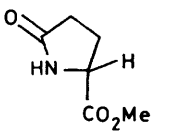
Regioselective Chlorination of Valine Derivatives

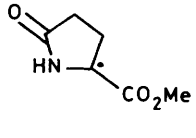
Nigel J. Bowman, Michael P. Hay, and Stephen G. Love
Department of Chemistry, University of Canterbury, Christchurch 1, New Zealand
Christopher J. Easton*
Department of Organic Chemistry, University of Adelaide, G.P.O. Box 498, Adelaide, S.A. 5001, Australia

Reaction of *N*-benzoylvaline methyl ester (**5a**) with sulphuryl chloride gave the β-chlorovaline derivative (**6a**) and lesser amounts of diastereoisomers of the γ-chlorovaline derivative (**7a**). A similar mixture of products was obtained through photolysis of the *N*-chloroamide (**13**). The reactions of the valine derivatives (**5a**) and (**13**) involve regioselective intermolecular transfer of the β-valinyl hydrogen. There is no evidence for reaction at the α-position. The β-chloroalanine derivative (**23**) was produced through reaction of *N*-benzoylalanine methyl ester (**17a**) with sulphuryl chloride and by photolysis of the *N*-chloroamide (**22**). Chlorination of the azetidinone (**16a**) gave (**16b**) in modest yield. These reactions establish the chemical validity of a regiospecific hydrogen-atom abstraction proposed in penicillin biosynthesis.

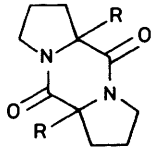
There have been several reports of regioselective hydrogen-atom transfer reactions affording amidocarboxy-substituted radicals. Irradiation of a mixture of methyl pyroglutamate (**1**) and di-t-butyl peroxide afforded products attributed to dimerization of the radical (**2**),[1] and oxidation of (**3a**) gave the diperoxide (**3b**), presumably *via* (**4a**) and (**4b**).[2] The radicals (**2**), (**4a**), and (**4b**) are stabilized by the combined action of an electron-releasing amido substituent and an electron-withdrawing carboxy substituent. They may be classified as captodative,[3] mero-stabilized,[4] or push-pull stabilized[5] radicals. Although synergistic stabilization by electron-donating and electron-withdrawing groups has not been demonstrated,[6] nevertheless these types of radicals are relatively stable and comparatively easy to form.



(**1**)

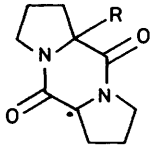


(**2**)



(**3**)

a; R = H
b; R = OOH

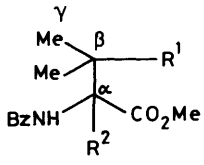


(**4**)

a; R = H
b; R = OOH

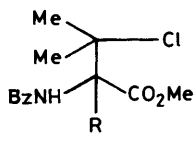
We reported recently that reaction of *N*-benzoylvaline methyl ester (**5a**) with sulphuryl chloride gave the β-chlorovaline derivative (**6a**) and lesser amounts of diastereoisomers of the γ-chlorovaline derivative (**7a**).[7] On the assumption that the chlorination proceeds by intermolecular hydrogen-atom transfer from (**5a**) with subsequent chlorine incorporation at the site of hydrogen abstraction,[8] this result is at variance with the earlier work as it indicates that the radicals (**8**) and (**9**), intermediates in the reactions to give (**6a**) and (**7a**) respectively, are formed in preference to the amidocarboxy-substituted radical (**10**).

There are alternative explanations for the regioselective



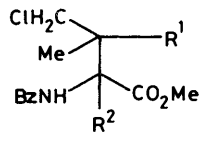
(**5**)

a; $R^1 = R^2 = H$
b; $R^1 = D, R^2 = H$
c; $R^1 = H, R^2 = D$



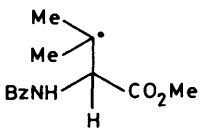
(**6**)

a; R = H
b; R = D

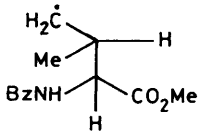


(**7**)

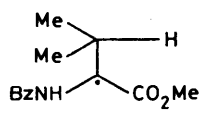
a; $R^1 = R^2 = H$
b; $R^1 = D, R^2 = H$
c; $R^1 = H, R^2 = D$



(**8**)

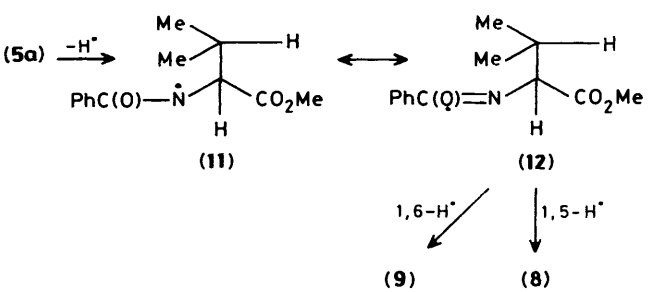


(**9**)



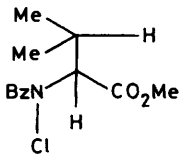
(**10**)

chlorination. For example, the reaction could involve the amido radical (**11**) as an intermediate (Scheme 1). Intramolecular hydrogen-atom transfer to the nitrogen-centred radical (**11**) is unlikely to occur because of geometrical constraints.[9,10] Although hydrogen transfer to amide oxygen has not been observed previously,[10] it is conceivable that intramolecular 1,5-hydrogen-atom transfer to the oxygen-centred radical (**12**) could occur. This would involve the same size cyclic transition state as that preferred by alkoxy radicals[11] and would account for the regioselective formation of (**8**). Reaction at the γ-position could be the result of less facile 1,6-hydrogen transfer to amide oxygen.



