Synthesis of New Tricyclic Cephalosporins from Cephalosporin 3'-Triphenylphosphorane

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Cephalosporin 3'-triphenylphosphorane reacted with α-halogeno ketones to give new tricyclic cephalosporins; their aminothiazole oximino derivatives showed a significant activity against gram-negative bacteria.

In the course of a study of the reactions of cephalosporin 3'-triphenylphosphoranes,[1] we found that the phosphorane **1** reacted with α-halogeno ketones to give new tricyclic cephalosporins **2** (87%) and **3** (70%) which were bridged by a cyclopentene ring between the 3 and 4 positions of cephalosporin (Scheme 1).

In analogy with the previously reported [3 + 2] annulation for the preparation of cyclopentadienes,[2] this reaction can be rationalized in terms of initial alkylation at the 4 position of the 1,4-dipolar resonance form of **1** followed by an intramolecular Wittig reaction. This is supported by the fact that treatment of the phosphorane **1** with iodomethane followed by formaldehyde produced **6** in 45% yield. These reactions gave exclusively single diastereoisomers and created a new chiral centre at the 4 position. Structural elucidation of the tricyclic cephalosporins was carried out on the basis of NMR studies.

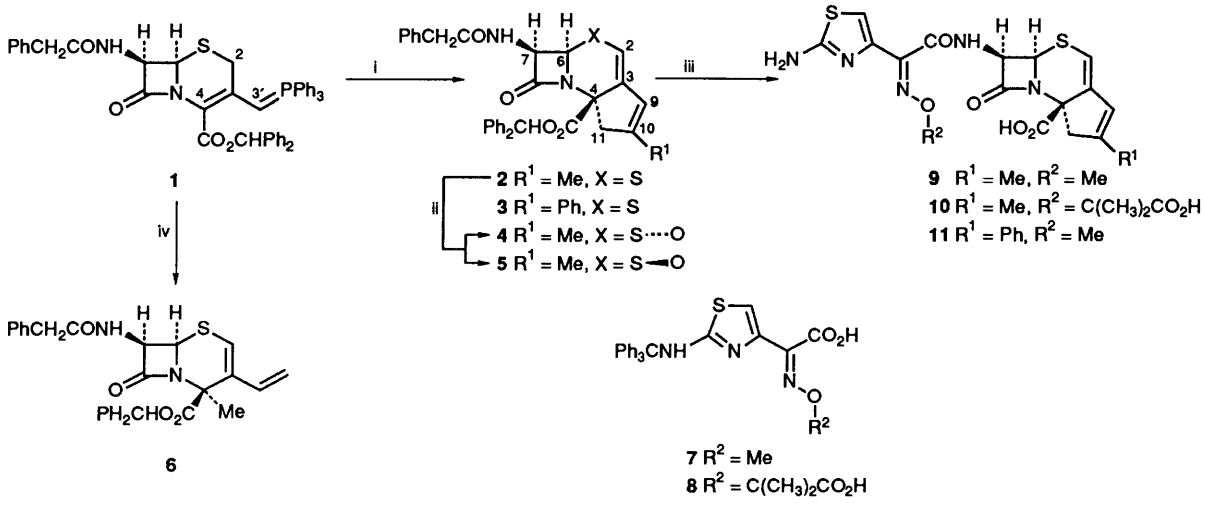
Oxidation of **2** with peracetic acid in dichloromethane gave a mixture of the sulphoxides **4** and **5** in 75 and 5% yields, respectively. Notable features of the NMR spectra† of the tricyclic cephalosporins include: (1) spin decoupling experiments of **2** revealed long-range couplings between 6-H and 2-H and between 9-H and 11-H, couplings not observed in the sulphoxides **4** and **5**; (2) a heteronuclear multiple bond connectivity (HMBC) spectrum of the sulphoxide **4** showed long-range couplings of the vinyl 2-H with C-4, -6 and -9; (3) an NOE was observed between 2-H and 9-H.

The stereochemistry of the sulphoxide bond was determined by the procedure of Cooper *et al.*[3] Observed benzene-induced solvent-shift values‡ led to the assignment of *R*-stereochemistry for the major sulphoxide **4** and *S*-stereochemistry for the minor sulphoxide **5**. This assignment is further supported by greater downfield shift [$\delta(CDCl_3)$–$\delta[(CD_3)_2SO] = -2.90$] of the amide protons of **4** in [$(CD_3)_2SO$] in comparison with that (− 0.72) of **5**.

