

# Wittig Reactions with $\beta$ -Lactam Carbonyls: A Convenient Means of Protection. X-Ray Crystal Structure of *p*-Nitrobenzyl-(2*R*,5*R*)-*Z*-7-Methoxy- carbonylmethylene-*Z*-3-( $\beta$ -phthalimidoethylidene)-4-oxa-1- azabicyclo[3.2.0]heptane-2-carboxylate

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**Summary** Clavulanic acid derivatives and penicillin V esters undergo Wittig reactions at the  $\beta$ -lactam carbonyl and the  $\beta$ -lactam can be regenerated by low-temperature ozonolysis; the crystal structure of one of the products is reported.

RECENT studies on the chemistry of clavulanic acid, a potent  $\beta$ -lactamase inhibitor,<sup>1</sup> have prompted us to report a new reaction of the  $\beta$ -lactam ring system.

Wittig modification of the clavulanic acid derivative (**1a**) by reaction with methoxycarbonylmethylenetriphenylphosphorane in toluene at reflux gave *p*-bromobenzyl (2*R*,

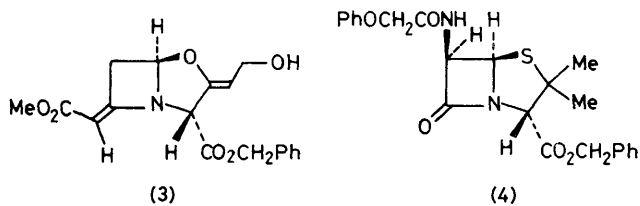
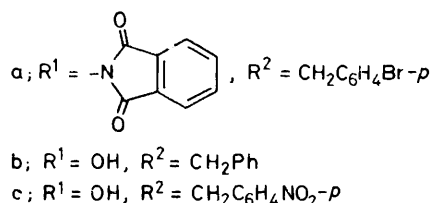
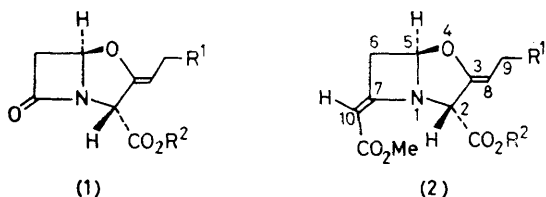
5*R*)-*Z*-7-methoxycarbonylmethylene-*Z*-3-( $\beta$ -phthalimidoethylidene)-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate (**2a**) (23%), m.p. 144–145 °C. Similarly benzyl clavulanate (**1b**) provided the analogous azetidine (**2b**) (7%),<sup>2</sup> m.p. 85–87 °C. Whilst  $\gamma$ -lactams are known to undergo the Wittig reaction at >150 °C<sup>3</sup>, we believe that this represents the first example of a successful reaction with a  $\beta$ -lactam carbonyl.

The assignment† of structures (**2a**) and (**2b**) to the Wittig products follows from the absence of a  $\beta$ -lactam stretching frequency in the i.r. spectrum and the appearance of two new peaks at 1700 and 1660 cm<sup>-1</sup> corresponding to the  $\alpha\beta$ -unsaturated ester system. The <sup>1</sup>H n.m.r. spectrum of (**2b**) included two new resonances at  $\delta$  3.57 (3H, s) and 5.02 (1H, dd, *J* 1.5 and 1.4 Hz) which are assigned to the methyl ester and the C-10 olefinic proton respectively. Furthermore, resonance-decoupling experiments demonstrated an allylic relationship between the C-10 olefinic and C-6 protons. <sup>1</sup>H n.m.r. data strongly suggested‡ a *Z*-geometry for the C-7 double bond and this was confirmed by X-ray crystallographic analysis of the *p*-nitrobenzyl ester (**2c**), m.p. 88–89 °C.

*Crystal data*: C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>8</sub>, *M* = 390.3, monoclinic, *a* = 8.068(1), *b* = 47.721(6), *c* = 4.825(1) Å,  $\beta$  = 99.15(1)°, *U* = 1834.0 Å<sup>3</sup>, *D*<sub>c</sub> = 1.41, *D*<sub>m</sub> = 1.40 g cm<sup>-3</sup>, *Z* = 4, *F*(000) = 896, space group *P*2<sub>1</sub>. Cu-K $\alpha$  radiation ( $\beta$ -filter),  $\lambda$  = 1.5418 Å,  $\mu$  = 9.7 cm<sup>-1</sup>. Intensities were measured for  $\theta \leq 66^\circ$  on a Nonius CAD-4 diffractometer, and a total of 3239 reflections were scanned of which 2646 had *I*  $\geq 3\sigma$  and were used in the refinement.

