Synthesis of α-Aminophosphonic and α-Aminophosphinic Acids and Derived Dipeptides from 4-Acetoxyazetidin-2-ones

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Summary 4-Oxoazetidin-2-ylphosphonates and 4-oxoazetidin-2-ylphosphinates, obtained from the Arbusov reactions of 4-acetoxyazetidin-2-one and 4α-acetoxy-3β-phthalimidoazetidin-2-one with a variety of phosphites and phosphonites, were hydrolysed to β-phosphono- and β-phosphino-β-alanine derivatives which were converted into alanyl dipeptides, conditions for the sequential removal of protecting groups for carboxylic acids, phosphonic acids, and amines were investigated

ORGANOPHOSPHORUS-CONTAINING molecules of actual or potential pharmaceutical use, such as the α-aminophosphonic acid dipeptide, alaphosphin (**1**), which inhibits alanine racemase,[1] are becoming increasingly important

$$\underset{(S)}{H_2NCH(Me)CO}\ \underset{(R)}{NHCH(Me)PO_3H_2}$$

(**1**)

The emerging importance of aminophosphonic acids as analogues of the natural amino acids has resulted in recent syntheses involving a variety of different strategies [2] This note describes a new synthetic entry to a range of β-phosphino- and β-phosphono-β-alanines, which may be considered as phosphorus analogues of aspartic acid (which is implicated in biologically important processes including purine and pyrimidine biosynthesis) Additionally, we discuss preliminary investigations of the synthetic incorporation of α-aminophosphonic acids into dipeptides and the removal of protecting groups in these systems

4-Acetoxyazetidin-2-one (**2**) has been the basis of many recent syntheses of β-lactams, the acetoxy group being readily displaced by heteronucleophiles We therefore investigated displacements by trivalent phosphorus nucleophiles, extending an earlier brief study by Hoechst workers[3] who effected an atypical Michaelis–Arbusov reaction of (**2**) with triethyl phosphite The four phosphites (**3**)—(**6**) were treated with (**2**) at 110—120 °C, the first two reacting readily (1—2 h) to give high yields of the 4-oxoazetidin-2-ylphosphonates (**7**) and (**8**),† whereas (**5**) reacted more slowly (7 h)‡ to give a 46% yield of (**9**) and (**6**) failed to react § 4α-Acetoxy-3β-phthalimidoazetidin-2-one (**10**) also reacted with (**3**) to give the *cis*-phosphonate (**11**) In parallel investigations the phosphonites (**12**) and (**13**) were prepared from methylphosphonous dichloride by standard

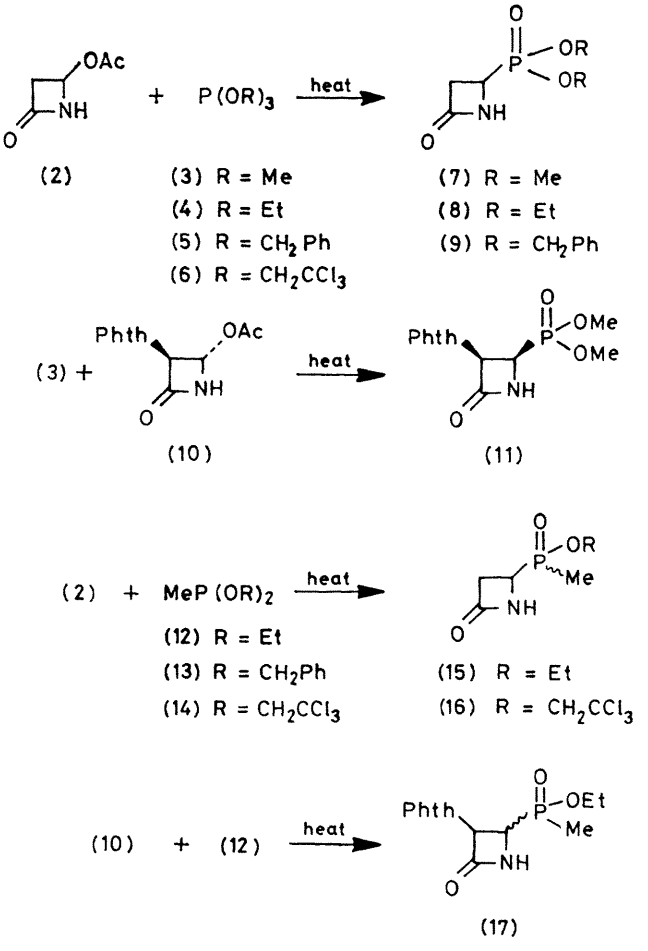
† New compounds were characterized analytically and spectroscopically Dipeptides were characterized as mixtures of diastereoisomers in the model studies

