Reduction of 6α-Alkyl-6β-isocyanopenicillanates by Tri-n-butyltin Hydride. A Stereoselective Synthesis of 6β-Alkylpenicillanates

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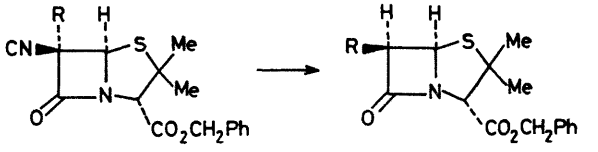
Summary 6β-Benzyl-, 6β-(1-hydroxy-1-methylethyl)-, 6β-methoxycarbonylmethyl-, and 6β-(2-methoxycarbonylethyl)-penicillanates (**5**)—(**8**) have been prepared stereoselectively, and in good yield, by tri-n-butyltin hydride reduction of the corresponding 6α-alkyl-6β-isocyanopenicillanates (**1**)—(**4**); similarly 6,6-dibromopenicillanate (**12**) has been reduced to give a mixture of 6β- and 6α-bromopenicillanates (**13**) and (**14**) in the ratio of 85:15, respectively.

THE preparation of 6-alkylpenicillanates is of current interest because of the presence of an alkyl side chain in thienamycin and olivanic acid.[1,2] At present the most widely used procedure for introducing a 6β-alkyl group into the penam nucleus involves hydrogenation of the corresponding 6-alkylidene penam[3] which can be obtained *via* a Wittig reaction on the 6-oxo compound,[3] or by dehydration of the corresponding 6-(2-hydroxyalkyl) compound.[4] We here report a new procedure for the preparation of 6-alkyl-

penicillanates, which involves tri-n-butyltin hydride reduction of the corresponding 6α-alkyl-6β-isocyanopenicillanate, and which is extremely stereoselective, only the 6β-alkyl isomer being obtained.

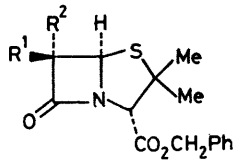
Reduction of isocyanides by trialkyltin hydrides has not been widely studied, but it has been reported that benzyl isocyanide is reduced to toluene by tri-n-butyltin hydride at 120—130 °C in the presence of di-t-butyl peroxide.[5] Since 6α-alkyl-6β-isocyanopenicillanates are readily available by alkylation of 6-isocyanopenicillanates,[6] it was decided to study reduction of these compounds as a possible route to 6-alkylpenicillanates.

6α-Benzyl-, 6α-(1-hydroxy-1-methylethyl)- 6α-methoxycarbonylmethyl-, and 6α-(2-methoxycarbonylethyl)-6β-isocyanopenicillanates (**1**)—(**4**) were prepared according to the published procedure,[6] and were treated with tri-n-butyltin hydride[7] (15% excess) in refluxing benzene, in the presence of a catalytic amount (20%) of azobisisobutyronitrile. A mildly exothermic reaction was usually observed, after which the mixture was heated under reflux for a further hour to ensure the reaction had gone to completion. Evaporation of the benzene, and column chromatography of the residue, gave in each case a 50—70% yield of the pure 6β-alkylpenicillanate (**5**)—(**8**).† Similar reduction of a 6α/6β mixture of the 6-isocyanopenicillanates (**9**) and (**10**) gave benzyl penicillanate (**11**) (60—65%).



(1); R = $PhCH_2$
(2); R = Me_2CHOH
(3); R = $MeO_2C{\cdot}CH_2$
(4); R = $MeO_2C{\cdot}CH_2{\cdot}CH_2$

(5); R = $PhCH_2$
(6); R = Me_2CHOH
(7); R = $MeO_2C{\cdot}CH_2$
(8); R = $MeO_2C{\cdot}CH_2{\cdot}CH_2$

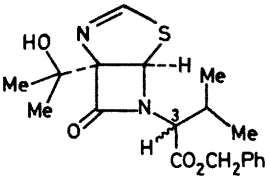


(9); R^1 = H, R^2 = NC
(10); R^1 = NC, R^2 = H
(11); R^1 = R^2 = H
(12); R^1 = R^2 = Br
(13); R^1 = Br, R^2 = H
(14); R^1 = H, R^2 = Br
(15); R^1 = H, R^2 = Cl

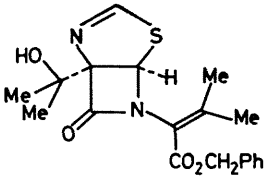
The stereoselective reduction of a halogen atom from C-6 was also studied. Thus benzyl 6,6-dibromopenicillanate (**12**)[8] was reduced by tri-n-butyltin hydride to a mixture of 6β- and 6α-bromopenicillanates (**13**) and (**14**) (62%), in which the 6β-isomer (**13**) predominated; (**13**):(**14**) = 85:15. Further reduction of the 6β- and 6α-bromopenicillanates (**13**) and (**14**) gave benzyl penicillanate (**11**) (65%), but the reduction of 6α-chloropenicillanate (**15**) was inefficient under our conditions.‡

The reductions of the 6α-alkyl-6β-isocyanopenicillanates (**1**)—(**4**) were extremely stereoselective; in each case only the corresponding 6β-alkylpenicillanate was isolated after column chromatography. Examination of the crude product mixtures by ^1H n.m.r. spectroscopy and t.l.c. was confused by the presence of tri-n-butyltin residues, but in no case could significant quantities (> 5%) of 6α-alkyl product be detected. The products were assigned the β-configuration at C-6 both on the basis of the H(5)—H(6) coupling constant, which in all cases was in the region of 4·4 Hz,[9] and by analogy with the reduction of the 6,6-dibromopenicillanate (**12**), which gave predominantly the 6β-bromo product.

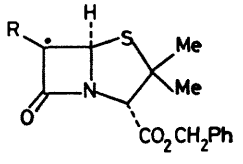
A side product was isolated in 15% yield from the reduction of the 6α-(1-hydroxy-1-methylethyl)-6β-isocyanopenicillanate (**2**), and was identified as the thiazoline-azetidinone (**16**) on the basis of spectroscopic data (the configuration at C-3 was not determined). An analogous product was also detected in the product from reduction of the 6α-methoxycarbonylmethyl-6β-isocyanopenicillanate (**3**) (*ca.* 5%) but was not fully characterised. The mechanism of formation of these side products has not been studied; one possibility involves base catalysed rearrangement of the isonitrile to an unsaturated thiazoline-azetidinone, *e.g.* (**17**),[6] which is then (stereoselectively?) reduced by tri-n-butyltin hydride.[7]



(16)



(17)



(18)

The high stereoselectivity of reduction of the 6α-alkyl-6β-isocyanopenicillanates (**1**)—(**4**) is a little surprising. The stereochemical determining step probably involves the transfer of a hydrogen atom from a molecule of tri-n-butyltin hydride to the less hindered α-face of the 6-alkylpeni-

† Satisfactory spectroscopic and analytical or accurate mass data were obtained for all new compounds. The yields are the yields of pure product, after column chromatography.

‡ Recently, reduction of other chloroazetidinones by trialkyltin hydrides has been reported, but stoicheiometric quantities of azobisisobutyronitrile were used, not the catalytic quantities used in our procedure (see C. A. Whitesitt and D. K. Herron, *Tetrahedron Letters*, 1978, 1737).

cillanate radical (**18**) to give the 6β-alkyl product. This selectivity is analogous to the selectivity of alkylation of C-6 penicillanate anions.[10]

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