Direct Introduction of a Benzoyloxy Substituent at the Ring Junction of Fused β-Lactam Rings[1]

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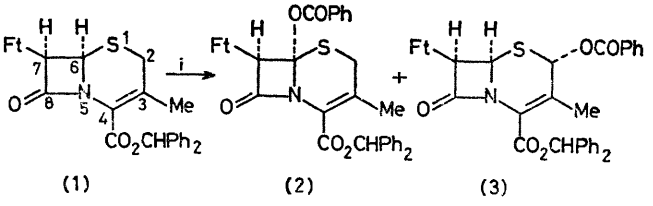
Summary Treatment of the 7-phthalimido-3-methylceph-3-em-4-carboxylate (**1**) and 6-phthalimido-penicillins (**4**) with t-butyl perbenzoate in the presence of copper(I) chloride gave compounds bearing a benzoyloxy substituent at the ring junction of the fused β-lactam rings, (**2**) and (**5**) respectively.

PENICILLINS and cephalosporins having a substituent at the ring junction of their fused β-lactam rings have been prepared by total synthesis.[2] However, direct introduction of substituents at C-6 in cephalosporins and at C-5 in penicillins has not been reported so far. We report here the direct introduction of a benzoyloxy group at these bridgehead positions. The Kharasch–Sosnovsky reaction, which is often used to introduce acyloxy groups at an allylic carbon or a carbon adjacent to sulphur, nitrogen, carbonyl *etc.*,[3] appeared to be a possible method for introducing a substituent at the ring junction.

Treatment of benzhydryl 7-phthalimido-3-methylceph-3-em-4-carboxylate (**1**) with a mixture of t-butyl perbenzoate (1·5 equiv.) and copper(I) chloride (catalytic amount) in benzene under reflux for 25 h gave a mixture of the 6-substituted cephem (**2**) and the 2-substituted cephem (**3**) in 70% yield along with recovered (**1**). Compounds (**2**) and (**3**) have similar polarities (R_F = 0·44, benzene–EtOAc, 5:1) on t.l.c. (Merck Silica gel F254). Repeated careful chromatography [Merck 60 (70—230 mesh) containing 10% H_2O; benzene as eluant] gave (**2**) (12·4%) {m.p. 179·5—180·0 °C (decomp.), $[\alpha]_D^{24}$ −162·1 ± 4·6° ($CHCl_3$), i.r. ($CHCl_3$) 1802, 1785, and 1725 cm^{-1}} and

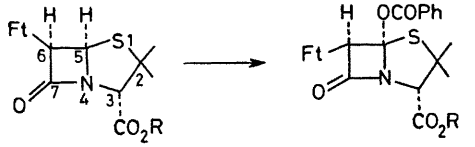


(1) (2) (3)

i, But_3CPh, CuCl, benzene, reflux. Ft = phthalimido

(**3**) (28·0%), foam {$[\alpha]_D^{24}$ −26·3 ± 1·3° ($CHCl_3$), i.r. ($CHCl_3$) 1795, 1778 (sh), and 1722 cm^{-1}}.

Analogous treatment of methyl 6-phthalimido-penicillanate (**4a**) gave the 5-substituted penam (**5a**) (41·1%) [i.r. ($CHCl_3$) 1815, 1790, 1760, 1735, and 1725 (sh) cm^{-1}] besides recovered (**4a**) (43%); (**4b**) gave (**5b**) (42%) [i.r. ($CHCl_3$) 1818, 1792, 1760 (sh), 1740, and 1730 (sh) cm^{-1}].



