Photochemistry of Dehydrodipeptides Related to β-Lactam Antibiotics †

By **Prabir K. Sen, Christopher J. Veal,** and **Douglas W. Young,*** School of Molecular Sciences, University of Sussex, Falmer, Brighton BN1 9QJ

The photochemistry of a series of β-thioacrylamides has been investigated. The acyclic compounds (9)—(12) undergo *cis–trans* isomerisation and cyclisation to oxazoles such as (13) and (21). The cyclic β-thioacrylamide (23) undergoes a $\pi_2 s + \pi_2 s$ cycloaddition reaction to give the interesting tricyclic β-lactam (29).

SYNTHESIS of β-lactams related to the antibiotics penicillin (1) and and cephalosporin (2) has excited considerable interest in recent years and many synthetic methods have been employed to this end. One method yet to be applied as the key β-lactam-forming step in a total synthesis is the electrocyclic reaction (3) ⟶ (4) ⟶ (5). Chapman and Adams [3] have reported that photolysis of the acrylamides (6) results in a stereospecific cyclisation to the *cis*-disubstituted β-lactams (8). Since there will be a contribution from the resonance form (7) to the structure of the amide (6), it is possible to view this reaction as an analogy for the electrocyclic reaction (3) ⟶ (5). We have prepared a series of compounds (9), (10), (11), and (12) by total stereospecific synthesis [4] and so we were well-placed to examine the possible synthesis of β-lactam antibiotics by the electrocyclic reaction (3) ⟶ (5).

RESULTS AND DISCUSSION

When the (*Z*)-acrylamide (9) was photolysed using a Hanovia 125-W medium-pressure lamp at $\lambda > 250$ nm in pyridine for 24 h, a red oil was obtained which could be purified by preparative t.l.c. In addition to the starting acrylamide (9), the (*E*)-isomer (10) was obtained in 14% yield together with a compound $C_{17}H_{18}N_2O_4$, m.p. 106 °C, in 13% yield. This compound had a ^{1}H n.m.r. spectrum which exhibited, in addition to resonances typical of the benzyl and methyl dehydrovalinate moieties, a sharp aromatic singlet at τ 1.88 and an NH proton at τ 1.95. The i.r. spectrum exhibited ester and amide absorptions and the absorption associated with the chromophore in the starting thioacrylamide was no longer present in the u.v. spectrum. These data were consistent with the oxazole structure (13) for the photoproduct. This would arise by attack of the oxygen of the phenylacetamido-side-chain on the acrylamide followed by elimination of methanethiol. Similar results were obtained when the (*E*)-isomer (10) was photolysed under the same conditions.

An independent synthesis of the oxazole (13) was undertaken to verify its structure Since treatment of the thiazoline-β-lactam (14) with trifluoroacetic acid had yielded the thiazole (15),[5] we were curious to see whether the oxazoline-β-lactam (16) [6] would yield the desired oxazole (13) when treated in the same way. The oxazoline-β-lactam (16) was therefore dissolved in CF_3CO_2H and the ensuing reaction was followed using ^{1}H n.m.r. spectroscopy. An intermediate formed which reached its maximum concentration after 10—15 min. Starting material had been consumed after 5 h and after 32 h a more stable product could be isolated. This had a parent ion, *m/e* 314, in the mass spectrum and an i.r. band at 1 760 cm^{-1} suggested [7] an oxazolone structure. The u.v. absorption at $\lambda_{max.}$ 329 nm, shifting to 335 nm in base, was in keeping [7] with the oxazolone structure (17) and the ^{1}H n.m.r. spectrum suggested that only one of the two possible geometric isomers was present. Since the (*E*)-isomer shown would be expected to be the thermodynamically more stable isomer due to the intramolecular hydrogen bond, it would seem the more likely product. Verification of the structure (17) was obtained by independent synthesis by condensation of the oxazolone (18) [8] with methyl dehydrovalinate. We were interested to discover the identity of the intermediate in the reaction of CF_3CO_2H with the oxazoline-β-lactam (16), and isolated this as an impure unstable product after a reaction time of 13 min. The spectra were in keeping with the formulation of this compound as (19; R = CO_2Me) and a similar product (19; R = H) from a similar reaction was reported [9] after completion of our work.[10]

We were eventually able to achieve an independent synthesis of the oxazole photoproduct (13) by reacting the aldehyde (20) [11] with thionyl chloride.

