J_{gem} = 15 Hz, H–C(7)); 2.19 (*s*, 3H, acetyl). – MS.: M^+ = 355/357.

At this stage we were in a good position for introducing the double bond at C(3), C(4) in **12a** and **12b** since the vicinal halogeno acetoxy compounds were known to yield olefines more readily than the corresponding hydroxy compounds [12] [13] by treatment with zinc. As expected the acetates **12a** and **12b** on reduction with zinc and acetic acid gave the desired cephem **14** in almost quantitative yield[4]).

Cephem lactone **14**: m.p. 194°. – IR. ($CHCl_3$): 1805, 1775, 1670 cm^{-1}. – NMR. (DMSO-d_6): 5.02 (*s*, 2H, lactone CH_2); 4.81 (*d*×*d*, 1H, J_{cis} = 6, J_{trans} = 4 Hz, H–C(6)); 3.84 (*d*×*d*, 1H, J_{cis} = 6, J_{gem} = 16 Hz, H–C(7)); 3.76 (*s*, 2H, SCH_2); 3.06 (*d*×*d*, 1H, J_{trans} = 4, J_{gem} = 16 Hz, H–C(7)). – MS.: M^+ = 197. – UV. λ_{max}^{EtoH} (ε): 257 (9250).

Thus the bromination of enol **5** turned out to be an added advantage because it gave way for the smooth introduction of the double bond at C(3), C(4). In comparison the yields of dehydration in the corresponding cepham derivative **17** without bromine at C(3) were always very poor [5].

Scheme 3



15 **16** **17** **18**

The synthesis of cepham derivatives of type **17** by the condensation of β-mercaptocarbonyl compound **15** bearing at least one substituent at β-position was reported earlier [5]. In the absence of a substituent the mercaptan undergoes thiolactonisation before addition to the azetidinone **1**, under the reaction conditions, resulting in the side product **18**.

By our method, using the butenolide **3** in which the mercaptan function could no longer participate in lactonisation, we obtained 2-unsubstituted cephem derivatives very easily and in high yield.

Application of this method for the conversion of penicillin to cephalosporin lactones is being reported in the next communication.

REFERENCES

[1] *W. Häfliger & T. Petrzilka*, Helv. *49*, 1937 (1966).
[2] *T. Petrzilka, C. Fehr & G. Schmid*, Helv. (in press).
[3] *E. Galantay, H. Engel, A. Szabo & J. Fried*, J. org. Chemistry *29*, 3560 (1964).
[4] *D. M. Green, A. G. Long, P. J. May & A. F. Turner*, J. chem. Soc. *1964*, 766.
[5] *H. W. Schnabel, D. Grimm & H. Jensen*, Liebigs Ann. Chem. *1974*, 477.

[4]) Comparatively bromohydrins **11a** and **11b** gave very poor yield (~1%) of the cephem **14** on similar treatment.

[6] *J. C. Sheehan, D. Ben-Ishai & J. U. Piper*, J. Amer. chem. Soc. *95*, 3064 (1973).
[7] *R. Heymes, G. Amiard & G. Nominé*, C. r. hebd. séances Acad. Sc. *263*, 170 (1966).
[8] *E. J. Corey, N. M. Weinshenker, T. K. Schaaf & W. Huber*, J. Amer. chem. Soc. *91*, 5675 (1969).
[9] *R. Schwyzer*, Helv. *35*, 1903 (1952).
[10] *K. D. Barrow & T. H. Spotwood*, Tetrahedron Letters *1965*, 3325.
[11] *H. Schinz & M. Hinder*, Helv. *30*, 1349 (1947).
[12] *J. W. Cornforth, (Mrs) R. H. Cornforth & K. K. Mathew*, J. chem. Soc. *1959*, 112.
[13] *H. O. House & R. S. Ro*, J. Amer. chem. Soc. *80*, 182 (1958).

244. Conversion of Penicillin to Cephalosporin Lactones

Preliminary Communication

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

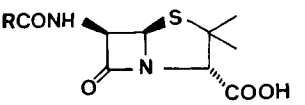
(18. VIII. 76)

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



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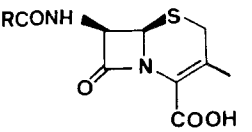

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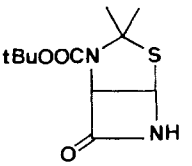

3

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

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