Scheme 1.

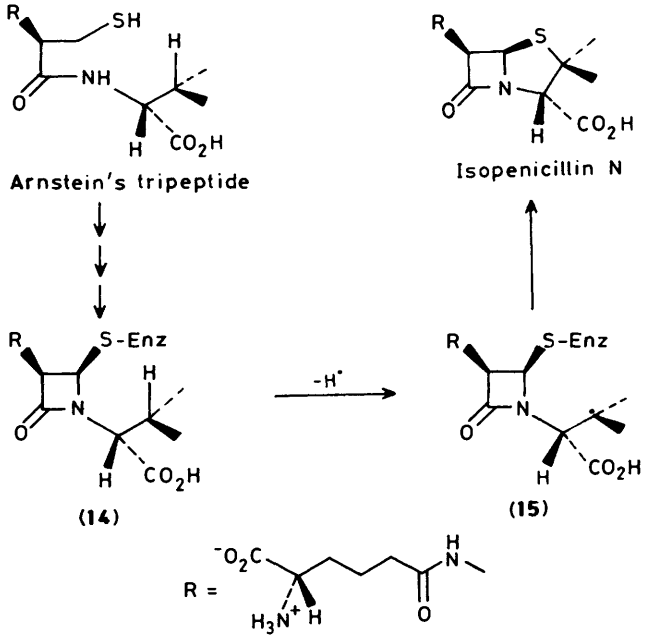
The work described here examines the mechanism of the chlorination of the valine derivative (**5a**). We have studied the reaction to determine if it involves intermolecular β-hydrogen transfer from (**5a**). We have studied photolyses of the *N*-chloroamide (**13**) to investigate reactions of the amido radical (**11**) and



(**13**)

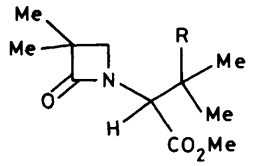
to probe for intramolecular hydrogen transfer to the oxygen-centred radical (**12**).

Initially we set out to examine hydrogen-atom transfer reactions of valine derivatives in order to assess the chemical validity of the regiospecific hydrogen-atom transfer (**14**)→(**15**) proposed in penicillin biosynthesis (Scheme 2).[12] Our original



Scheme 2.

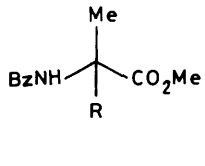
work with (**5a**) has been extended to study reaction of the azetidinone (**16a**), a closer analogue of (**14**). In addition we have studied chlorination of the alanine derivative (**17a**).



(**16**)

a; R = H

b; R = Cl



(**17**)

a; R = H

b; R = D

Results and Discussion

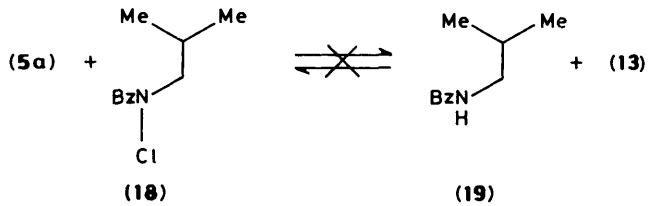
Treatment of *N*-benzoylvaline methyl ester (**5a**) with sulphuryl chloride in carbon tetrachloride or benzene at reflux under nitrogen afforded mixtures of the β-chlorovaline derivative (**6a**) and diastereoisomers of the γ-chlorovaline derivative (**7a**). The components were separated by h.p.l.c. The structure of the principal product, the β-chlorovaline derivative (**6a**), was confirmed by comparison with an authentic sample.[13] The combined yield of the chlorinated products (**6a**) and (**7a**) was high provided the extent of reaction of (**5a**) was restricted to less than 80%. More extensive reaction resulted in decomposition of the primary products.

Reaction of the β-chlorovaline derivative (**6a**) with triphenyltin hydride gave (**5a**). Use of enantiomerically pure (2*S*)-(**5a**) in the reaction with sulphuryl chloride gave the β-chlorovaline derivative (**6a**) which upon reduction with triphenyltin hydride, afforded the pure enantiomer (2*S*)-(**5a**). This sequence of reactions has been exploited in the synthesis of (2*R*)- and (2*S*)-[3-^{2}H]-valine.[14]

Photolysis of the *N*-chloroamide (**13**), obtained from the reaction of (**5a**) with t-butyl hypochlorite, afforded (**6a**) and (**7a**). Considerable quantities of (**5a**) were also produced. When the (2*S*)-valine derivative (**5a**) was used to prepare the *N*-chloroamide (**13**), photolysis of (**13**) and reduction of the product (**6a**) with triphenyltin hydride afforded (2*S*)-(**5a**). The reactions occur without racemisation at the α-position.

