Regioselective Chlorination of *N*-Benzoylvaline Methyl Ester

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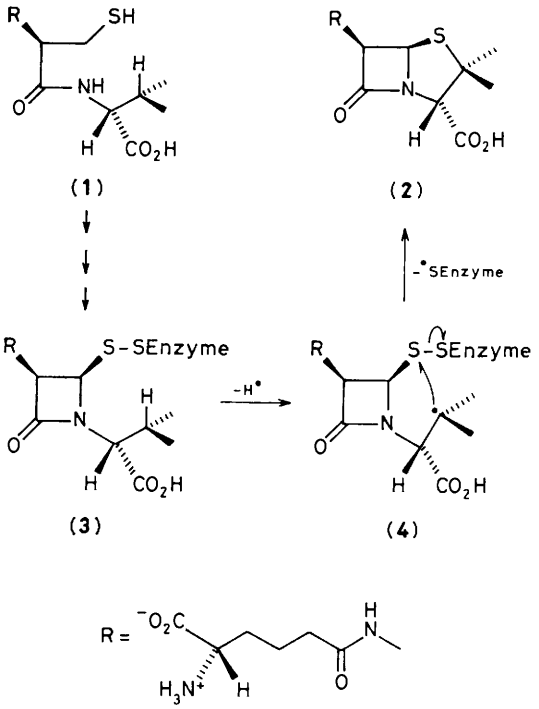
Regioselective chlorination of valine derivatives establishes the chemical validity of a regiospecific hydrogen-atom abstraction proposed in penicillin biosynthesis and provides a viable synthetic method for direct and selective functionalisation of these compounds.

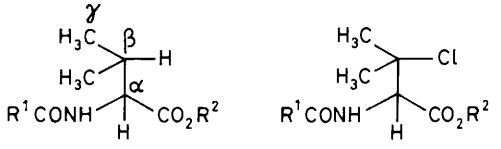
Details of the biosynthesis of penicillins and cephalosporins have not been elucidated. Oxidative cyclisation of Arnstein's tripeptide (**1**) affords isopenicillin N (**2**),[1] but the mechanism of this conversion remains unknown. On the basis of *in vitro* experiments with model compounds[2] and *in vivo* studies with labelled tripeptides,[1] a mechanism for formation of the carbon–sulphur bond has been proposed [(**4**) → (**2**)];[2,3] however, no consideration has been given to production of the radical (**4**) from (**3**), fundamental to this hypothesis. In this report we describe synthetically viable chlorinations of valine derivatives that establish the chemical validity of the hydrogen-atom transfer (**3**) → (**4**).

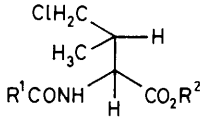
H.p.l.c.† of the mixture obtained when *N*-benzoylvaline methyl ester (**5a**)[4] (1 mmol), sulphuryl chloride (1.1 mmol), and benzoyl peroxide (5 mg) in dry CCl_4 (10 ml) under N_2 were

† H.p.l.c. analyses were performed on a Brownlee Laboratories OH-10A Diol column (26 cm × 4.6 mm i.d.) and a DuPont Zorbax cyanopropyl column (25 cm × 9.4 mm i.d.), using hexane–propan-2-ol (9 : 1) as eluant, monitoring at 220 nm. Product separations were achieved on the Zorbax column. Similar, but less efficient, separations were accomplished by chromatography on silica, eluting with ethyl acetate–dichloromethane (1 : 9).



Scheme 1





a R^1 = Ph, R^2 = CH_3
b R^1 = Ph, R^2 = H
c R^1 = R^2 = CH_3

heated under reflux for 0.5 h, afforded the β-chlorovaline (**6a**) [35—40%; oil; ^{1}H n.m.r. δ (CCl_4) 1.60 (s, 3H), 1.74 (s, 3H), 3.77 (s, 3H), 4.90 (d, *J* 9 Hz, 1H), 6.50 (br. d, *J* 9 Hz, 1H), and 7.10—8.00 (m, 5H)], identical with an authentic sample,[5] and diastereoisomers of the γ-chloro derivative (**7a**) [(i) 15—20%; m.p. 72—74 °C; ^{1}H n.m.r. δ (CCl_4) 1.09 (d, *J* 7 Hz, 3H), 2.50 (m, 1H), 3.50 (m, 2H), 3.80 (s, 3H), 4.95 (dd, *J* 4 and 8 Hz, 1H), 6.65 (br. d, *J* 8 Hz, 1H), and 7.30—7.90 (m, 5H), and (ii) 15—20%; m.p. 108—110 °C; ^{1}H n.m.r. δ (CCl_4) 1.14 (d, *J* 7 Hz, 3H), 2.50 (m, 1H), 3.60 (m, 2H), 3.84 (s, 3H), 5.00 (dd, *J* 5 and 9 Hz, 1H), 6.80 (br. d, *J* 9 Hz, 1H), and 7.30—8.00 (m, 5H)].‡ ^{1}H N.m.r. spectroscopy and h.p.l.c. analysis of crude mixtures at 10—50% reaction of (**5a**) showed ratios of (**6a**):(**7a**) (i): (**7a**) (ii) of *ca.* 2:1:1, and no other products were detected. More extensive reactions afforded small amounts of unidentified secondary products.

Presumably this peroxide-initiated chlorination proceeds by initial hydrogen-atom transfer, with subsequent chlorine incorporation at the site of hydrogen abstraction.[6] The lack of *N*-chlorinated product is consistent with reports that formation of acylamino radicals by hydrogen-atom loss is not a facile process,[7] and the phenyl and ester-methyl groups were unreactive as expected.[8] The absence of α-chlorinated product is surprising since the amide function in (**5a**) would be expected to facilitate Cα–H bond homolysis[9] and prevail over the deactivating effect of the ester group.[8] In fact, since sulphuryl chloride is a relatively random halogenating agent,[8] the lack of α-chlorinated product indicates a strong preference for abstraction of β- and γ-hydrogens.

Production of equal amounts of (**6a**) and (**7a**) indicates a 6:1 selectivity for homolysis of the Cβ–H bond, which can be attributed to the relative reactivities of the tertiary and primary hydrogens.[8] Reactions of (**5a**) with sulphuryl chloride in benzene, a more selective free-radical halogenating system,[8] afforded near quantitative yields of (**6a**) and (**7a**) in ratios of *ca.* 3:2. This represents a 9:1 selectivity for Cβ–H bond homolysis. Reactions of the acid (**5b**)[10] with sulphuryl chloride afforded complex mixtures; however, (**5c**)[4] afforded (**6c**) and (**7c**) in yields comparable to those of the products obtained from (**5a**). Again a clear preference for Cβ–H bond homolysis was observed.

To the extent that (**5a**) and (**5c**) may be considered as models of (**3**), these chlorinations proceeding *via* regioselective Cβ–H bond homolysis establish the chemical validity of the hydrogen-atom abstraction (**3**) → (**4**) and support the proposed mechanism for carbon–sulphur bond formation in penicillin biosynthesis shown in Scheme 1. Reactions of (**5a**) and (**5c**) with sulphuryl chloride provide a viable synthetic procedure for direct and selective β-chlorination, with relevance to the synthesis of penicillins. It should be noted that the synthesis of cephalosporins from valine derivatives requires γ-functionalisation, the other process observed in these reactions.

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‡ All new compounds gave satisfactory n.m.r., i.r., and mass spectral, and microanalytical data.

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