

## Olivanic Acids and Related Compounds: Total Synthesis of ( $\pm$ )-PS-5 and ( $\pm$ )-6-Epi PS-5

By JOHN H BATESON, ROGER I HICKLING, PATRICIA M ROBERTS, TERENCE C SMALE, and ROBERT SOUTHGATE\*  
(Beecham Pharmaceuticals, Research Division, Brockham Park, Betchworth, Surrey RH3 7AJ)

**Summary** The *trans*- and *cis*-substituted  $\beta$ -lactam isomers of *p*-nitrobenzyl 3-(2-acetamidoethylthio)-6-ethyl-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate can be oxidised with iodobenzene dichloride-pyridine under anhydrous conditions to give the 3,4-unsaturated esters, which after isomerisation and deprotection afford the sodium salts of ( $\pm$ )-PS-5 and ( $\pm$ )-6-*epi* PS-5

In the context of preparing  $\beta$ -lactam systems related to the olivanic acids,<sup>1</sup> we have shown<sup>2</sup> how thiols react readily with C(3)-unsubstituted 1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates to give products resulting from addition of thiol to the 2,3-double bond. Such addition products have now been utilised to prepare the racemic form of the  $\beta$ -lactam antibiotic PS-5<sup>3</sup> (**7b**), a naturally occurring relative of the olivanic acids, and also its racemic C(6)-epimer (**7d**).

4-Allylazetid-2-one<sup>4</sup> (**1a**) was converted by a sequence of *N*-silylation (Bu<sup>t</sup>Me<sub>2</sub>SiCl, Et<sub>3</sub>N, DMF),<sup>†</sup> alkylation (LICA, THF, EtI, -78 °C to room temp),<sup>†</sup> and desilylation (KF, MeOH, room temp, 5 min) into the *trans*-substituted  $\beta$ -lactam (**1b**)<sup>‡</sup> ( $J_{3,4}$  2 Hz), in 60% overall yield from (**1a**)

Conversion of (**1b**) into the phosphorane (**1c**) was by the standard procedure.<sup>5</sup> Subsequent cyclisation<sup>4</sup> (CF<sub>3</sub>CO<sub>2</sub>H, O<sub>3</sub>, Ph<sub>3</sub>P, NaHCO<sub>3</sub>) gave (**2a**) (60% from the phosphorane),  $\nu_{\max}$  (CHCl<sub>3</sub>) 1775 cm<sup>-1</sup> ( $\beta$ -lactam carbonyl) ( $J_{5,6}$  3 Hz)

Reaction of (**2a**) in dimethylformamide with an excess of 2-acetamidoethanethiol in the presence of potassium carbonate (20 min, room temp) gave a 70% yield of an inseparable mixture of the isomers (**3a**) ( $\delta$  4.76, d,  $J$  7 Hz, 2-H), (**4a**) ( $\delta$  4.41, d,  $J$  5 Hz), and (**5a**) ( $\delta$  4.14, d,  $J$  8 Hz) in the ratio 5:3:2. On treatment with DBU,<sup>†</sup> (**5a**) was converted into the more thermodynamically favoured epimer (**4a**) (h p l c and n m r monitoring)

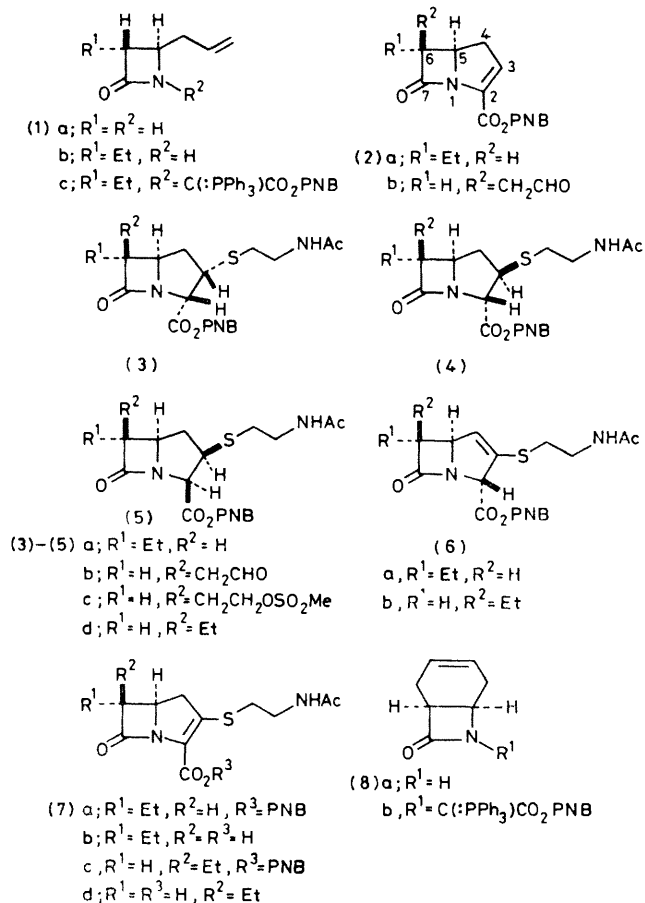
Reintroduction of the double bond was by a method that we have found to have some general application to thiol addition products of type (**3**)—(**5**). Oxidation of a mixture of (**3a**) and (**4a**) under rigorously anhydrous conditions with iodobenzene dichloride (PhICl<sub>2</sub>) (1 equiv) in dichloromethane containing pyridine (2 equiv) (5 °C, 3 h) gave the 1-azabicyclo[3.2.0]hept-3-ene isomer<sup>§</sup> (**6a**) (60%), m p 95–97 °C, without any detection of  $\alpha$ -chlorosulphide.<sup>6</sup> Treatment of (**6a**) with a catalytic amount of DBU<sup>¶</sup> (CH<sub>2</sub>Cl<sub>2</sub>, room temp, 5 h) followed by rapid fractionation