Photolysis of the *N*-chloroamide (**13**), prepared from the (2*S*)-valine derivative (**5a**), in the presence of the (2*R*)-valine derivative (**5a**), gave (**6a**) which reacted with triphenyltin hydride to give a mixture of the (2*R*)- and (2*S*)-valine derivative (**5a**). Since the production of (**6a**) from (2*S*)-(**5a**) *via* the *N*-chloroamide (**13**) occurs without racemisation in the absence of (2*R*)-(**5a**), the racemisation in the presence of the (2*R*)-valine derivative (**5a**) must result from interaction with this compound.

It is unlikely that the racemisation is due to reaction of the (2*R*)-valine derivative (**5a**) with the *N*-chloroamide (**13**) to give (2*S*)-(**5a**) and the enantiomer of (**13**). No interconversion between the valine derivative (**5a**) and the *N*-chloroamide (**18**) to give the amide (**19**) and the *N*-chlorovaline derivative (**13**), or *vice versa* (Scheme 3), was observed under the reaction



Scheme 3.

conditions. Presumably the radical (**11**), formed by photolysis of (**13**), reacts by intermolecular hydrogen abstraction. Reaction of the radical (**12**) by intramolecular hydrogen transfer (Scheme 1) would not result in racemisation. Although the possibility of some intramolecular reaction cannot be excluded, it is clear that intermolecular hydrogen transfer to the amidyl radical (**11**) competes effectively with intramolecular hydrogen transfer to the oxygen-centred radical (**12**), even in dilute solution. The radical (**11**) reacts by intermolecular hydrogen-atom abstraction to give (**8**) and (**9**), the precursors of (**6a**) and (**7a**) respectively.

Photolysis of mixtures of the valine derivative (**5a**) and *N*-chloro-*N*-t-butylbenzamide (**20**) or *N*-chloro-*N*-phenylbenzamide (**21**) in benzene afforded the chlorinated products

(**6a**) and (**7a**). Since (**13**) was not detected under the reaction conditions, it appears that the amidyl radicals produced by irradiation of the *N*-chloroamides (**20**) and (**21**), react by intermolecular hydrogen-atom abstraction from (**5a**) to give (**8**) and (**9**), which react to give (**6a**) and (**7a**) respectively.

To investigate the mechanism of the reaction of the valine derivative (**5a**) with sulphuryl chloride we examined reactions of the deuteriated analogues (**5b**) and (**5c**). (2*S*)-[3-^{2}H]Valine was prepared using the method of Baldwin and Wan,[15] and converted into (**5b**) using standard procedures.[16] Alternatively (**5b**) was prepared from the (2*S*)-valine derivative (**5a**) as outlined above, by reaction with sulphuryl chloride to give (**6a**), followed by reduction with triphenyltin deuteride.[14] (2*S*)-[2-^{2}H]Valine was prepared using the method of Greenstein and Winitz[17] and converted into (**5c**) using standard procedures.[16]

Whereas reaction of the valine derivative (**5a**) (0.0085M) with sulphuryl chloride in benzene afforded (**6a**) and (**7a**) in the ratio *ca.* 1.75:1.0, reaction of (**5b**) under identical conditions gave (**6a**) and (**7b**) in the ratio *ca.* 1.10:1.0. Reaction of (**5c**) gave (**6b**) and (**7c**) in the ratio *ca.* 1.75:1.0. These results indicate that there is a deuterium isotope effect of β-C–H bond cleavage.

In measuring the relative rates of reaction of the valine derivatives (**5a**—**c**) with sulphuryl chloride we exploited their chirality. The enantiomers exhibit identical reactivity in reactions with sulphuryl chloride, but they are physically separable for analysis by g.l.c. on a Chrompack XE-60-S-VAL-S-A-PEA column. Thus we were able to measure the relative rates of reaction of (**5a**—**c**) using a mixture of the (2*S*)-valine derivative (**5a**) and the (2*S*)-valine derivative (**5b**), and a mixture of (2*R*)-(**5a**) and (2*S*)-(**5c**). The ratios of the rate constants for the reactions of (**5a**—**c**) with sulphuryl chloride were calculated from the relative rates of consumption.[18] Whereas the β-deuteriated compound (**5b**) reacts with sulphuryl chloride *ca.* 0.80 times as fast as the unlabelled compound (**5a**) reacts, (**5a**) and the α-deuteriated derivative (**5c**) react at the same rate. The relative rate constants for reaction of (**5a**—**c**) show a deuterium isotope effect for β-C–H bond cleavage but no isotope effect for α-C–H bond cleavage.

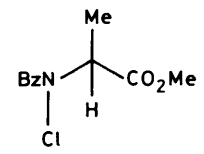
The deuterium isotope effects reflected in the relative rates of reaction of (**5a**) and (**5b**) and in the relative ratios of the products obtained from the reactions of those compounds, indicate that reaction of (**5a**) with sulphuryl chloride involves direct intermolecular hydrogen transfer from (**5a**) leading to (**6a**) and (**7a**). Assuming that abstraction of the β-hydrogen from (**5a**) or (**5b**) results in the production of (**6a**), and that abstraction of a γ-hydrogen from (**5a**) and (**5b**) leads to (**7a**) and (**7b**) respectively, on the basis of the product ratios (**5a**) would be expected to react *ca.* 1.31 times faster than (**5b**) [equation (1)] if

$$\frac{k(\mathbf{5a})}{k(\mathbf{5b})} = \frac{(\mathbf{6a}) + (\mathbf{7a})}{(\mathbf{6a}) + (\mathbf{7b})} = \frac{1.75 + 1.0}{1.10 + 1.0} = 1.31 \qquad (1)$$

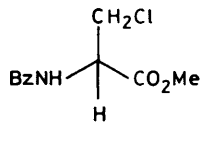
hydrogen abstraction from (**5a**) and (**5b**) is the irreversible rate-determining step. This value is, within experimental error, the same as the observed value of *ca.* 1.25.

