Synthesis of Tricyclic Cephalosporins

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Cephalosporin 3'-triphenylphosphonium ylide (1) reacted with acrylaldehyde to give the C-3,C-4 tricyclic compound (3), while the sulphoxide of the ylide (1) upon similar treatment gave the C-2,C-3 tricyclic compound (4) which was converted into the ring-fused analogue (7) of nocardicin; desulphurization of this compound afforded the nocardicin nucleus (10).

Although reaction of cephalosporin 3'-triphenylphosphonium ylide (1) with aldehydes is a useful tool for elongation at C-3', such reactions are accompanied by formation of the C-2 and/or C-4 substituted products arising from the resonancestabilized tautomers [*e.g.*, (A) and (B)].¹ Here we report that the ylide (1) is also a useful precursor for preparation of tricyclic cephalosporins, which are bridged by a cyclohexene ring between the C-2 and C-3 positions or between the C-3 and C-4 positions.²

An excess of acrylaldehyde was treated with a suspension of (1) in dichloromethane to give the C-3,C-4 tricyclic compound (3)⁺ [56% yield, m.p. 143—145 °C]. In contrast, the sulphoxide (2) [readily available in 86% yield from (1) by peracid oxidation in the presence of hydrochloric acid] gave the C-2,C-3 tricyclic compound (4) [62% yield, m.p. 228—230 °C (decomp.)] upon similar treatment with acrylaldehyde. These tricyclic compounds appear to arise from initial Michael addition at C-4 or C-2 followed by intramolecular Wittig reaction. The complete switching of the reaction course in the Michael addition from C-4 to C-2 by the sulphoxidation of (1)



† All new compounds were fully characterized by spectroscopic and microanalytical methods. However the stereochemistry of the carboxy moieties of compound (**3**) was not determined. Selected physical data: (**3**): colourless amorphous solid; i.r. (Nujol) 1770, 1735, and 1670 cm⁻¹; λ_{max} . (EtOH) 274 nm (log ϵ 4.17); ¹H n.m.r. (CDCl₃) δ 2.08 (m, 1H), 2.20 (m, 1H), 2.50 (m, 1H), 2.76 (br. d, *J* 5.0 and 13.4 Hz, 1H), 3.62 (dd, 2H), 4.69 (d, *J* 4.2 Hz, 1H), 5.37 (dd, *J*, 4.2 and 8.6 Hz, 1H), 5.62 (m, 1H), 6.08 (br. dd, *J* 8.7 Hz, 1H), 6.15 (d, *J* 8.7 Hz, 1H), and 7.2—7.4 (m, 16H), (**4**): colourless needles; i.r. (Nujol) 1775, 1720, and 1650 cm⁻¹; λ_{max} . (EtOH) 317 nm (log ϵ 4.20); ¹H n.m.r. [(CD₃)SO] δ 1.82 (m, 1H), 2.33 (m, 1H), 3.63 (dd, 2H), 3.70 (br.d, *J* 14.2 Hz, 1H), 5.08 (dd, *J* 1.5 and 4.8 Hz, 1H), 5.90 (dd, *J* 4.8 and 8.3 Hz, 1H), 6.12 (m, 1H) 6.74 (d, *J* 10.0 Hz, 1H), 6.94 (s, 1H), and 7.2—7.6 (m, 15H). (7): fine needles; i.r. (Nujol) 1775, 1742, and 1655 cm⁻¹; λ_{max} (EtOH) 287 nm (log ϵ 2.98); ¹H n.m.r. (CDCl₃) δ 3.61 (s. 2H), 5.43 (d, *J* 3.8 Hz, 1H), 5.56 (s, 1H), 5.64 (dd, *J* 3.8 and 8.6 Hz, 1H), 6.32 (d, *J* 8.6 Hz, 1H), and 6.8—7.7 (m, 20H).



Scheme 1. i, acrylaldehyde (3.0 equiv.), CH_2CI_2 , room temp., 1 h; ii, PBr₃, CH_2CI_2 , -20 °C, 1 h; iii, PCI₅ (1.1 equiv.), pyridine, 0 °C, work-up with MeOH, -50 to 0 °C, 1 h, and then with H₂O, 0 °C, 30 min; iv, *N*-t-butoxycarbonyl-*D*-phenyglycine (1 equiv.), dicyclohexyl-carbodiimide (1 equiv.), 1-hydroxybenzotriazole (1 equiv.), CH_2CI_2 , room temp., 3 h; v, CF_3CO_2H , anisole, CH_2CI_2 , room temp., 30 min; vi, $(CF_3CO)_2O$ (2 equiv.), CH_2CI_2 , 0 °C, 1 h, and then pyridine (2 equiv.), 0 °C, 1 h; vii, PCI₅ (2.1 equiv.), pyridine (6 equiv.), 0 °C, work-up with MeOH, -50 to 0 °C, 1 h, and then H_2O , 0 °C, 30 min; viii, Raney Ni, dioxane, 50 to 60 °C, 2 h.

is attributable to stabilization of the resonance form (**B**) by the sulphoxide group. Attempted reactions with other vinyl aldehydes including crotonaldehyde and methacrylaldehyde failed and (1) was recovered. The stereochemistry at C-2 of (4) was determined on the basis of its 360 MHz ¹H n.m.r. spectrum, which showed long-range W coupling ($J_{2.6}$ 1.5 Hz) between H-2 and H-6.³

Deoxygenation of (4) with phosphorus tribromide afforded (5) [64% yield, m.p. 220-223 °C], which was then transformed to (6) by the standard sequence consisting of cleavage of the 7-amide bond, acylation, and subsequent deprotection. Alternatively, reaction of (4) with trifluoroacetic anhydride and pyridine resulted in aromatization of the newly formed cyclohexene ring via the carbosulphonium ion to give (7) [35% yield, m.p. 158-161 °C]. The aromatization was also effected by phosphorus pentachloride and pyridine. Finally, interchange of the acyl groups as above gave (8) (32%). These compounds can be regarded as fused analogues of the monocyclic β-lactam antibiotics, nocardicins.⁴ The diphenylmethyl ester (7) was converted into the methyl ester (9) by treatment with trifluoroacetic acid and then diazomethane. Desulphurization of (9) with Raney nickel afforded $(10)^5$ [30% yield, m.p. 143-145 °C] which possessed the nocardicin nucleus. Thus a simple transformation of a cephalosporin to the nocardicin nucleus was achieved, in which the full carbon skeleton of the cephalosporin nucleus was retained.

The *in vitro* biological activities of (6) and (8) were poor and almost same as that of Δ^2 -cephalosporins.⁶

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