Carbocyclic Analogues of Penicillin

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The synthesis of the title systems is described by cycloaddition of dimethylketen to cyclopentadiene, addition of hypobromous acid to the product and use of a nitrile-mediated rearrangement to give 4-cyano-6-*exo*-benzyloxy-3,3-dimethylbicylo[3.2.0]heptan-2-one (**5b**) and its derivatives by further modification.

The role of β-lactamase inhibitors such as clavulanic acid to deal with micro-organisms resistant to penicillins has dramatically improved both the range and understanding of penicillin action.[1] Furthermore, the search for new inhibitors amongst penicillin-related structures has grown significantly.[1] We envisaged that replacement of the heteroatoms of the penicillin ring system by carbon functions could lead to potential β-lactamase inhibitors and herein describe the synthesis of such systems.†

The cycloaddition of dimethylketen to cyclopentadiene and subsequent addition of hypobromous acid or its equivalent to give the bicycle (**2**) follows well established precedents.[2] The rearrangement of this cyclobutanone by the action of a nucleophile to a cyclopentanone by way of a tricyclic intermediate has also been described by our group[3] and allows the ready synthesis of (**4b**) and (**5b**) by way of (**3b**) by the action of cyanide ion.‡ The epimers (**4b**) and (**5b**) are readily separated by chromatography. Surprisingly, the nature of the protecting group, R, played a vital role in the course of the rearrangement and the subsequent chemistry. Using analytical grade potassium cyanide, the reaction with R = tetrahydropyran-2-yl gave a complex mixture from which an inseparable mixture of the epimers (**4**) and (**5**) was isolated in 20% yield. With t-butyldimethylsilyl protection it gave only a very poor yield. However, using the benzyl ether (**2b**) the reaction proceeded cleanly and efficiently. A careful h.p.l.c. study of the rearrangment mixture§ revealed a third significant product, difficult to separate from the *exo*-nitrile (**5b**) by other methods, to which we assign structure (**6a**) on the basis of decoupling studies on the 300 MHz ^{1}H n.m.r. spectrum of the derived acid (**6c**). We propose its formation as shown in Scheme 2.

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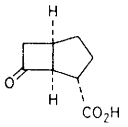
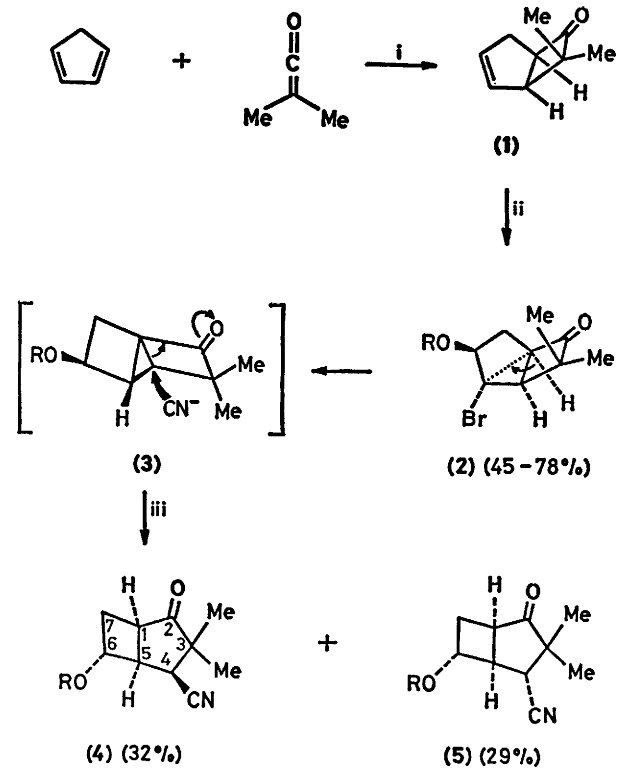
† A recent paper (E. M. Gordon, J. Pluscev, and M. A. Ondetti, *Tetrahedron Lett.*, 1981, **21**, 1871) reported the synthesis of the di-normethyl analogue (i).



(i)

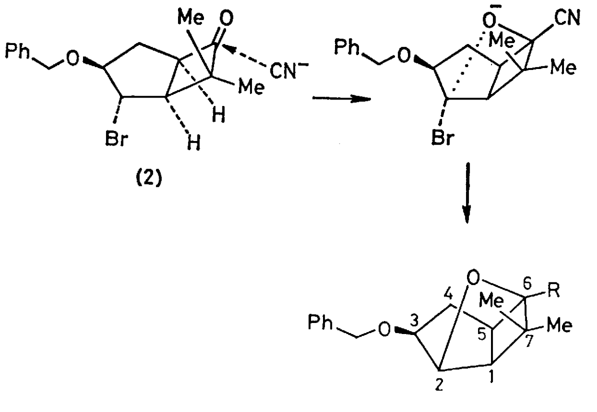
‡ All new compounds gave appropriate combustion analytical data, i.r., ^{1}H and ^{13}C n.m.r., and mass spectra.

§ Stainless steel column, 250 × 10 mm, packed with Whatman Partisil-10 silica and using hexane–ethyl acetate (95 : 5) as solvent; flow-rate, 11.2 ml/min; pressure, 1071 lb in^{-2}; detector, u.v. at 254 nm.



a, R = H; b, R = CH_2Ph

Scheme 1. *Conditions:* i, $CHCl_3$, NEt_3, 10—15 °C, 15 h (76%); ii, R = H; AcNHBr, H_2O, Me_2CO, 15 °C, 18 h; R = CH_2Ph; $PhCH_2OH$, AcNHBr, 15 °C, 18 h; iii, KCN, MeOH, NaOMe, Heat, 36 h.