We can not exclude the possibility that the amidyl radical (**11**) may be an intermediate in the reaction of (**5a**) with sulphuryl chloride. It does appear that reaction of the amidyl radical (**11**), generated by photolysis of the *N*-chloroamide (**13**), and the reaction of (**5a**) with sulphuryl chloride both involve intermolecular transfer of β- and γ-valinyl hydrogens. We believe the most reasonable rationalisation of the chlorination of (**5a**) with sulphuryl chloride is that intermolecular hydrogen-atom transfer from (**5a**) affords (**8**) and (**9**), which react by chlorine incorporation to give (**6a**) and (**7a**) respectively. There was no deuterium isotope effect for α-C–H bond cleavage and no evidence for products resulting from reaction at the α-position. High yields of (**6a**) and (**7a**) were obtained and the chlorination to give (**6a**) occurred without racemisation at the α-position. These points indicate that the radicals (**8**) and (**9**) are formed, by intermolecular hydrogen-atom transfer, in preference to the captodative radical (**10**).

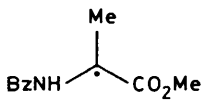
Treatment of *N*-benzoylalanine methyl ester (**17a**) with sulphuryl chloride afforded moderate amounts of the β-chloroalanine derivative (**23**), identical with an authentic sample.[19] Photolysis of the *N*-chloroalanine derivative (**22**) also gave the chlorinated product (**23**) in moderate yield. To probe for α-C–H bond cleavage in the reaction of (**17a**) with sulphuryl chloride, we studied the relative rates of reaction of the (2*R*)-alanine derivative (**17a**) and the (2*S*)-α-deuteriated analogue (**17b**) using the procedures described above. (2*S*)-[2-^{2}H]Alanine was prepared using the same procedure as that used to prepare (2*S*)-[2-^{2}H]valine.[17] The small deuterium isotope effect that was observed in the relative rates of reaction of (**17a**) and (**17b**) [k(**17a**)/k(**17b**) = 1.16], indicates that some reaction does occur at the α-position. It appears that formation of the tertiary captodative radical (**24**) occurs in competition with hydrogen-atom transfer from (**17a**) to give the primary radical (**25**).



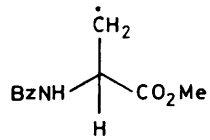
(**22**)



(**23**)



(**24**)



(**25**)

The original aim of this work was to examine hydrogen-atom transfer reactions of valine derivatives in order to assess the chemical validity of the regiospecific hydrogen-atom transfer (**14**)→(**15**) proposed in penicillin biosynthesis (Scheme 2).[12] To the extent that (**5a**) may be considered as a model of (**14**), the chlorinations of (**5a**) proceeding *via* regioselective β-C–H bond homolysis establish the chemical validity of the hydrogen-atom abstraction (**14**)→(**15**) and support the proposed mechanism for carbon–sulphur bond formation in penicillin biosynthesis shown in Scheme 2. In a more closely related system we found that reaction of the azetidinone (**16a**) with sulphuryl chloride, and photolysis of a mixture of the azetidinone (**16a**) and *N*-chloro-*N*-t-butylbenzamide (**20**), resulted in formation of the chlorinated azetidinone (**16b**) in each case.

During the course of this work Baldwin *et al.*[20] reported studies of the interaction of penicillin synthetase enzyme with modified substrates, supporting the previous contention[12] that abstraction of the β-valinyl hydrogen in penicillin biosynthesis is a homolytic process. Our work has shown that abstraction of the β-valinyl hydrogen from species analogous to (**14**) does occur despite the predicted relative stabilities of β-centred radicals such as (**15**) compared to the corresponding α-centred radicals. A rationale for the regioselectivity of these hydrogen transfer reactions is presented in the accompanying paper.[21]

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra as liquid films, unless otherwise stated, were recorded on either a Shimadzu IR-27G or a Pye-Unicam

SP3-300 spectrophotometer. ^{1}H N.m.r. spectra were recorded in carbon tetrachloride using Me_4Si as internal standard, unless otherwise stated, on either a Varian T-60, a Varian CFT-20, or a Varian XL-300 spectrometer. Mass spectra were recorded on an AEI MS902 spectrometer and a Hewlett-Packard 5982A spectrometer. Microanalyses were performed by the microanalytical laboratory, University of Otago. G.l.c. analyses were performed on a Varian 3700 gas chromatograph fitted with a Chrompack XE-60-S-VAL-S-A-PEA column. Unless otherwise stated, preparative chromatography was carried out on a Chromatotron (a preparative, centifugally accelerated, radial thin layer chromatograph, Model 7924, Harrison Research Inc.) equipped with rotors coated with silica gel PF-254 (type 60 for t.l.c. Merck 7749) of varying thickness (generally 1 or 2 mm). H.p.l.c. analyses were performed with a Shimadzu LC-4A chromatograph 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. Preparative h.p.l.c. was carried out using the Zorbax column.