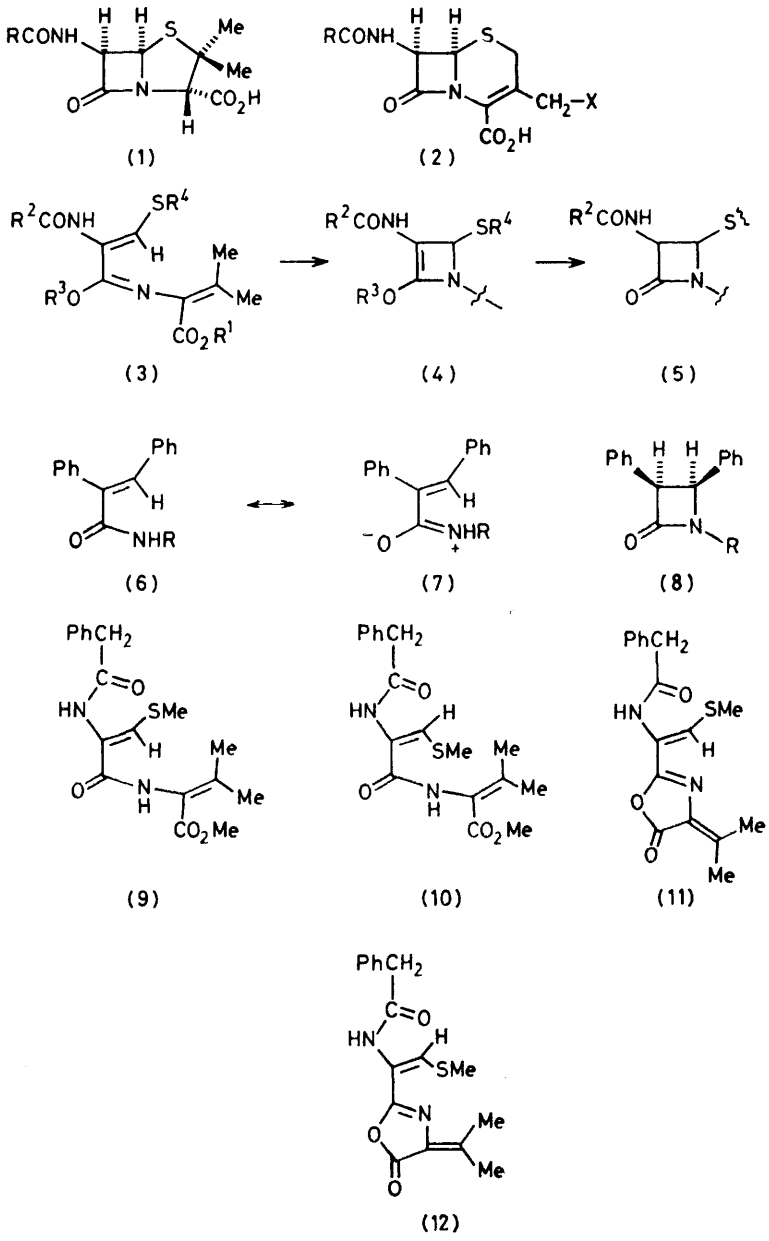
When the oxazolone (11) was photolysed in pyridine, a compound $C_{16}H_{14}N_2O_3$ was obtained in 23% yield. The spectra of the product indicated that a similar reaction had occurred to that found with the amides (9) and (10). Thus although we now had a compound more analogous to (3) in which the third conjugated π-bond was constrained to be away from the diene system, we had still observed participation of the side-chain to yield the product (21). The structure of this compound was verified by treatment of the compound with methanolic NaOH when the product (13) was obtained.

Since photolysis of the compounds (9), (10), and (11) had resulted in participation of the side-chain amide, we investigated the photolysis of the phthalimido-derivative (22).[4] No reaction was observed when a medium-pressure lamp was used, but use of a high-pressure lamp resulted in rearrangement of the (*E*)-isomer to the (*Z*)-isomer.‡

We now felt that if we were to achieve our original

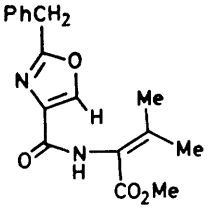
† Aspects of this work have been reported as preliminary communications in references 1 and 2.

