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1-PHOSPHACEPHALOSPORIN. I.
SYNTHESIS OF RACEMIC 7-UNSUBSTITUTED-1-PHOSPHADETHIA-3-CEPHEM 1-OXIDES

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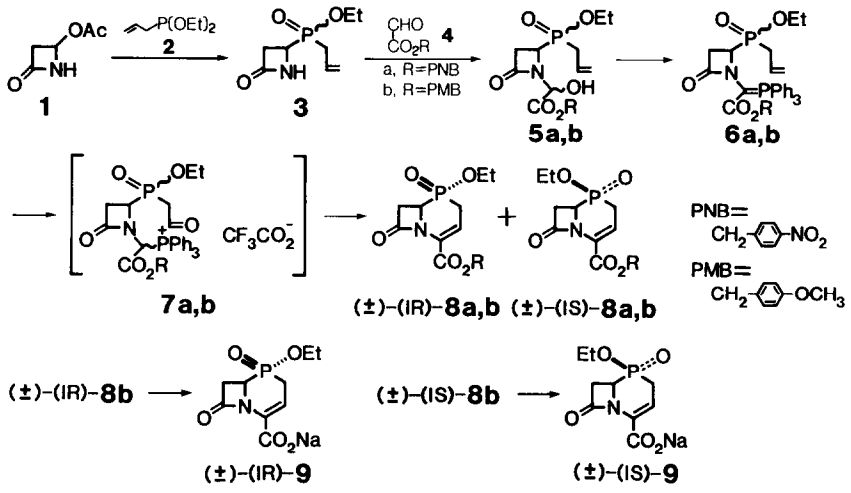
Abstract: The novel unnatural ring system, 1-phosphacephalosporin, was synthesized for the first time from 4-acetoxy-2-azetidinone.

The chemical reactivity of the β-lactam ring seems to play an important role in determining the biological activity of β-lactam antibiotics while the sulfur atom in the cephem ring is not essential.[1] We thought that replacement of the sulfur atom in the cephem nucleus with the electron-withdrawing, P(O)(OEt) group,[2] would enhance the reactivity of the β-lactam carbonyl and consequently modify the antibacterial activity. This paper reports the preparation of a novel ring system, 1-phosphacephalosporins 9. Although some cephem derivatives substituted by the phosphonic acid group, $-P(O)(OH)_2$, as a substituent at the C-3,[3a] C-4[3b] and C-7[3c] positions of the nucleus have been synthesized, no 1-phosphadethiacephem derivatives have been reported yet.

Our synthetic approach was to use an Arbusov reaction[4] and an intramolecular Wittig reaction[5] as the key steps. 4-Acetoxy-2-azetidinone 1[4a] reacted with diethyl allylphosphonite 2[6] (100°, 2 h) to give the phosphinate 3 in 77.0% yield.[7] Reflux of 3 with p-nitrobenzyl glyoxylate 4a in benzene gave a diastereomeric mixture of the hemiaminal 5a in 83.8% yield. Treatment of 5a with $SOCl_2$ in the presence of 2,6-lutidine in THF yielded the α-chloroacetate, which was subsequently treated (20°, 18 h and reflux 5 h) with Ph_3P and 2,6-lutidine in THF to provide the phosphorane 6a in 80.8% from 5a. Ozonolysis of 6a (1 eq. CF_3COOH,[5] CH_2Cl_2, -70°) followed by reduction of the ozonide (Me_2S) and aq. $NaHCO_3$ work-up gave the desired p-nitrobenzyl 1-phosphadethia-1-ethoxy-3-cephem-4-carboxylate 1-oxides, (±)-(1R)- [mp 162-165°C] and (±)-(1S)-8a [mp 174-180°C],[7] as a mixture of the epimeric isomers at phosphorus, which could be separated by chromatography on SiO_2 in a ratio of 2:1, in 23.3% yield from 6a. (±)-(1R)-8a: $C_{16}H_{17}N_2O_7P$; $\nu_{max}^{CHCl_3}$ 1785 cm^{-1}; λ_{max}^{EtOH} 265 nm. (±)-(1S)-8a: $C_{16}H_{17}N_2O_7P$; $\nu_{max}^{CHCl_3}$ 1780 cm^{-1}; λ_{max}^{EtOH} 265 nm. The ^1H NMR spectra (Fig. 1) of the (1R)- and (1S)-isomers showed all the resonances at the expected positions. In the former, the C-2 protons signal (δ 2.81) appears as a doublet-doublet. This splitting is due to coupling ($^3J_{HH}$ = 5.0 Hz) between the C-2 protons and the C-3 proton and to coupling ($^2J_{HP}$ = 18.0 Hz[8]) between the C-2 protons and phosphorus. The C-3 proton signal (δ 6.37) appears as a triplet-doublet. This is due to coupling ($^3J_{HH}$ = 5.0 Hz) between the C-2 protons and the C-3 proton and to coupling ($^3J_{HP}$ = 27.0 Hz[8]) between the C-3 proton and phosphorus. A similar signal pattern was also observed



