Total Synthesis of a Nuclear Analogue of the Penicillin–Cephalosporin Antibiotics

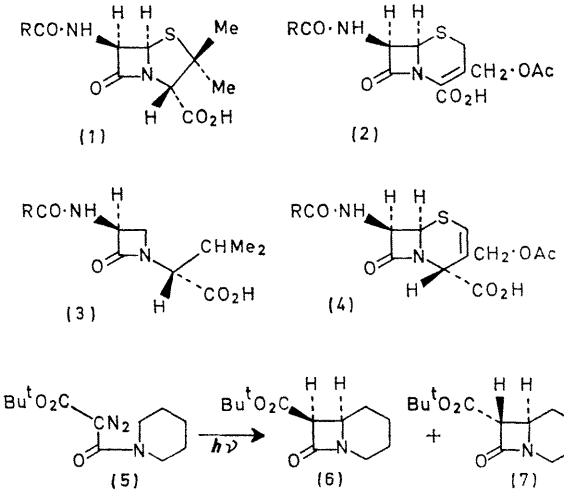
By D. M. BRUNWIN, G. LOWE,* and J. PARKER
(*The Dyson Perrins Laboratory, Oxford University, Oxford* OX1 3QY)

Summary A synthetic route has been developed for the preparation of nuclear analogues of the penicillin–cephalosporin group of antibiotics and is illustrated by the synthesis of (2*R*,6*R*,7*S*)-8-oxo-7-phenylacetamido-1-azabicyclo[4,2,0]octane-2-carboxylic acid (**17**) from D-pipecolic acid.

THE antibacterial properties of the penicillins (**1**) and cephalosporins (**2**) stem from their ability to inhibit the transpeptidase responsible for cross-linking the peptidoglycan chains used in bacterial cell wall synthesis. The structure and biosynthesis of bacterial cell walls and their peptidoglycan precursors, led to the suggestion that the acyl-dipeptide function of the antibiotics resembles features of the peptidoglycan chains by which the transpeptidase recognizes its natural substrate. When the antibiotic binds to the enzyme, the β-lactam irreversibly inhibits it.[1] The β-lactam however needs to be especially reactive and in the penicillins (**1**) this is achieved largely if not wholly by ring strain induced by fusion with the thiazolidine ring. In the cephalosporins (**2**) the β-lactam appears to be activated electronically. The ineffectiveness of dethiopenicillin (**3**)[2] and Δ^2-cephalosporins (**4**)[3] support this hypothesis as does the crystallographic evidence.[4] It would seem therefore that modification of the sulphur heterocycle in the penicillins (**1**) and cephalosporins (**2**) could lead to new families of β-lactam antibiotics.

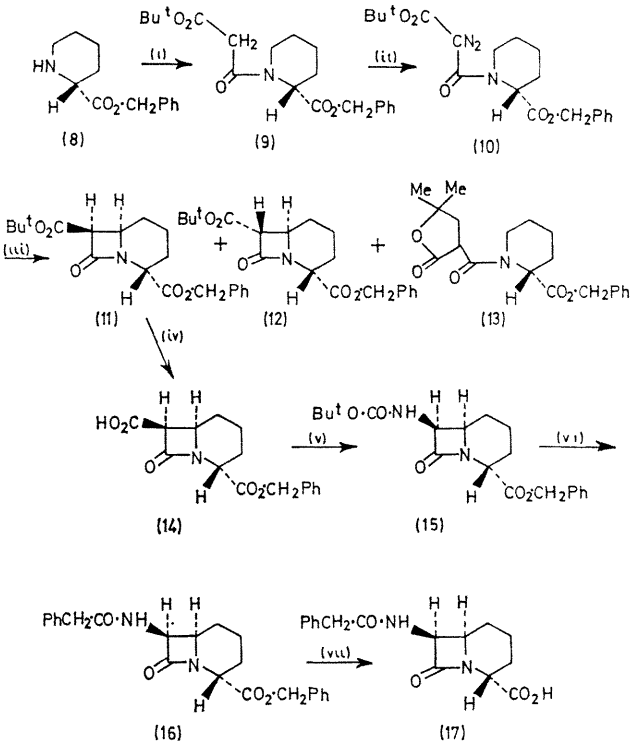
The photolysis of the diazo-amide (**5**) has been shown to give both diastereoisomers (**6**) and (**7**).[5] The presence of a

substituent at C-2 in the diazoamide was expected to direct the carbene insertion into the least hindered C–H bond and so generate stereoselectively the β-lactam–heterocyclic system with the required *trans*-2,6-stereochemical relationship. This expectation has been realized and provides a key step in a synthetic route developed for the preparation of nuclear analogues of the penicillins (**1**) and cephalosporins (**2**).