It is well established that peracid oxidation of 7-acylaminocephalosporins and 6-acylaminopenicillins gives predominantly *S*-sulphoxides due to the directing effect of the 7-amide groups.[4] Preferential formation of unusual *R*-sulphoxide from the tricyclic cephalosporins **2** might be interpreted on a 'reagent approach control effect' due to increased nonbonded interactions on the β-face. Therefore, the molecular geometries of two possible isomers of **2** were evaluated by using the molecular dynamics program CHARMm in QUANTA system[5] and the molecular orbital program MNDO in AMPAC package.[6] This demonstrated that the isomer having the β-carboxy group is

† Assignments of all ^1H and ^{13}C chemical shifts were unambiguously carried out by decoupling experiments including ^1H–^1H and ^1H–^{13}C and ^1H–^{13}C COSY measurements. Compound **2**: δ_H(400 MHz; $CDCl_3$) 1.88 (3 H, s, 10-CH_3), 2.68 (1 H, br d, *J* 18, 11-H), 3.63 (2 H, ABq, CH_2CO), 3.84 (1 H, br d, *J* 18, 11-H), 5.24 (1 H, dd, *J* 2, 4.4, 6-H), 5.43 (1 H, dd, *J* 4.4, 9, 7-H), 5.62 (1 H, d, *J* 2, 2-H), 5.94 (1 H, m, 9-H), 6.01 (1 H, d, *J* 9, NH), 6.86 (1 H, s, OCH) and 7.15–7.50 (15 H, m, Ar); δ_C(100 MHz; $CDCl_3$) 16.9 (10-CH_3), 43.4 (C-11), 43.5 ($COCH_2Ph$), 58.1 (C-6), 58.5 (C-7), 68.8 (C-4), 78.4 ($CHPh_2$), 105.7 (C-2) and 126.1 (C-9).

‡ Compound **5** showed 0.52 ppm highfield shift of 6-H in C_6D_6, while both 6-H and 7-H of **4** shifted downfield by 0.15 and 0.50 ppm, respectively.



Scheme 1 *Reagents and conditions:* i, $BrCH_2COCH_3$ or $BrCH_2COPh$, aqueous $NaHCO_3$–CH_2Cl_2, 20 °C, 17 h; ii, 40% $MeCO_3H$, CH_2Cl_2, − 40 °C; iii, (1) PCl_5, CH_2Cl_2, −20 to − 5 °C, 2 h, then MeOH, 5 °C, 1 h, (2) **7** or **8**, $POCl_3$, pyridine, CH_2Cl_2, − 20 °C, 2 h, (3) CF_3CO_2H, anisole, 5 °C, 1 h; iv, (1) MeI, DMF, 40 °C, 5 h, (2) HCHO, aqueous $NaHCO_3$–CH_2Cl_2, 20 °C, 20 h

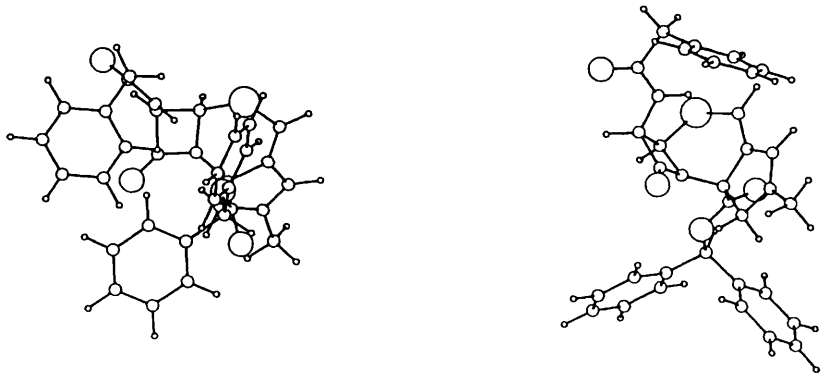


Fig. 1 Optimized structures of two possible isomers of compound **2** (CHARMm and MNDO calculation)

more stable than that having the 4α-carboxy group.* Inspection of the structures after minimization (Fig. 1) indicates that preferred formation of the *R*-sulphoxide would be expected from the 4β-isomer as a result of steric hindrance from the β-oriented carboxy group. A similar configuration for the 4-methylcephalosporin **6** in which the 4-carboxy group is in the β-position was supported by the observation of an NOE between 4-methyl and 6-H.[7] β-Orientation of the carboxy group is consistent with favoured attack of the halides from the less hindered α-face of the starting phosphorane.

Biological evaluation of these tricyclic cephalosporins is interesting, because the 4β stereostructure having a fixed β-oriented pseudoaxial carboxy group fits well the geometrical requirements of the carboxy group for antibacterial activity in β-lactam antibiotics as discussed by Cohen.[8] Compounds **2** and **3** were converted into the aminothiazole oximino derivatives **9**, **10** and **11** (Scheme 1), the first two compounds, **9** and **10**, exhibiting significant activity (MIC 0.78–25 μg/ml) against gram-negative organisms, *E. coli*, *K. pneumoniae*, *P. vulgaris*, *E. cloacae and S. marcescens*.

* Dynamics simulation was carried out in the usual manner on lowest energy conformations obtained from MM calculation for each isomer. Optimized lowest energy conformations were further submitted to MNDO semiempirical calculation. This calculation showed that the C-4β isomer is more stable by 9.9 kcal mol^{-1} (CHARMm) or 14.06 kcal mol^{-1} (MNDO) than C-4α isomer.

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7 The corresponding NOE from 4-CH_2 to 6-H in the tricyclic cephalosporins **2** and **9** was not observed, probably due to longer distances between the 4-CH_2 and 6-H than that between the 4-Me and 6-H in **6**.
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Paper 1/01445E
Received 26*th March* 1991
Accepted 23*rd April* 1991