<sup>†</sup> DMF = dimethylformamide, LICA = lithium *N*-isopropylcyclohexylamide, THF = tetrahydrofuran, DBU = 1,5-diazabicyclo-[5.4.0]undec-5-ene, HMPA = hexamethylphosphoramide

<sup>‡</sup> Only one enantiomer is shown for each ( $\pm$ )-mixture

<sup>§</sup> With certain other substituents, the 1-azabicyclohept-2-ene isomer was also observed as a minor product, with more soluble substrates reactions were conducted in benzene

<sup>¶</sup> Pyridine was ineffective in establishing this equilibrium



on silica gel gave recovered (**6a**) (45%), and the *p*-nitrobenzyl ester of ( $\pm$ )-PS-5 (**7a**) (30%), m.p. 135–139 °C,  $\lambda_{max}$  (EtOH) 268 and 317 nm;  $\nu_{max}$  (CHCl<sub>3</sub>) 1780 ( $\beta$ -lactam carbonyl), 1700 (ester), and 1670 (amide carbonyl) cm<sup>-1</sup>, having the *trans*-stereochemistry of  $\beta$ -lactam ring protons ( $J_{5,6}$  2.8 Hz). The u.v., i.r., n.m.r., and mass spectral data for ester (**7a**) were identical to those of semi-synthetic material derived<sup>7</sup> from the naturally occurring olivanic acid MM 17880. Hydrogenolysis (i; H<sub>2</sub>, Pd-C, dioxan-H<sub>2</sub>O; ii; NaHCO<sub>3</sub>) afforded the sodium salt of ( $\pm$ )-PS-5 (**7b**), which was indistinguishable by u.v. and 250 MHz n.m.r. spectroscopy and h.p.l.c. from authentic material kindly supplied by Sanraku-Ocean Co. Ltd.

Preparation of the corresponding *cis*-substituted  $\beta$ -lactam isomer (**7d**) utilized the  $\beta$ -lactam (**8a**),<sup>8</sup> which was converted into the phosphorane (**8b**), and cyclised by our previously reported<sup>4</sup> method to the aldehyde (**2b**), m.p. 132–133 °C. Addition of 2-acetamidoethanethiol to (**2b**) produced (**3b**), (**4b**) (major component), and (**5b**) (71% total yield). Without separation this mixture was subjected to reduction (NaBH<sub>4</sub>, THF, H<sub>2</sub>O; 0 °C), followed by mesylation (MeSO<sub>2</sub>Cl, pyridine), to give a separable mixture (81% overall) of (**3c**), (**4c**), m.p. 137–138 °C, and (**5c**), m.p. 148–150 °C. The methanesulphonate isomer (**4c**), on treatment with excess of sodium cyanoborohydride (HMPA; 95 °C; 4 h) gave (**4d**) (74%), m.p. 127–129 °C. Introduction of the double bond into (**4d**) resulted in a 66% yield of (**6b**) m.p. 122–123 °C. Isomerisation as before led to (**7c**) (14%), m.p. 143–144 °C, having the *cis*-arrangement of  $\beta$ -lactam ring protons ( $J_{5,6}$  6 Hz), and unchanged (**6b**) (70%) which could be re-equilibrated. Deprotection gave the sodium salt of ( $\pm$ )-6-*epi* PS-5 (**7d**),  $\lambda_{max}$  (EtOH) 299 nm. The sodium salts of (**7b**) and (**7d**) have also been prepared<sup>7</sup> from MM 17880. All compounds were satisfactorily characterised.

(Received, 6th August 1980; Com. 870.)

- <sup>1</sup> A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J. Antibiotics*, 1979, **32**, 961, and references cited therein.  
<sup>2</sup> J. H. Bateson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1980, 185.  
<sup>3</sup> K. Yamamoto, T. Yoshioka, Y. Kato, N. Shibamoto, K. Okamura, Y. Shimauchi, and T. Ishikura, *J. Antibiotics*, 1980, **33**, 796, and references cited therein.  
<sup>4</sup> A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1979, 236.  
<sup>5</sup> R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta.*, 1972, **55**, 408.  
<sup>6</sup> K. G. Schreiber and V. P. Fernandez, *J. Org. Chem.*, 1961, **26**, 2910.  
<sup>7</sup> D. F. Corbett and A. J. Eglington, *J. Chem. Soc., Chem. Commun.*, 1980, preceding communication.  
<sup>8</sup> L. A. Paquette and T. Kakihana, *J. Am. Chem. Soc.*, 1968, **90**, 3897.