The benzyl ester of D-pipecolic acid (**8**)[6] was coupled to t-butyl hydrogen malonate[7] with dicyclohexylcarbodi-imide, and the malonic acid derivative (**9**) smoothly converted into the diazo-compound (**10**) by base-catalysed diazo-exchange with toluene-*p*-sulphonyl azide (see Scheme).[8] Irradiation of (**10**) with a medium-pressure mercury lamp in a water-cooled Pyrex vessel for 1 h gave three products which were isolated chromatographically: two β-lactams (ν_{max} 1770 cm^{-1}) and the third was the γ-lactone (**13**). The latter was not unexpected as it is known that the photolysis of t-butyl α-diazo-esters can give rise to γ-lactones.[5,9] The stereochemistry of the β-lactams was established by their ^1H n.m.r. spectra, the less polar isomer (on silica gel) having the characteristic coupling constant (5·5 Hz at τ 6·05) for a *cis*-β-lactam, whereas the more polar isomer had the characteristic coupling constant (2·0 Hz at τ 6·50) for a *trans*-β-lactam.[10] The assignment of 2α- and 2β-H in the n.m.r. spectrum of the β-lactams (**6**) and (**7**) had been possible from considerations of the diamagnetic anisotropy of the β-lactam carbonyl group and by comparison with the spectra of 1-azabicyclo[4,4,0]decan-2-one and its derivatives where similar chemical shifts and line shapes were observed.[11] The stereoisomeric β-lactams (**11**) and (**12**) had essentially identical broad doublets near τ 5·5 and the line shape was characteristic of 2β-H in the β-lactams (**6**) and (**7**) except that the geminal coupling due to 2α-H was absent. The ready base-catalysed isomerization of (**11**) into (**12**) firmly established their epimeric relationship. Thus insertion of the transient carbene intermediate generated by photolysis of the diazo-compound (**10**) had occurred stereoselectively as anticipated. The ratio of (**11**) to (**12**) was estimated from the n.m.r. spectrum of the photolysis mixture to be *ca.* 1:2.

Removal of the t-butyl group from the *cis*-β-lactam (**11**) with trifluoroacetic acid occurred smoothly and with retention of configuration, but attempts to convert the acid (**14**) into the azide *via* the acid chloride led, under the mildest conditions, to some epimerization. A less direct route however was satisfactory. The 7*S*-acid (**14**) was coupled with t-butyl carbazate. Removal of the t-butyl group followed by treatment with sodium nitrite in hydrochloric acid gave the expected azide. Rearrangement to the isocyanate was effected in benzene under reflux.



SCHEME

(i) $Bu^tO_2C{\cdot}CH_2{\cdot}CO_2H$–$C_6H_{11}{\cdot}N{:}C{:}N{\cdot}C_6H_{11}$–$CH_2Cl_2$; (ii) *p*-Me-$C_6H_4{\cdot}SO_2{\cdot}N_3$–$NEt_3$; (iii) $h\nu > 300$ nm–CCl_4; (iv) $CF_3{\cdot}CO_2H$; (v)(a) $Bu^tO{\cdot}CO{\cdot}NH{\cdot}NH_2$–$C_6H_{11}{\cdot}N{:}C{:}N{\cdot}C_6H_{11}$–$CH_2Cl_2$, (b) $CF_3{\cdot}CO_2H$, (c) $NaNO_2$–10% HCl, (d) Δ–benzene, (e) Bu^tOH; (vi)(a) $CF_3{\cdot}CO_2H$, (b) $PhCH_2{\cdot}COCl$–NEt_3; (vii) H_2–Pd.

Although the direct conversion of the isocyanate into the phenylacetamido-derivative by treatment with phenylacetic acid was attractive,[12] it was not in practice satisfactory. Accordingly, the isocyanate was converted without isolation into the urethane (**15**) by the addition of t-butyl alcohol to the benzene solution. The 7*S*-urethane (**15**) was obtained as colourless needles, m.p. 116·5—118·5°; $[\alpha]_D^{20}$ +72 (EtOH); ν_{max} ($CHCl_3$) 1753 (β-lactam), 1740 (ester), and 1715 cm^{-1} (urethane); τ ($CDCl_3$) 4·95 (1H, q, $J_{NH,7\alpha}$ 7·2 Hz, $J_{6,7\alpha}$ 4·8 Hz, 7α-H), 5·35 (1H, characteristic broad doublet, 2β-H), and 6·10 (1H, characteristic multiplet, 6-H). The epimeric 7*R*-urethane was not detected.

Deprotection of the 7*S*-urethane (**15**) followed by acylation gave (**16**) as colourless needles, m.p. 107—109°; $[\alpha]_D^{20}$ +106 (EtOH); ν_{max} ($CHCl_3$) 1753 (β-lactam), 1743 (ester), and 1670 cm^{-1} (amide); τ ($CDCl_3$) 4·85 (1H, q, $J_{NH,7\alpha}$ 7 Hz, $J_{6,7\alpha}$ 4·5 Hz, 7α-H) 5·5 (1H, characteristic broad doublet, 2β-H), and 6·15 (1H, characteristic multiplet,

$J_{6,7\alpha}$ 4·5 Hz, $J_{5,6}$ 4·5 and 11 Hz, 6-H). Catalytic hydrogenolysis of (**16**) gave (**17**) as colourless needles, m.p. 172—176°, its structure and stereochemistry being confirmed by the n.m.r. spectrum of its methyl ester.

Compound (**17**), the nuclear analogue of the penicillins (**1**) and cephalosporins (**2**), showed no antibacterial activity against *Staphylococcus aureus*, *Salmonella typhi*, or *Alcaligines faecalis* at 1 mg ml^{-1} which was not unexpected in view of the relatively low reactivity of the β-lactam. The synthetic route should however be useful for the synthesis of other nuclear analogues with more reactive β-lactam–heterocyclic systems, which may be expected to possess antibacterial properties.

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