All solvents were purified and dried by standard methods. Light petroleum refers to the fraction with b.p. 50—70 °C. Valine, (2*R*)- and (2*S*)-valine, alanine, and (2*R*)-alanine were purchased from Sigma Chemical Co. (2*S*)-[3-^{2}H]Valine,[15] (2*S*)-[2-^{2}H]valine,[17] (2*S*)-[2-^{2}H]alanine,[17] t-butyl hypochlorite,[22] and triphenyltin hydride[23] were all prepared and purified by literature procedures. The chloroamides (**20**) and (**21**) were prepared by the reaction of benzoyl chloride with t-butylamine and aniline to give the respective amides, which were subsequently treated with t-butyl hypochlorite. The valine derivatives (**5a**), (2*S*)- and (2*R*)-(**5a**), (2*S*)-(**5b**), and (2*S*)-(**5c**), and the alanine derivatives (**17a**), (2*R*)-(**17a**), and (2*S*)-(**17b**), were prepared and purified using standard procedures.[16] Where appropriate, chiral purity was shown to be greater than 99% by g.l.c. analysis. By mass spectrometery, the deuterium content of (2*S*)-(**5b**), (2*S*)-(**5c**), and (2*S*)-(**17b**) was found to be 92, 85, and 83%, respectively.

Reaction of N-*Benzoylvaline Methyl Ester* (**5a**) *and the Deuteriated Analogues* (**5b**) *and* (**5c**) *with Sulphuryl Chloride*.—A mixture of *N*-benzoylvaline methyl ester (**5a**) (0.2 g, 0.85 mmol), sulphuryl chloride (0.1 ml, 1.2 mmol), and benzoyl peroxide (*ca.* 2 mg), in benzene (15 ml), was heated at reflux under nitrogen for 1 h and then cooled. H.p.l.c. of the mixture gave *N*-benzoyl-3-chlorovaline methyl ester (**6a**) as an oil (92 mg, 40%); ^{1}H n.m.r. δ 1.60 (s, 3 H), 1.74 (s, 3 H), 3.77 (s, 3 H), 4.90 (d, *J* 9 Hz, 1-H), 6.50 (br d, *J* 9 Hz, 1-H), and 7.10—8.00 (m, 5-H), identical with a sample synthesized using methods described previously.[13] Also obtained were diastereoisomers of *N*-benzoyl-4-chlorovaline methyl ester (**7a**), each of which crystallised from ethyl acetate–light petroleum as colourless needles. One isomer (28 mg, 12%) had m.p. 72—74 °C; δ 1.09 (d, *J* 7 Hz, 3-H), 2.50 (m, 1-H), 3.50 (m, 2-H), 3.80 (s, 3-H), 4.95 (dd, *J* 4 and 8 Hz, 1-H), 6.65 (br d, *J* 8 Hz, 1-H), and 7.30—7.90 (m, 5-H); $\nu_{max.}$(Nujol) 692, 1 641, and 1 750 cm^{-1}; *m/z* 271 and 269 (M^+, 1 and 3%, respectively), 234 (63), 212 (23), 210 (60), and 105 (100); *m/z* 269.0817 (M^+) [Calc. for $C_{13}H_{16}ClNO_3$ (M^+) *m/z* 269.0819] (Found: C, 57.64; H, 6.01. Calc. for $C_{13}H_{16}ClNO_3$: C, 57.89; H, 5.98%). The other isomer (33 mg, 14%) had m.p. 108—110 °C; δ 1.14 (d, *J* 7 Hz, 3-H), 2.50 (m, 1-H), 3.60 (m, 2-H), 3.84 (s, 3-H), 5.00 (dd, *J* 5 and 9 Hz, 1-H), 6.80 (br d, *J* 9 Hz, 1-H), and 7.30—8.00 (m, 5-H); $\nu_{max.}$(Nujol) 697, 1 642, and 1 747 cm^{-1}; *m/z* 271 and 269 (M^+, 1 and 4% respectively), 234 (55), 212 (17), 210 (42), and 105 (100); *m/z* 269.0799 (M^+) [Calc. for $C_{13}H_{16}ClNO_3$ (M^+) *m/z* 269.0819] (Found: C, 57.7; H, 5.85. Calc. for $C_{13}H_{16}ClNO_3$: C, 57.89; H, 5.98%).

The products were separated on a larger scale, but in lower percentage yield, when separation was carried out using the Chromatotron or by column chromatography on silica. Analysis of crude reaction mixtures by h.p.l.c. showed that the ratio of products (**6a**):(**7a**)(i):(**7a**)(ii) was *ca.* 3.2:1:1. This ratio was dependent on the solvent used in the reaction. In carbon tetrachloride the ratio of products (**6a**):(**7a**)(i):(**7a**)(ii) was *ca.* 2:1:1. The product ratio varied slightly with solvent concentration when benzene was used as a solvent.