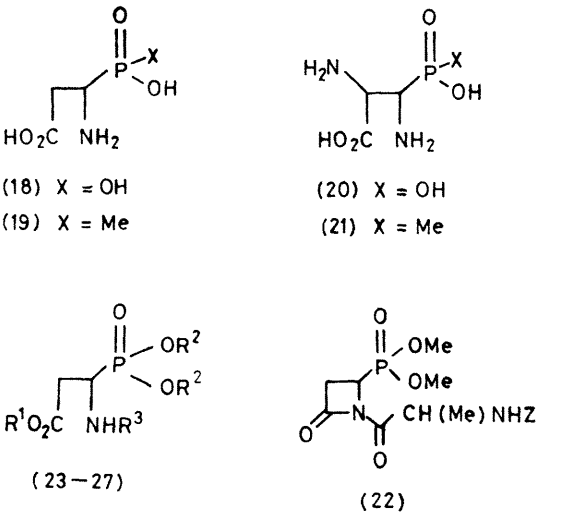
‡ This reaction may be compared with a literature report (A Holy, *Tetrahedron Lett*, 1967, 881) which states that tribenzyl phosphite does not readily afford Arbusov reactions

§ The failure of tris-(2,2,2-trichloroethyl) phosphite to undergo Arbusov reaction is well known and is accounted for by its low nucleophilicity (R M Harvey and E R Desombre in 'Topics in Phosphorus Chemistry,' Vol 1, eds M Grayson and E J Griffith, Wiley, New York, 1964, p 57)

procedures,[4,5] as was compound (**14**) in which the protecting groups were potentially easily removable. Diethyl methylphosphonite, for example, reacted even more readily with (**2**) (60 °C, 1 h, 89%) than did triethyl phosphite, giving the Arbusov product (**15**). Bis-(2,2,2-trichloroethyl) methylphosphonite, in distinct contrast to the unreactive tris-(2,2,2-trichloroethyl) phosphite (**6**), also reacted, at 120 °C, to give (**16**) in 42% yield. The phosphinates (**15**) and (**16**) were diastereoisomeric mixtures as shown by ^{13}C and ^{31}P n.m.r. studies.¶ The reaction of the phthalimidoazetidinone (**10**) with the phosphonite (**12**) gave a *cis/trans* mixture of products (**17**), the separation of which is under study.

Acid hydrolysis of the appropriate 4-oxoazetidin-2-yl-phosphonates and phosphinates provides a new route to





(**23**) $R^1 = R^2 = Me$, $R^3 = H$
(**24**) $R^1 = R^2 = Me$, $R^3 = COCH(Me)NHZ$
(**25**) $R^1 = H$, $R^2 = Me$, $R^3 = COCH(Me)NHZ$
(**26**) $R^1 = R^2 = Me$, $R^3 = COCH(Me)NH_2$
(**27**) $R^1 = Me$, $R^2 = H$, $R^3 = COCH(Me)NHZ$
(**28**) $R^1 = R^2 = H$, $R^3 = COCH(Me)NH_2$
$Z = CO_2CH_2Ph$

α-aminophosphonic and α-aminophosphinic analogues of aspartic acid; for example, (**18**), (**19**), (**20**), and (**21**).

Incorporation of (**18**)—(**21**) into bacteria *via* dipeptide and oligopeptide transport systems[6] and *via* alanyl and alanyl alanyl peptide derivatives is being investigated. Thus, racemic (**7**) was coupled with *N*-benzyloxycarbonyl-D,L-alanine in model studies to give the diastereomeric dipeptides (**22**). Selective deprotection (hydrogenolysis, trimethylsilyl halides) was not possible because the *N*-acylated β-lactam ring was extremely labile. However, HCl–MeOH methanolysis of (**7**) gave (**23**) in quantitative yield which was converted into the fully protected dipeptide (**24**). The carboxylate ester of (**24**) was preferentially cleaved by sodium hydroxide to give (**25**), the benzyloxycarbonyl-group was hydrogenolysed to give (**26**), and the phosphonate esters were selectively cleaved by trimethylsilyl bromide to give (**27**). The mono-deprotected peptides offer considerable scope for tripeptide synthesis. Complete deprotection to give (**28**) was best achieved by HBr–CH_3CO_2H hydrolysis of (**25**).

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¶ Detailed ^{31}P n.m.r. studies of the major classes of organophosphorus products will be reported elsewhere.

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