The structure was solved routinely using MULTAN 78. Final refinement was by least squares, each independent molecule being treated as a block. Non-hydrogen atoms were refined anisotropically and hydrogen atoms (all previously located on a difference map) were included in found positions where this was possible, otherwise in the calculated positions. The final conventional *R* value was 3.7%. We do not propose to publish further details of the crystallographic work.§

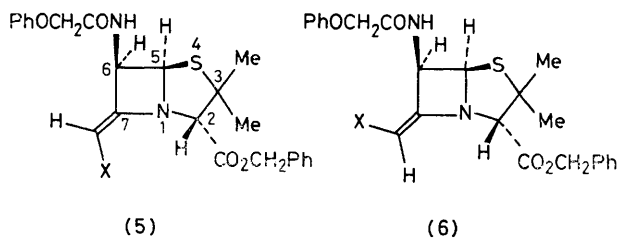
The  $\beta$ -lactam carbonyl of penicillins can be similarly modified but in these cases both geometrical isomers are



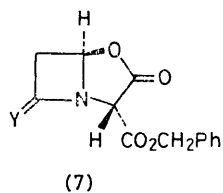
† Satisfactory analytical and spectroscopic data were obtained for all new compounds herein reported. Chemical shifts ( $\delta$ ) are from tetramethylsilane for solutions in CDCl<sub>3</sub>.

‡ Treatment of (**2b**) with strong base resulted in partial isomerisation to the *E*-isomer (**3**). The <sup>1</sup>H n.m.r. spectrum of (**3**) indicated an upfield shift of 0.75 p.p.m. in the position of the C-2 proton when compared with the *Z*-isomer.

§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication. The structure factor table is available as Supplementary Publication No. Sup. 23164 (25 pp.) from the British Library. For details see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans. 1* or 2, Index issues.



- (5)  
 (6)
- a; X = CO<sub>2</sub>Me  
 b; X = CN  
 c; X = CO<sub>2</sub>CH<sub>2</sub>Ph



- (7)
- a; Y = CHCO<sub>2</sub>Me, Z-isomer  
 b; Y = O

observed. With methoxycarbonylmethylenetriphenylphosphorane penicillin V benzyl ester (4) afforded an almost quantitative conversion into the Z-compound (5a) (57%) and the corresponding E-isomer (6a) (42%).

The geometry of the C-7 double bond was determined from a consideration of the chemical shifts of the C-2 protons in the <sup>1</sup>H n.m.r. spectra of (5a) and (6a). The low-field proton ( $\delta$  5.00) (presumably deshielded by the adjacent methyl ester function) was assigned to the Z-isomer (5a)<sup>4</sup> and the proton of higher field ( $\delta$  3.91) to the E-isomer (6a).

Cyanomethylenetriphenylphosphorane also reacts with (4) in toluene at reflux to give 7-cyanomethylene derivatives (5b) and (6b) in good yields.

The methoxycarbonylmethylene substituent on the penicillin V derivatives (5a) and (6a) can easily be removed in good yield by ozonolysis in EtOAc at -70 °C to regenerate the  $\beta$ -lactam (4)<sup>†</sup> and therefore the Wittig reaction constitutes a convenient means of protection.

Ozonolysis of the clavulanic acid derivative (2b) with 1 equiv. of ozone gave the lactone (7a) whilst regeneration of the  $\beta$ -lactam lactone (7b) required 2 equiv.

(Received, 15th June 1981; Com. 698.)

<sup>†</sup> Spectral properties were identical with those of authentic material.

<sup>1</sup> T. T. Howarth, A. G. Brown, and T. J. King, *J. Chem. Soc., Chem. Commun.*, 1976, 266.

<sup>2</sup> Protection of the free hydroxy-group in (1b) as an ether leads to greatly improved yields; I. Stirling, unpublished results from these laboratories.

<sup>3</sup> M. Natsume, M. Takahashi, and H. Sugaya, *Chem. Pharm. Bull. Jpn.*, 1971, 19, 2648.

<sup>4</sup> The geometry of the C-7 double bond in the analogue (5c) was shown to be Z by X-ray crystallographic analysis; T. J. King, unpublished results.