‡ The experimental for this reaction was reported in reference 4.

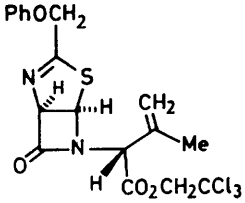


goal we should not only have to use a substrate for the photochemical reaction in which the side-chain could not interfere with the acrylamide moiety, but also one which had a double bond which would be stable to isomerisation. The dipeptide (23) seemed admirable, since not only did it have both of these qualities but we felt that if it were to cyclise in the desired manner, the stereochemistry in the resultant β-lactam (24) would be *cis* as found in natural β-lactam antibiotics for both kinetic [3] and thermodynamic reasons, the resultant 5/4 ring system preferring to be *cis*-fused.

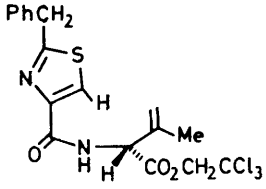
The dipeptide (23) was prepared by first hydrolysing the methyl ester (25; R = OMe) [12] to the acid (25; R = OH). This acid readily formed a mixed anhydride using ethyl chloroformate and this reacted with aniline to yield the anilide (25; R = NHPh) and with methyl dehydrovalinate to yield the dipeptide (23). When the dipeptide (23) was photolysed, a band at 1 780 cm^{-1} became apparent in the i.r. spectrum of aliquots from the reaction. This was present in the crude product but proved very ephemeral on attempted purification. The major product of the photochemical reaction, $C_{12}H_{18}N_2O_3S$, lacked the characteristic chromophore of the dipeptide in the u.v. and a CH_2 group replaced the formyl and olefinic protons in the ^1H n.m.r. spectrum. The product was therefore concluded to be the imine (26), formed by photochemical deformylation, and it was prepared independently by alkaline hydrolysis of the dipeptide (23) in an attempt to hydrolyse the ester function. The structure of the imine was verified by



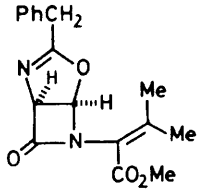
(13)



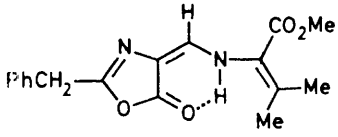
(14)



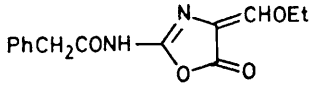
(15)



(16)

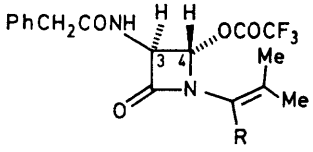


(17)

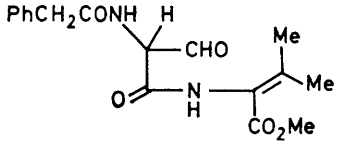


(18)

treating it with formic acetic anhydride when the dipeptide (23) was obtained. It was found that alkaline hydrolysis of the anilide (25; R = NHPh) also resulted in deformylation to the imine (27).

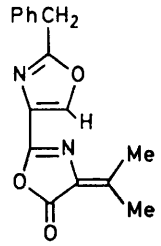


(19)

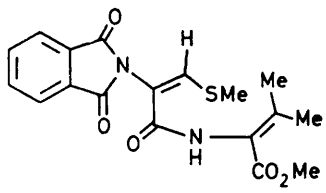


(20)

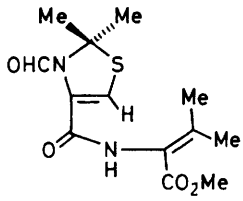
It eventually proved possible to purify the unstable material responsible for the band at $\nu_{max.}$ 1 780 cm^{-1} in the i.r. by t.l.c. on silica plates which had been deactivated by exposure to the atmosphere for 48 h. After a preliminary separation, an eluant containing a small amount of 0.1M aqueous ammonium acetate gave the pure product which could be crystallised from ether–light petroleum. The product $C_{13}H_{18}N_2O_4S$, m.p. 148—150 °C, had only end absorption in the u.v. and the ^1H n.m.r. spectrum showed the presence of four singlet C-methyls, one methoxyl, and one formyl group. The olefinic proton in the starting dipeptide had been replaced by a singlet at τ 6.1 and there was an exchangeable NH proton at τ 3.02. These data suggested two structures (28) and (29) for the product. The i.r. absorption was more in keeping with the β-lactam



