Synthesis of 7-Oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates: the Olivanic Acid Ring System

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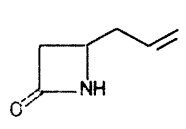
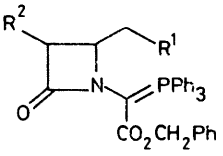
Summary The β-lactams prepared from penta-1,4-diene and cyclohexa-1,4-diene by reaction with chlorosulphonyl isocyanate can be readily converted into the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene ring system, using an intramolecular Wittig reaction to form the 2,3-double bond.

THE isolation of the olivanic acids[1] and thienamycin[2] has led us to synthesise a number of compounds having the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene ring system present in these natural products.[3] Interaction of penta-1,4-diene and chlorosulphonyl isocyanate (CSI) followed by reduction with sodium sulphite afforded the new 4-allyl-

azetidin-2-one (**1**)† (40%) as an oil, b.p. 76—80 °C at 0·2 mmHg. Condensation of (**1**) with benzyl glyoxylate followed by the sequence originated by Scartazzini *et al.*[4] gave, in 70% overall yield, the phosphorane (**2a**),† m.p.

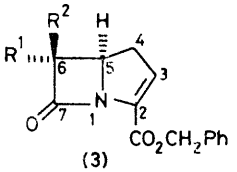


(1)



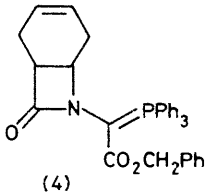
(2)

a; $R^1 = CH{=}CH_2$, $R^2 = H$
b; $R^1 = CHO$, $R^2 = H$
c; $R^1 = CH{=}CH_2$, $R^2 = CH(OH)Me$

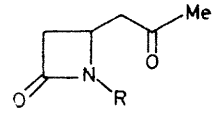


(3)

a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = {}^{8}CH(OH)Me$
c; $R^1 = {}^{6}CH(OH)Me$, $R^2 = H$
d; $R^1 = H$, $R^2 = CH_2CHO$
e; $R^1 = H$, $R^2 = CH_2CH{=}CHCO_2Me$

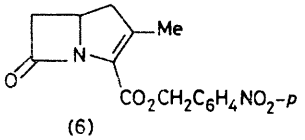


(4)



(5)

a; R = H
b; $R = C(:PPh_3)CO_2CH_2C_6H_4NO_2$-*p*



(6)

156—157 °C. Selective oxidation of the terminal double bond of (**2a**) in the presence of the phosphorane could be achieved by ozonolysis in ethyl acetate (−70 °C) in the presence of trifluoroacetic acid.[5] Reduction of the ozonide (Ph_3P) followed by regeneration of the phosphorane with aqueous sodium bicarbonate (0 °C, two-phase system) led to the aldehyde (**2b**), which immediately cyclised to the bicyclic system (**3a**)† (75%),‡ ν_{max} ($CHCl_3$) 1780 (β-lactam carbonyl) cm^{-1}, δ ($CDCl_3$) 6·44 (t, =CH, *J* 3 Hz), λ_{max} (EtOH) 270 nm (ε 4250).

Reaction of the phosphorane (**2a**) with 2 equiv. of lithium *N*-isopropylcyclohexylamide in tetrahydrofuran (−70 °C) followed by the addition of acetaldehyde gave, in 65% yield, an inseparable mixture of *cis*- and *trans*-isomers of the β-lactam (**2c**). Cyclisation§ of the mixture followed by fractionation on silica gave a single *cis*-isomer (**3b**)† (9%), m.p. 94—99 °C ($J_{5,6}$ 6 Hz), and a single *trans*-isomer (**3c**)† (29%) ($J_{5,6}$ 3 Hz) of the bicyclic system (**3**) having a thienamycin type hydroxyethyl¶ substituent α to the β-lactam carbonyl group.

Replacement of 4-allylazetidin-2-one with the β-lactam[6] derived from cyclohexa-1,4-diene and CSI yielded the phosphorane (**4**), which on ozonolysis and cyclisation produced the bicyclohept-2-ene (**3d**), having exclusively the *cis*-configuration about the β-lactam. The aldehyde (**3d**) could conveniently be trapped with methoxycarbonylmethylenetriphenylphosphorane giving predominantly the product (**3e**)† (42% from **4**), m.p. 81—82 °C, having the *trans*-configuration about the C(6) side chain double bond.

We have also demonstrated the cyclisation process when the carbonyl component is a ketone. Oxypalladation[7] of (**1**) gave a 70% yield of the ketone (**5a**),† m.p. 77—78 °C, which was converted in this case with *p*-nitrobenzyl glyoxylate into the phosphorane (**5b**),† m.p. 185—187 °C. Heating (**5b**) in toluene (100 °C, 6 h) resulted in cyclisation to the 3-methyl substituted derivative (**6**)† (64%), m.p. 116—118 °C. All compounds showed the expected spectroscopic properties; most of these bicyclic esters showed only a low level of antibacterial activity.

We thank Professor T. J. King, University of Nottingham, for *X*-ray work.

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† Satisfactory elemental analysis and/or accurate mass data were obtained.

‡ After silica gel chromatography; in most cases the bicyclic systems showed some instability towards silica. Non-crystalline samples were best kept in ethyl acetate solution.

§ After ozonolysis and regeneration of the phosphorane, cyclisation of the *trans*-isomer was shown (by t.l.c. analysis) to be spontaneous; the *cis*-isomer required 24 h at room temperature. This is attributed to interaction between the free hydroxy group and the aldehyde.

¶ The stereochemistry of the crystalline *cis*-isomer has been established by *X*-ray crystallography to be 5-*RS*, 6-*RS*, 8-*RS*, while a crystalline derivative of the *trans*-isomer was shown to have the 5-*RS*, 6-*SR*, 8-*SR* configuration.

[1] A. G. Brown, D. Butterworth, M. Cole, J. D. Hood, C. Reading, and G. N. Rolinson, *J. Antibiotics*, 1976, **29**, 668; A. G. Brown, D. F. Corbett, A. J. Eglington, and T. T. Howarth, *J.C.S. Chem. Comm.*, 1977, 523.
[2] U.S.P. 3,950,357; papers presented at the Sixteenth Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, October, 1976.
[3] D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Amer. Chem. Soc.*, 1978, **100**, 313, have described a total synthesis of (±)-thienamycin *via* the bicyclohept-3-ene which with base partially isomerises to the desired bicyclohept-2-ene system.
[4] R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta.*, 1972, **55**, 408.
[5] R. B. Woodward, 'Recent Advances in the Chemistry of β-lactam Antibiotics,' ed. J. Elks, Special Publication No. 28, The Chemical Society, London, 1977, p. 167.
[6] L. A. Paquette and T. Kakihana, *J. Amer. Chem. Soc.*, 1968, **90**, 3897.
[7] G. T. Rodeheaver and D. F. Hunt, *Chem. Comm.*, 1971, 818.