Exactly analogous behaviour to that described above, was observed when the (2*S*)-valine derivative (**5a**) was treated with sulphuryl chloride.

To compare the reactions of (**5a**) and the deuteriated analogues (**5b**) and (**5c**) with sulphuryl chloride, each of the valine derivatives (8.5mM) was treated with sulphuryl chloride in benzene as described above. Product ratios for experiments performed in triplicate were determined by h.p.l.c. analyses carried out in triplicate. Reaction of (**5a**) gave (**6a**) and (**7a**) in the ratio 1.75 ± 0.1 : 1.0, reaction of (**5b**) gave (**6a**) and (**7b**) in the ratio 1.10 ± 0.10:1.0, and reaction of (**5c**) gave (**6b**) and (**7c**) in the ratio 1.75 ± 0.10:1.0.

To determine the relative rates of reaction of (**5a**), (**5b**), and (**5c**) with sulphuryl chloride, mixtures of (2*R*)-(**5a**) (4.25mM) and (2*S*)-(**5b**) (4.25mM), and of (2*R*)-(**5a**) (4.25mM) and (2*S*)-(**5c**) (4.25mM) in benzene were treated with sulphuryl chloride as described above. The extent of reaction of the valine derivatives (**5a—c**) was determined for experiments carried out in triplicate, by g.l.c. analyses performed in triplicate, and used to calculate the relative rates of reaction[18] of (**5a**), (**5b**), and (**5c**) as 1.0:0.80 ± 0.04:1.0 ± 0.03.

Reaction of N-*Benzoyl*-3-*chlorovaline Methyl Ester* (**6a**) *with Triphenyltin Hydride*.—A mixture of *N*-benzoyl-3-chlorovaline methyl ester (**6a**) (0.15 g, 0.56 mmol) and triphenyltin hydride (0.50 g, 1.42 mmol) in benzene (10 ml), was heated at reflux under nitrogen for 5 h, then cooled, concentrated, and chromatographed on silica. Elution with ethyl acetate–dichloromethane (1:9) afforded *N*-benzoylvaline methyl ester (**5a**) (89 mg, 68%).

When a sample of (**6a**), obtained by treatment of (2*S*)-(**5a**) with sulphuryl chloride, was treated with triphenyltin hydride, the product was the pure enantiomer (2*S*)-(**5a**) as determined by g.l.c. analysis.

N-*Benzoyl*-N-*chlorovaline Methyl Ester* (**13**).—A solution of *N*-benzoylvaline methyl ester (**5a**) (1.0 g, 4.3 mmol) and t-butyl hypochlorite (3 ml, 26.5 mmol) in toluene (20 ml) was left for 16 h in the dark. Excess of t-butyl hypochlorite was destroyed by the addition of potassium t-butoxide and the solvent was removed. The residue was dissolved in chloroform (25 ml) and the solution washed with water (4 × 60 ml), dried ($MgSO_4$), and concentrated to give crude *N*-benzoyl-*N*-chlorovaline methyl ester (**13**) as a red oil; δ($CDCl_3$) 1.00 (d, *J* 7 Hz, 3-H), 1.04 (d, *J* 7 Hz, 3-H), 2.47 (m, 1-H), 3.76 (s, 3-H), 4.55 (d, *J* 10 Hz, 1-H), and 7.20—7.90 (m, 5-H).

A sample of (**13**) was prepared from (2*S*)-(**5a**) in a similar manner.

Photolysis of N-*Benzoyl*-N-*chlorovaline Methyl Ester* (**13**).—Irradiation of a solution of the crude *N*-chlorovaline derivative (**13**) (0.2 g, 0.74 mmol) in benzene (20 ml), in a Rayonet photochemical reactor equipped with 16 RPR 3000 lamps, for 14 h, gave a mixture of (**5a**), (**6a**), and (**7a**) in the ratio *ca.* 45:3:1, as determined by h.p.l.c. analysis. In more concentrated solution relatively more (**6a**) and (**7a**) were produced, but the ratio of (**6a**) to (**7a**) remained constant. The products were separated by chromatography.

Photolysis of a sample of (**13**), obtained by treatment of (2*S*)-(**5a**) with t-butyl hypochlorite, afforded similar mixtures of products. When a sample of the β-chlorovaline derivative (**6a**),

prepared from (2*S*)-(**5a**) *via* the *N*-chlorovaline derivative (**13**), was treated with triphenyltin hydride, the product was the pure enantiomer (2*S*)-(**5a**) as determined by g.l.c. analysis.

Photolysis of a 1:1 mixture of the *N*-chlorovaline derivative (**13**), prepared from (2*S*)-(**5a**), and the (2*R*)-valine derivative (**5a**), gave a mixture of products from which the β-chlorovaline derivative (**6a**) was separated and treated with triphenyltin hydride to give a mixture of the (2*R*)- and (2*S*)-valine derivative (**5a**) in the ratio 1.0:1.20 ± 0.05 as determined by g.l.c. analysis.