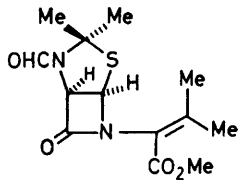
(21)



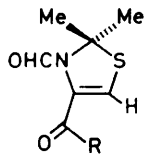
(22)



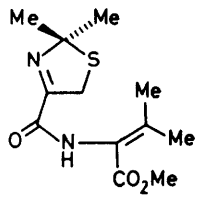
(23)



(24)

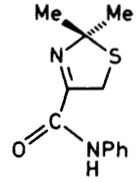


(25)

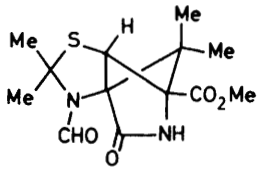


(26)

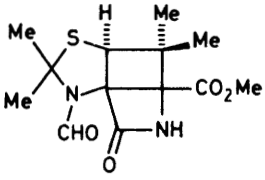
structure (29),[13] models for the alternative formulation (28) having an amide carbonyl absorption at 1 745 cm^{-1}.[14] Ions at *m/e* 270 ($M^+ - CO$) and 255 ($M^+ -$ CONH) were also in accord [13] with the mass spectral fragmentation of other β-lactam compounds.



(27)



(28)



(29)

The product of the photochemical reaction is evidently the result of a photochemical $\pi_2 s + \pi_2 s$ cycloaddition reaction of the diene system rather than of the alternative electrocyclic reaction which would have given the β-lactam (24). Photolysis of pyridones has long been known [15] to yield β-lactams fused to cyclobutenes and it is possible to view the peptide (23) as a *seco*-pyridone. The reaction might then be regarded as a special case of the general reaction of pyridones.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded on Perkin-Elmer 237 and 257 instruments, and u.v. spectra on a Unicam SP800 spectrophotometer. N.m.r. spectra were recorded with a Varian T60 or HA100 or Perkin-Elmer R32 instrument.

Electron impact mass spectra were run on Hitachi RMU-6, or AEI MS9 and MS30 instruments by Mr A. Greenway and the field-desorption mass spectrum was run by Dr D. Games, University College, Cardiff. Photochemical experiments were conducted using a Hanovia 1-l photochemical reactor with a suitably modified outer flask for smaller scale work. T.l.c. was carried out with Kieselgel G (Merck) in 0.25-mm layers for analytical work and 0.75-mm layers for preparative work. The compound (29) was finally purified using commercial plates (Merck F24 No. 5715). Microanalyses were performed by Mr and Mrs A. G. Olney.

Photolysis of Methyl (Z)-N-*Phenylacetyl*-S-*methyldehydrocysteinyldehydrovalinate* (9).—The acrylamide (9) (175 mg, 0.48 mmol) was dissolved in dry pyridine (550 ml) and the solution was degassed by freeze-thawing followed by passage of nitrogen for 12 h. The solution was photolysed for 24 h. under nitrogen using a 125-W medium-pressure lamp constructed of M84 quartz. When the absorption at λ 285 nm remained constant, the solvent was removed *in vacuo* to yield a red oil which was purified by preparative t.l.c. [SiO_2; EtOAc–$CHCl_3$ (1 : 1)]. A fraction, R_F 0.14, (60 mg, 34%) proved to be starting material. A second fraction, R_F 0.23, (24 mg, 14%), m.p. 127—130 °C, had spectra identical to those of an authentic sample of the *E*-isomer (10).[4] The third fraction of R_F 0.5, the *oxazole* (13), was recrystallised from benzene–light petroleum as a white solid (20 mg, 13%), m.p. 106 °C (Found: C, 65.2; H, 5.9; N, 8.9. $C_{17}H_{18}N_2O_4$ requires C, 65.0; H, 5.7; N, 8.9%); *m/e* 314 (M^+); $\nu_{max.}$ ($CHCl_3$) 3 370 (NH), 1 720 (ester), and 1 675 cm^{-1} (amide); τ ($CDCl_3$) 8.10 (3 H, s, MeC=), 7.79 (3 H, s, MeC=), 6.25 (3 H, s, OMe), 5.87 (2 H, s, PhCH_2), 2.68 (5 H, s, aromatics), 1.95 (1 H, br s, NH), and 1.88 (1 H, s, oxazole H).