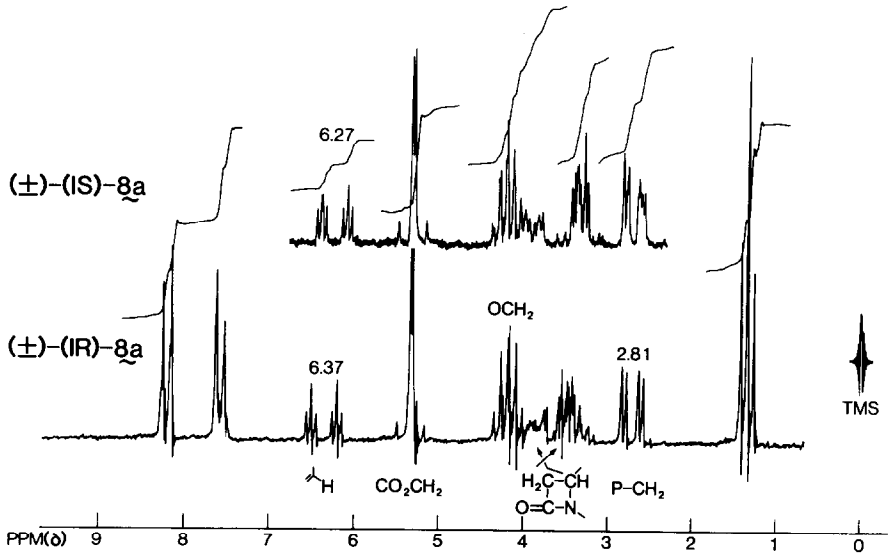


Fig. 1. ^{1}H NMR spectra of (±)-(IR)- and (±)-(IS)-8a in $CDCl_3$(90MHz)

in the spectrum of the (1S)-isomer (Fig. 1). The upfield shift (Δ ca. 0.1 ppm) of C-3 proton in (1S)-isomer compared to that in (1R)-isomer and the partly complicated signal pattern of C-2 protons in the (1S)-isomer relative to that in the (1R)-isomer can be efficiently used to distinguish between the (1R)- and (1S)-isomers, including other 1-phosphacephem derivatives reported later (see Fig. 1).

To determine the stereochemistry of this novel ring system, an X-ray crystallographic study[9] on (±)-(1S)-8a was undertaken. The results are summarized in Table I and the molecular

Table I. Structural Characteristics of 1-Phosphadethiacephalosporin (±)-(IS)-**8a** and Representative β-Lactam Antibiotics

Compound	Sum of bond angles about nitrogen, deg	Distance of N atom from plane of three C atoms, Å	β-Lactam bond length (N-CO), Å
(±)-(IS)-**8a**	355.7	0.165	1.387
1-Oxacephem[11]	352.3	0.220	1.393
Cephaloridine[12]	350.7	0.24	1.382
Cephalosporin C[12]	345.0	0.32	1.385

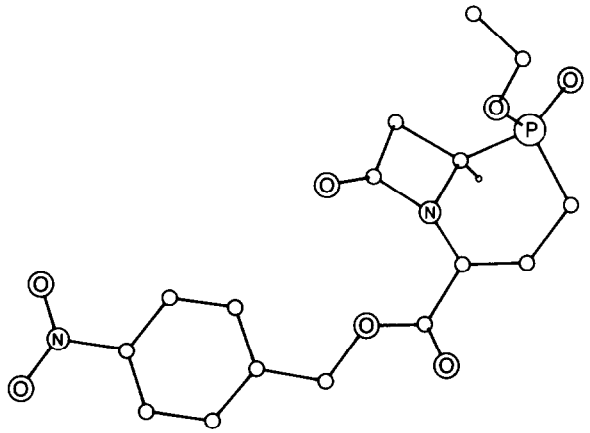


Fig. 2. A perspective view of (±)-(IS)-8a based on X-ray data ; hydrogen atoms have been omitted for clarity except for that at C-6.

geometry is illustrated in Figure 2. In the crystal state, the six-membered ring exists in a half-chair like conformation similar to that in 3-cephem 1-oxide[10] and the relative configuration between the H atom at C-6 and the O atom of the P=O group is cis. The β-lactam nitrogen is not planar, but is 0.165 Å above the plane defined by the three attached atoms.[12]

The conversion from 3 into the analogous p-methoxybenzyl (PMB) esters, (±)-(1R)- and (±)-(1S)-8b, which could be separated by chromatography in a ratio of 2:1, proceeded uneventfully. (±)-(1R)-8b: $\nu_{C=O}^{CHCl_3}$ 1778 cm^{-1}; NMR ($CDCl_3$, δ, Hz) 2.62 (d-d, $^3J_{HH}$ = 5.0, $^2J_{HP}$ = 18, 2H, C-2), 3.76 (s, 3H, OCH_3), 6.26 (t-d, $^3J_{HH}$ = 5.0, $^3J_{HP}$ = 27.0, 1H, C-3). (±)-(1S)-8b: NMR 2.69 (partly complex d-d, $^3J_{HH}$ = 5.0, $^2J_{HP}$ = 17.5, 2H, C-2), 3.79 (s, 3H, OCH_3), 6.17 (t-d, $^3J_{HH}$ = 5.0, $^3J_{HP}$ = 27.0, 1H, C-3). $AlCl_3$-anisole[13] (CH_2Cl_2, room temp.) rapidly deprotected the above PMB esters followed by treatment with aq. $NaHCO_3$ to afford the expected sodium carboxylates (±)-(1R)- and (±)-(1S)-9, respectively. (±)-(1R)-9: mp ca. 95°C, $\nu_{C=O}^{KBr}$ 1751 cm^{-1}, $\lambda_{max}^{H_2O}$ 250 nm (ε 7761). (±)-(1S)-9: mp ca. 110°C, $\nu_{C=O}^{KBr}$ 1752 cm^{-1}, $\lambda_{max}^{H_2O}$ 250 nm (ε 7682). The antibacterial activities of both sodium salts were disappointing.

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