Enlargement of the Thiazolidine Ring of Penicillanic Acid Derivatives

By B. G. RAMSAY and R. J. STOODLEY*

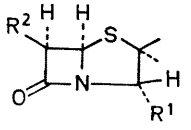
(*Department of Organic Chemistry, The University, Newcastle upon Tyne* NE1 7RU)

Summary 6β-Phthalimidopenicillanoylchloromethane undergoes a base-promoted rearrangement to a mixture of 4-isopropylidene-3-oxo-7β- and 4-isopropylidene-3-oxo-7α-phthalimidocepham.

THE chemical transformation of penicillin V (I) into cephalosporin (IX) has been achieved[1] by converting the penicillin into its methyl ester sulphoxide which, when treated with tolyl-*p*-sulphonic acid, forms deacetoxycephalosporin V methyl ester (VIII), from which the cephalosporin (IX) was obtained.

Our approach to the thiazolidine-ring-enlargement step is similar to that of Wolfe *et al.* who have reported[2] that penicillinic acid chlorides (II) rearrange to anhydropenicillins (X) in the presence of triethylamine. These authors suggest that the acid chloride undergoes a base-induced β-elimination to the thiolate anion (XI) which ring closes to the anhydropenicillin.

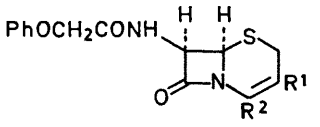
We considered that if a penicillanoylchloromethane (III) underwent a similar β-elimination then the intermediate (XII) should ring close to the cepham system (XIII). We now report evidence which supports this speculation: the procedure offers a potentially valuable entry to cepham derivatives.



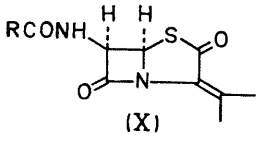
(I) $R^1 = CO_2H$, $R^2 = PhOCH_2CONH$
(II) $R^1 = COCl$, $R^2 = RCONH$
(III) $R^1 = COCH_2Cl$
(IV) $R^1 = COCHN_2$, R^2 = phthalimido
(V) $R^1 = COCH_2Cl$, R^2 = phthalimido
(VI) $R^1 = COCH_2I$, R^2 = phthalimido
(VII) $R^1 = CO_2Me$, R^2 = phthalimido

6β-Phthalimidopenicillanoyldiazomethane[3] (IV) was treated with 1 equiv. of 1N-HCl in Me_2CO to afford, after silica gel chromatography, the chloro-ketone (V) (60%), m.p. 169—171°, $[\alpha]_D$ + 361° ($CHCl_3$). On treatment with 1 equiv. of triethylamine in dichloromethane, (V) was converted quantitatively into a product which appeared to be homogeneous on t.l.c., but was shown by n.m.r. spectroscopy to be a mixture of two closely-related

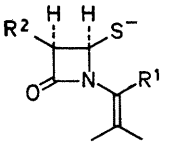
compounds present in the ratio of *ca.* 2 : 3. The components were separated by chromatography on a silica-gel column.



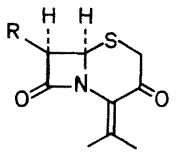
(VIII) R^1 = Me, R^2 = CO_2Me
(IX) R^1 = CH_2OAc, R^2 = CO_2H



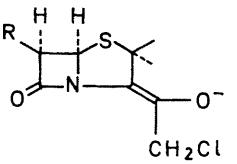
(X)



(XI) R^1 = COCl, R^2 = RCONH
(XII) R^1 = $COCH_2Cl$



(XIII)



(XIV) R = phthalimido (XV) R = phthalimido

The minor constituent, m.p. 191—193°, $[\alpha]_D$ + 290° ($CHCl_3$), which was eluted first, is formulated as 4-isopropylidene-3-oxo-7β-phthalimidocepham (XIV) on the following evidence. Micro-analysis and mass spectrometry indicated the molecular formula, $C_{17}H_{14}N_2O_4S$. I.r. analysis (KBr) revealed absorptions at 1775 (azetidinone and phthalimide CO), 1720 (phthalimide CO), 1690 ($\alpha\beta$-unsaturated CO), and 1610 cm^{-1} (C=C), while u.v. spectroscopy (EtOH) showed a maximum at 265 nm (ϵ 7100) consistent with the $\alpha\beta$-unsaturated-ketone chromophore. The n.m.r. spectrum ($CDCl_3$) showed singlets at τ 7·92 and 7·65, which indicated that the methyl groups were attached to a double bond, doublets at 7·13 and 5·71 (J 14 Hz) for the 2-methylene group and at 4·72 and 4·21 (J 4 Hz) for the β-lactam protons, and a singlet at 2·08 for the aromatic protons.

The major constituent, m.p. 206—208°, $[\alpha]_D$ + 349° ($CHCl_3$), was isomeric with (XIV), and it had similar i.r. and u.v. spectra. However, n.m.r. spectroscopy clearly revealed that it differed from (XIV) in the stereochemistry of the β-lactam protons. These were present as doublets at τ 4·78 and 4·41 and their coupling constant (J 2 Hz) indicated that they were *trans*-orientated.[4] The *gem*-dimethyl group appeared as singlets at τ 7·78 and 7·67, the 2-methylene group as doublets at 7·03 and 6·28 (J 14 Hz), and the aromatic protons as a singlet at 2·18. The compound is, therefore, 4-isopropylidene-3-oxo-7α-phthalimidocepham.

The epimerisation of penicillanic acid derivatives at position 6[5] and of cephalosporanic acid derivatives at position 7[6] has been reported recently. Particularly pertinent to the present example is the observation of Wolfe and Lee that methyl 6β-phthalimidopenicillanate (VII) is converted into the 6α-isomer in the presence of triethylamine in dichloromethane.

In our case, the chloro-ketone (V), the cepham (XIV), or both derivatives may undergo epimerisation. However, since (XIV) was recovered unchanged after being left under the reaction conditions, it is evident that only (V) epimerises and, therefore, 6-H of (V) is more acidic than 7-H of (XIV).

In an attempt to exclude epimerisation, the influence of the solvent, the leaving group, and the base upon the reaction was investigated. The most successful result was obtained from the reaction of 6β-phthalimidopenicillanoyliodomethane† (VI), m.p. 143—144°, $[\alpha]_D$ + 241° ($CHCl_3$), with 1 equiv. of 1,5-diazabicyclo[4,3,0]non-5-ene (DBN) in dimethyl sulphoxide, when the ratio of (XIV) to its 7α-isomer was *ca.* 6 : 1.

The ring enlargement of (V) presumably involves a base-promoted β- elimination to afford the enethiolate (XII) which ring closes to (XIV). The β-elimination step may proceed *via* an intermediate enolate (XV) (*i.e.*, *EIcB* mechanism) or it may be a concerted process (*i.e.*, *E2* mechanism). To obtain information about the rate-controlling step, the chloro-ketone (V) was treated with 0·5 equiv. of DBN in dimethyl sulphoxide containing 15% deuterium oxide. Examination of the product by n.m.r. spectroscopy indicated the presence of *ca.* 50% of (V). Although the protons of the chloromethylene group were replaced completely by deuterium there was no detectable exchange of 3-H. Consequently, the slow step of the ring expansion is either the formation of the enolate (XV) (if an *EIcB* process is involved) or the generation of the enethiolate (XII) (if an *E2* process is operating).

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† This was obtained (28%) from the reaction of (IV) with iodine in dichloromethane.

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