Reaction of Methyl 2-(3-*Benzyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3,2,0]*hept*-2-*en*-6-*yl*)-3-*methylbut*-2-*enoate* (16) *with Trifluoroacetic Acid*.—(a) *For* 32 h. The β-lactam-oxazoline (16) (20 mg; 0.064 mmol) was dissolved in CF_3CO_2H (0.5 ml) and the solution was left at room temperature for 32 h in an n.m.r. tube. When reaction was judged to be complete, chloroform (50 ml) was added and the organic solution was washed with saturated aqueous sodium hydrogencarbonate and water, and dried ($MgSO_4$). The solvent was removed *in vacuo* to leave the *oxazolone* (17) as a pure oily compound (15 mg; 75%); *m/e* 314 (M^+); $\nu_{max.}$ ($CHCl_3$) 3 360 (NH), 1 760 (sh), and 1 715 cm^{-1} (oxazolone and ester); τ ($CDCl_3$) 8.10 (3 H, s, MeC=), 7.89 (3 H, s, MeC=), 6.28 (3 H, s, OMe), 6.23 (2 H, s, PhCH_2), and 2.67—3.03 (*ca.* 6 H, m, aromatics and olefinics); $\lambda_{max.}$ (MeOH) 329 nm; $\lambda_{max.}$ (OH^-) 335 nm; $\lambda_{max.}$ (H^+) end absorption only.

(b) *For* 13 min. When the reaction was repeated as above but worked up after 13 min, a 1 : 1 mixture of starting material and an unstable new compound were obtained. The new compound showed in addition to the benzyl and methyl dehydrovalinate signals in the ^1H n.m.r. spectrum ($CDCl_3$) a singlet at τ 3.62 and a doublet (*J* 8 Hz) at τ 5.14, In the unstable compound (19; R = H) [9] bands at τ (CF_3CO_2H) 3.7 (d, *J* 1 Hz) and 5.5 (dd, *J* 7 and 1 Hz) for H-4 and H-3 were in keeping with the formulation of our intermediate as (19; R = CO_2Me).

Independent Synthesis of the Oxazolone (17).—2-Benzyl-4-ethoxymethylene-5-oxazolone (18) [8] (135 mg, 0.49 mmol) was dissolved in dry toluene (5 ml) and a solution of freshly prepared methyl dehydrovalinate [11] (100 mg, 0.78 mmol) in dry toluene (5 ml) was added and the mixture stirred at room temperature for 24 h. The solvent was removed *in vacuo* to yield an oil which was purified by preparative t.l.c. [SiO_2; EtOAc–$CHCl_3$ (1 : 1)]. A fraction, R_F 0.6, (20 mg, 13%) was a pale yellow oil with spectra which were identical to those of the oxazolone (17) prepared above.

Independent Synthesis of the Oxazole (13).—Freshly prepared methyl benzylpenaldyldehydrovalinate (20) [11] (500 mg, 1.5 mmol) was dissolved in dry re-distilled thionyl chloride (15 ml) and the solution was left overnight at room temperature. The solvent was removed *in vacuo* to yield an oil which was purified by preparative t.l.c. [SiO_2; EtOAc–$CHCl_3$ (1 : 1)] yielding an oil (40 mg, 8.5%) with ^1H n.m.r. and i.r. spectra which were identical to those of the product (13) from the photolytic reaction except for minor peaks due to impurity. The two samples had identical t.l.c. properties.