Photolysis of N-*Chloro*-N-*t-butylbenzamide* (**20**) *in the Presence of* N-*Benzoylvaline Methyl Ester* (**5a**).—Irradiation of a mixture of *N*-chloro-*N*-t-butylbenzamide (**20**) (4.0 g, 18.9 mmol) and *N*-benzoylvaline methyl ester (**5a**) (0.5 g, 2.1 mmol) in benzene (50 ml) as described above afforded, after chromatography, the 3-chlorovaline derivative (**6a**) (0.29 g, 51%) and a mixture of diastereoisomers of the 4-chlorovaline derivative (**7a**) (42 mg, 7%).

Photolysis of N-*Chloro*-N-*phenylbenzamide* (**21**) *in the Presence of* N-*Benzoylvaline Methyl Ester* (**5a**).—Irradiation of a mixture of *N*-chloro-*N*-phenylbenzamide (**21**) (5.0 g, 21.6 mmol) and *N*-benzoylvaline methyl ester (**5a**) (0.5 g, 2.1 mmol) in benzene (50 ml) as described above afforded, after chromatography, the 3-chlorovaline derivative (**6a**) (114 mg, 20%) and a mixture of diastereoisomers of the 4-chlorovaline derivative (**7a**) (13 mg, 2%).

N-*Benzoyl*-3-*chloroaniline Methyl Ester* (**23**).—*Method A.* Treatment of *N*-benzoylalanine methyl ester (**17a**) with sulphuryl chloride in benzene as described above gave, after chromatography, *N*-benzoyl-3-chloroalanine methyl ester (**22**) in 36% yield, identical with a sample synthesized using methods described previously.[19]

Method B. Treatment of *N*-benzoylalanine methyl ester (**17a**) with t-butyl hypochlorite as described above gave *N*-benzoyl-*N*-chloroalanine methyl ester (**22**). Photolysis of the *N*-chloroalanine derivative (**22**) as described above gave, after chromatography, the 3-chloroalanine derivative (**23**) in 21% yield.

Reaction of the Alanine Derivatives (**17a**) *and* (**17b**) *with Sulphuryl Chloride.*—The relative rates of reaction of the alanine derivatives (**17a**) and (**17b**) with sulphuryl chloride were determined as described above for the valine derivatives (**5a**—**c**).

1-(1-*Methoxycarbonyl*-2-*methylpropyl*)-3,3-*dimethylazetidin*-2-*one* (**16a**).—Thionyl chloride (18.3 ml, 256 mmol) was added dropwise to methanol. Valine (10.0 g, 85 mmol) was then added and the solution was stirred at room temperature for 3 h after which it was concentrated to give crude valine methyl ester hydrochloride. A solution of 3-chloro-2,2-dimethylpropionic acid (10.4 g, 76 mmol) in thionyl chloride (11 ml, 152 mmol) was heated under reflux for 3 h and then concentrated. The residual oil was dissolved in dichloromethane (100 ml) and added dropwise to a solution of the crude valine methyl ester hydrochloride in dichloromethane (50 ml) and water (50 ml), to which potassium hydrogen carbonate was added as required to keep the solution basic. The mixture was stirred for 4 h and then the dichloromethane layer was separated, washed with water, dried ($MgSO_4$), and concentrated to give a solid which recrystallised from light petroleum as colourless crystals of *N*-(3-chloro-2,2-dimethylpropionyl)valine methyl ester (3.1 g, 16%), m.p. 62—63 °C; δ($CDCl_3$) 0.92 (d, *J* 7 Hz, 3-H), 0.94 (d, *J* 7 Hz, 3-H), 1.33 (s, 6-H), 2.16 (m, 1-H), 3.61 (s, 2-H), 3.75 (s, 3-H), 4.55 (dd, *J* 4 and 9 Hz, 1-H), and 6.26 (br d, *J* 9 Hz, 1-H); $\nu_{max.}$ 1 630 and 1 760 cm^{-1} (Found: C, 52.95; H, 8.15: N, 5.55. Calc. for $C_{11}H_{20}ClNO_3$: C, 52.90; H, 8.07; N, 5.61%).

Sodium hydride (50% in oil; 383 mg, 8 mmol) pre-washed with light petroleum, was suspended in a mixture of dichloromethane and dimethylformamide (3:1; 80 ml). To this suspension a solution of *N*-(3-chloro-2,2-dimethylpropionyl)-valine methyl ester (1.26 g, 5.1 mmol) in dichloromethane and dimethylformamide (3:1; 20 ml) was added dropwise. The solution was stirred under nitrogen for 6 h and then diluted with water (10 ml). The dichloromethane layer was separated, washed with water, dried ($MgSO_4$), and concentrated to give a residual oil which distilled to give the title azetidin-2-one (**16a**) as a colourless oil (0.39 g, 36%), b.p. 150—152 °C/18 mmHg block; δ 0.96 (d, *J* 6 Hz, 6-H), 1.28 (s, 6-H), 2.15 (m, 1-H), 3.10 (d, *J* 6 Hz, 1-H), 3.31 (d, *J* 6 Hz, 1-H), 3.73 (s, 3-H), and 4.06 (d, *J* 8 Hz, 1-H); $\nu_{max.}$ 1 722 and 1 740 cm^{-1}; *m/z* 213 (M^+, 72%) and 154 (100); *m/z* 213.1361 (M^+) [Calc. for $C_{11}H_{19}NO_3$ (M^+) *m/z* 213.1364].