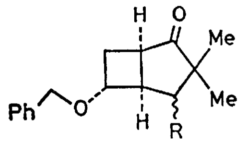
(6)

a; R = CN

b; R = $CONH_2$, m.p. 126 - 127 °C

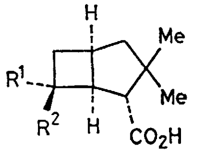
c; R = CO_2H, m.p. 122 - 123 °C

Scheme 2



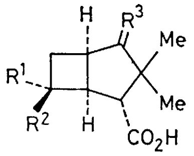
(7)

a; R = $CONH_2$
endo, m.p. 83—84 °C
exo, m.p. 126—127 °C
b: R = CO_2H
exo, m.p. 137—138 °C



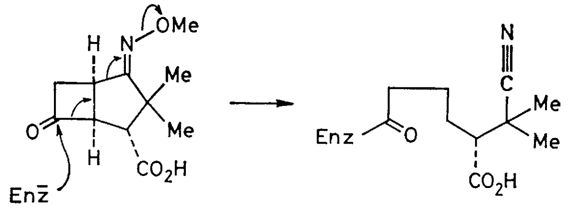
(8)

a; R^1 = $PhCH_2O$, R^2 = H
(79%) (m.p. 98—100 °C)
b; R^1 = HO, R^2 = H
(93%) (m.p. 108—110 °C)
c; R^1,R^2 = O
(79%) (m.p. 106—107 °C)



(9)

	R^1 R^2	R^3	% Yield	M.p. (t/°C)
a	HO H	O	90	166—167
b	O	O	88	165—167
c	HO H	NOMe	80	162—163
d	O	NOMe	74	158—160



Scheme 3

Hydrolysis of the nitriles (**4**) and (**5**) was not generally effective under acidic conditions and was best conducted stepwise. Thus phase-transfer hydrolysis in methylene dichloride with aqueous sodium hydroxide (20%) and aqueous hydrogen peroxide (30%) containing tetrabutylammonium hydrogen sulphate overnight at ambient temperature efficiently gave the amides (**7a**). The individual epimeric nitriles (**4b**) and (**5b**) gave the corresponding amides without epimerisation in 68 and 44% yield respectively, the latter product being admixed with the amide (**6b**) (38%) [derived from the unseparated by-product of the rearrangement (**6a**)]. The *exo*-nitrile (**5b**) hydrolysed more rapidly than its epimer (**4b**) in accordance with the steric accessibility of the former.

Conversion of the amides (**7a**) into the corresponding acid (**7b**) was most efficiently accomplished by brief hydrolysis with sodium hydroxide in triethylene glycol at 170 °C, both isomers giving the thermodynamically more stable *exo*-acid. (Thus the *endo*-amide gave the *exo*-acid in 45% yield.) The tricyclic acid (**6c**) was similarly produced. The *exo*-acid (**7b**) was readily reduced to the acid (**8a**) by Huang-Minlon reduction and this product was hydrogenolysed (10% Pd on C; H_2) to give the alcohol (**8b**) and this was oxidised to the keto-acid (**8c**). This oxidation proceeded inefficiently with buffered pyridinium chlorochromate but very efficiently with pyridine–sulphur trioxide in dimethyl sulphoxide and triethylamine.[4] Similarly, the *exo*-acid (**7b**) was readily debenzylated and the resulting hydroxy-acid (**9a**) oxidised with the same reagent to give (**9b**). Finally, we prepared the oxime derivative of the *exo*-acid (**9a**) but owing to its sensitivity in the attempted oxidation, worked instead with the *O*-methyloxime (**9c**) which was cleanly transformed into the analogous keto-acid (**9d**). It was hoped that β-lactamase inhibitory

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¶ The following data fully support this structure: δ ($CDCl_3$): 1.03 and 1.33 (each s, Me), 1.67 (dd, H-4_{exo}), 1.90 (dq, H-4_{endo}), 2.45 (d, H-1), 3.09 (dd, H-5), 3.98 (dd, H-3), 4.32 (s, H-2), 4.57 (dd′, CH_2Ph), and 7.32 (s, Ph); $J_{1,2}$ = $J_{2,3}$ = $J_{4exo,5}$ = 0, $J_{1,5}$ = 3, $J_{4endo,5}$ = 5, $J_{3,4exo}$ = 6, $J_{3,4endo}$ = 9·5, $J_{4exo,4endo}$ = 12 Hz.

activity might be optimised in these derivatives as shown in Scheme 3.

We thank the S.R.C. and Pfizer Limited for financial support, the S.R.C. and Mr. David Moorcroft for the 300 MHz n.m.r. spectra, and Dr. Colin W. Greengrass for helpful discussions.

Received, 2nd October 1981; Com. 1158

References

1 R. D. G. Cooper, *Top. Antibiot. Chem.*, 1980, **3**, 39.
2 M. Rey, S. M. Roberts, A. Dieffenbacher, and A. S. Dreiding, *Helv. Chim. Acta.*, 1970, **53**, 417; Z. Grudzinski and S. M. Roberts, *J. Chem. Soc., Perkin Trans.* 1, 1975, 1767.
3 Z. Grudzinski and S. M. Roberts, *Tetrahedron Lett.*, 1978, 389.
4 J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505.

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