Photolysis of the Oxazolone (11).—The oxazolone (11) [4] (150 mg, 0.46 mmol) was dissolved in dry pyridine (550 ml) and the solution was degassed by the method of freeze-thaw. Nitrogen was passed through the solution for 12 h and photolysis was performed using a Hanovia 125-W medium-pressure lamp in conjunction with a Pyrex filter for 4 h

under nitrogen. The solvent was removed *in vacuo* to yield a red oil which was purified by preparative t.l.c. [SiO_2; EtOAc–$CHCl_3$ (1 : 1)]. A fraction, R_F 0.6, the *oxazole* (21), was crystallised from ether (30 mg, 23%), m.p. 122 °C, (Found: C, 68.0; H, 5.3; N, 9.85%. $C_{16}H_{14}N_2O_3$ requires C, 68.1; H, 5.0; N, 9.9%); *m/e* 282 (M^+); $\lambda_{max.}$ (MeOH) 275 (sh), 289 (sh), 297 and 309 (sh) nm (log ε 3.81, 3.97, 4.0, and 3.88); $\nu_{max.}$ ($CHCl_3$) 1 815 (sh) and 1 780 cm^{-1} (oxazolone); τ ($CDCl_3$), 7.74 (3 H, s, MeC=), 7.70 (3 H, s, MeC=), 5.90 (2 H, s, PhCH_2) 2.77 (5 H, s, aromatic), and 2.0 (1 H, s, oxazole H).

Methanolysis of the Oxazolone (21).—The above product (10 mg, 0.035 mmol) was dissolved in 1M methanolic sodium hydroxide (5 ml) and left at room temperature for 10 min, when the u.v. absorption due to the chromophore in the starting material had disappeared. The mixture was diluted with chloroform (20 ml), washed with water, and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave an oil which crystallised from cyclohexane (10 mg, 91%), m.p. 104—105 °C. This compound had spectra identical to those of the ester (13), obtained from photolysis of the acrylamide (9).

2,2-*Dimethyl*-3-*formyl*-4-*thiazoline*-4-*carboxylic Acid* (25; R = OH).—1M Aqueous sodium hydroxide (18.9 ml, 0.018 9 mol) was added to a solution of methyl 2,2-dimethyl-3-formyl-4-thiazoline-4-carboxylate (25; R = OMe) [12] (3.8 g, 0.018 9 mol) in methanol (100 ml) and the solution was left at room temperature overnight. The solvent was removed *in vacuo* and the residue was dissolved in water and extracted with chloroform. The aqueous layers were acidified with 1M aqueous hydrochloric acid and extracted with chloroform. These later extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to give a *solid* which was recrystallised from ether–pentane (2.65 g; 75%), m.p. 132—133 °C, (Found: C, 44.95; H, 5.0; N, 7.3. $C_7H_9NO_3S$ requires C, 44.9; H, 4.8; N, 7.5%); *m/e* 187 (M^+); $\lambda_{max.}$ (MeOH) 278 (sh) and 315 nm (log ε 3.62 and 3.88); $\nu_{max.}$ ($CHCl_3$) 3 200—2 500 (CO_2H) and 1 700 cm^{-1} (acid); τ ($CDCl_3$) 7.99 (6 H, s, Me_2), 2.88 (1 H, s, olefinic), 1.6 (1 H, br, CO_2H, exchanges with ^2H_2O), and 0.18 (1 H, s, CHO).

2,2-*Dimethyl*-3-*formyl*-4-*thiazoline*-4-*carboxanilide* (25; R = NHPh).—The acid (25; R = OH) (800 mg, 4.3 mmol) was dissolved in dry acetonitrile (100 ml). Triethylamine (redistilled, 0.6 ml; 4.3 mmol) was added and the solution was cooled to −35 °C. Ethyl chloroformate (redistilled, 0.41 ml, 4.3 mmol) was added and the mixture was stirred at −35 °C for 5 h. Aniline (redistilled, 0.5 g, 5.4 mmol) was added and stirring was continued at −35 °C for a further 2 h. The solution was allowed to warm to room temperature overnight, chloroform was added and the mixture was washed with 0.5 M aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and water, and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a product which was purified by preparative t.l.c. [SiO_2; EtOAc–$CHCl_3$ (1 : 1)] to give a *solid*, R_F 0.6, which was recrystallised from ether–pentane (500 mg, 45%), m.p. 128 °C (Found: C, 59.3, H, 5.2; N, 10.5. $C_{13}H_{14}N_2O_2S$ requires C, 59.5; H, 5.4; N, 10.7%); *m/e* 262 (M^+); $\lambda_{max.}$ (MeOH) 267 and 315 nm (log ε 4.08 and 3.99); $\nu_{max.}$ ($CHCl_3$) 3 410 (NH) and 1 670 cm^{-1} (amide); τ ($CDCl_3$) 8.02 (6 H, s, Me_2), 3.26 (1 H, s, olefinic), 2.5 (5 H, br m, aromatic), and 1.34 (1 H, s, CHO).