1-(2-*Chloro*-1-*methoxycarbonyl*-2-*methylpropyl*)-3,3-*dimethylazetidin*-2-*one* (**16b**).—*Method A.* Treatment of the azetidin-2-one (**16a**) with sulphuryl chloride in benzene as described above gave, after chromatography, the title azetidin-2-one (**16b**) as a colourless oil in 6% yield; δ($CDCl_3$) 1.32 (s, 3-H), 1.35 (s, 3-H), 1.68 (s, 3-H), 1.75 (s, 3-H), 3.50 (d, *J* 6 Hz, 1-H), 3.63 (d, *J* 6 Hz, 1-H), 3.78 (s, 3-H), and 4.61 (s, 1-H); $\nu_{max.}$ 1 740 and 1 755 cm^{-1}; *m/z* 249 and 247 (M^+, 8 and 28%, respectively), 190 (38), and 188 (100); *m/z* 247.0970 (M^+) [Calc. for $C_{11}H_{18}ClNO_3$ (M^+) *m/z* 247.0975].

Method B. Irradiation of a mixture of *N*-chloro-*N*-t-butylbenzamide (**20**) (2.0 g, 9.5 mmol) and the azetidin-2-one (**16a**) (0.3 g, 1.4 mmol) in benzene (20 ml) as described above afforded, after chromatography, the title azetidin-2-one (**16b**) (0.13 g, 38%).

Acknowledgements

The authors acknowledge support from the Research Committee of the New Zealand Universities' Grants Committee.

References

1 N. Obata and K. Niimura, *J. Chem. Soc., Chem. Commun.*, 1977, 238.
2 U. Schmidt, J. Hausler, E. Ohler, and H. Poisel, *Prog. Chem. Org. Nat. Prod.*, 1979, **37**, 286.
3 H. G. Viehe, R. Merenyi, L. Stella, and Z. Janousek, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 917; H. G. Viehe, Z. Janousek, and R. Merenyi, *Acc. Chem. Res.*, 1985, **18**, 148.
4 R. W. Baldock, P. Hudson, A. R. Katritzky, and F. Soti, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1422.
5 A. T. Balaban, *Rev. Roum. Chim.*, 1971, **16**, 725.
6 D. Griller, *Annu. Rep. Prog. Chem., Sect. B*, 1984, **81**, 69.
7 C. J. Easton and N. J. Bowman, *J. Chem. Soc., Chem. Commun.*, 1983, 1193.
8 H. C. Brown and A. B. Ash, *J. Am. Chem. Soc.*, 1955, **77**, 4019; G. A. Russell and H. C. Brown, *ibid.*, p. 4031.
9 A. L. J. Beckwith and A. Goodrich, *Aust. J. Chem.*, 1965, **18**, 747; D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 1965, 181; R. S. Neale, N. L. Marcus, and R. G. Schepers, *J. Am. Chem. Soc.*, 1966, **88**, 3051.
10 Y. L. Chow and T. C. Joseph, *J. Chem. Soc., Chem. Commun.*, 1969, 490; R. A. Johnson and F. D. Greene, *J. Org. Chem.*, 1975, **40**, 2186; T. C. Joseph, J. N. S. Tam, M. Kitadani, and Y. L. Chow, *Can. J. Chem.*, 1976, **54**, 3517.
11 C. Walling and A. Padwa, *J. Am. Chem. Soc.*, 1963, **85**, 1597.
12 J. E. Baldwin and T. S. Wan, *J. Chem. Soc., Chem. Commun.*, 1979, 249.
13 J. Oh-Hashi and K. Harada, *Bull. Chem. Soc. Jpn.*, 1966, **39**, 2287.
14 C. J. Easton and N. G. Findlay, *J. Labelled Compds. Radiopharm.*, 1985, **22**, 667.
15 J. E. Baldwin and T. S. Wan, *Tetrahedron*, 1981, **37**, 1589.
16 T. H. Applewhite, H. Waite, and C. Niemann, *J. Am. Chem. Soc.*, 1958, **80**, 1465.

17 J. P. Greenstein and M. Winitz, 'Chemistry of the Amino Acids,' Wiley and Sons, London 1961, p. 2375.
18 K. Hayday and R. D. McKelvey, *J. Org. Chem.*, 1976, **41**, 2222; C. Walling and M. J. Gibion, *J. Am. Chem. Soc.*, 1965, **87**, 3361.
19 P. Hughes, M. Martin, and J. Clardy, *Tetrahedron Lett.*, 1980, **21**, 4579.
20 J. E. Baldwin, R. M. Adlington, N. J. Turner, B. P. Domayne-Hayman, H. H. Ting, A. E. Derome, and J. A. Murphy, *J. Chem. Soc., Chem. Commun.*, 1984, 1167; J. E. Baldwin, R. M. Adlington, A. E. Derome, H. H. Ting, and N. J. Turner, *ibid.*, p. 1211.
21 C. J. Easton, M. P. Hay, and S. G. Love, *J. Chem. Soc., Perkin Trans. 1*, 1988, following paper.
22 H. M. Teeter and E. W. Bell, *Org. Synth.*, Coll. Vol. IV, 1963, 125.
23 H. G. Kuivila and O. F. Beumel, *J. Am. Chem. Soc.*, 1961, **83**, 1246.

Received 12*th February* 1987; *Paper* 7/253