(**4**) (**5**)

a; R = Me
b; R = $CHPh_2$

The ^1H n.m.r. spectrum† of (**2**) [δ 2·73 and 4·15 (2-H), and 5·68 (7-H)] lacks one of the β-lactam proton signals and the long-range spin coupling between 2β-H and 6α-H observed in the spectrum of (**1**) [δ 2·87 and 3·77 (2-H), 5·08 (6-H), and 5·72 (7-H)]. One of the CH signals (C-6 and C-7) at δ_C 59·6 p.p.m. observed in the ^{13}C n.m.r. spectrum of (**1**) is absent from the spectrum of (**2**) and is replaced by a quaternary carbon signal at 100·3 p.p.m. assignable to C-6. The phthalimido group signals in (**2**) are almost the same as those of (**1**) and a steric γ-effect is exerted on C-8 [δ 159·2 p.p.m. for (**2**) compared with *ca.* 161 for (**1**)]. These data clearly show that the benzoyloxy group is introduced at C-6α. In the ^{13}C n.m.r. spectrum of (**3**), the C-2 signal observed at δ_C 31.8 p.p.m. for (**1**) is shifted to 71·7 p.p.m. and a γ-effect [δ 59·6 p.p.m. for (**1**) compared with 53·5 for (**3**)] is observed on the C-6 signal. This shows that the benzoyloxy group is introduced at C-2 of the cephem. Furthermore, the long-range spin coupling between 6α-H and 2β-H (*J ca.* 0·5 Hz) observed in the ^1H n.m.r. spectrum of (**3**) indicates that the benzoyloxy group at C-2 has the α-configuration.

The 5-H signal at δ 5·61 in the ^1H n.m.r. spectrum of (**4a**) is absent from the spectrum of (**5a**), and one of the group of CH signals at δ 58·6, 67·0, and 70·9 p.p.m. (C-6, C-5, and C-3) in the ^{13}C n.m.r. spectrum of (**4a**) is replaced by a quaternary carbon signal at 104·7 p.p.m. in the spectrum of (**5a**). The phthalimido ^{13}C resonances for (**5a**) are almost the same as those of (**4a**); a β- [δ 58·6 p.p.m. for (**4a**) and 65·1 for (**5a**)] and a γ-effect [δ 168·5 p.p.m. for (**4a**) and 165·6 p.p.m. for (**5a**)] are observed for the C-6 and C-7 signals, respectively. These data clearly show the benzoyloxy group is introduced at C-5α.

These results can be explained by the accepted mechanism for this type of reaction. Thus, the less hindered attack of the benzoyloxy anion upon the α-side of the intermediate cephalosporin C-6 (C-5 in penicillins) and C-2 cations, which are derived from the initially formed corresponding radicals by Cu^{2+} oxidation, gave the products (**2**) and (**3**) [(**5**) in the case of penicillins]. After de-esterification of (**2**), the corresponding free acid was tested *in vitro* for biological activity, but no antibacterial activity was observed.

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† ^1H and ^{13}C n.m.r. spectra were recorded on a Varian HA-100 (100 MHz) and an NV-FT (15·087 MHz) spectrometer, respectively. ^{13}C Signals were assigned by single-frequency off-resonance ^1H decoupling and by comparing chemical shifts observed with those reported for similar compounds (S. Kukolja, N. D. Jones, M. O. Chaney, T. K. Elzey, M. R. Gleissner, J. W. Paschal, and D. E Dorman, *J. Org. Chem.*, 1975, **40**, 2388; K. Tori, T. Tsushima, T. Tamura, H. Shigemoto, T. Tsuji, H. Ishitobi, and H. Tanida, *Tetrahedron Letters*, 1975, 3307, and references therein). Full details will be published elsewhere; only key resonances are discussed here.

[1] For previous paper in this series, see: M. Narisada, H. Onoue, and W. Nagata, *Heterocycles*, 1977, **7**, 839.
[2] B. G. Christensen, K. Hoogsteen, F. Plavac, and R. W. Ratcliffe, in 'Recent Advances in the Chemistry of β-Lactam Antibiotics,' ed. J. Elks, Special Publication No. 28, The Chemical Society, London, 1977, p. 260; A. K. Bose, W. A. Hoffman, III, and M. S. Manhas, *ibid.*, p. 209.
[3] D. J. Rawlinson and G. Sosnovsky, *Synthesis*, 1972, 1.