The Dipeptide (23).—Triethylamine (redistilled, 1.19 ml, 8.5 mmol) was added to a solution of 2,2-dimethyl-3-formyl-4-thiazoline-4-carboxylic acid (25; R = OH) (1.6 g, 8.5 mmol) in dry chloroform (30 ml) and dry toluene (70 ml). The solution was cooled to −50 °C, ethyl chloroformate (redistilled, 0.81 ml, 8.5 mmol) was added, and the mixture stirred for 3 h at −50 °C. Freshly prepared methyl dehydrovalinate [11] (1.3 g, 10 mmol) in dry chloroform (30 ml) was added slowly and the mixture was stirred for a further 3 h at −50 °C and 1 h at −30 °C. The solution was allowed to warm to room temperature overnight, and chloroform (100 ml) was added. The organic solution was washed with 0.5M aqueous hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and water, and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a brown oil which was purified by preparative t.l.c. [SiO_2; EtOAc–$CHCl_3$ (1 : 1)]. The solid *dipeptide* (23) was recrystallised from ether–pentane (1.2 g, 47%), m.p. 110—111 °C (Found: C, 52.2; H, 6.15; N, 9.2. $C_{13}H_{18}N_2O_4S$ requires C, 52.3; H, 6.0; N, 9.4%); *m/e* 298 (M^+); $\lambda_{max.}$ (MeOH) 265 (sh) and 310 nm (log ε 3.85 and 3.85); $\nu_{max.}$ ($CHCl_3$) 3 400 (NH) 1 710 (ester) and 1 665 cm^{-1} (amide); τ ($CDCl_3$) 8.11 (3 H, s, MeC=) 8.01 (6 H, s, Me_2), 7.81 (3 H, s, MeC=), 6.24 (3 H, s, OMe), 3.39 (1 H, br s, olefinic), 2.10 (1 H, br s, NH, exchangeable with ^2H_2O), and 1.3 (1 H, s, CHO). The starting acid (25; R = OH) (200 mg, 12%) could be recovered from the aqueous sodium hydrogencarbonate extract.

Photolysis of the Dipeptide (23).—(i) *To isolate the imine* (26). The dipeptide (23) (100 mg, 0.34 mmol) was dissolved in dry redistilled pyridine (500 ml) and degassed by the freeze-thaw method. Nitrogen was passed through the solution for 12 h and the mixture was irradiated for 6 h under nitrogen using a Hanovia 125-W medium-pressure mercury arc lamp constructed in M84 quartz. The solvent was removed *in vacuo* to yield an oil which was purified by preparative t.l.c. [SiO_2; EtOAc–$CHCl_3$ (1 : 1)]. A fraction, R_F 0.45, (14 mg, 15%) had identical properties to a sample of the imine (26) prepared by hydrolysis as described below. A further fraction, R_F 0.2 (17 mg) showed a band at $\nu_{max.}$ ($CHCl_3$) *ca.* 1 775 cm^{-1}, but could not on this occasion be purified.

(ii) *To isolate the* β-*lactam* (29). Photolysis of the dipeptide (23) (500 mg, 1.67 mmol) in pyridine (500 ml) was carried out as above using a normal Hanovia medium-pressure arc tube and a Pyrex filter. The lamp was cooled by circulating distilled water and photolysis was continued for 70 h under nitrogen. After preliminary separation as above, the fraction with $\nu_{max.}$ ($CHCl_3$) 1 780 cm^{-1} was rechromatographed on commercial plates (Merck 5 715, 0.25 mm) which had been exposed to the atmosphere for 48 h before use. The eluant was 1,4-dioxan–light petroleum (1 : 1) (100 ml) to which 0.1M aqueous ammonium acetate (1.2 ml) had been added. The *product* was recrystallised from ether–pentane, m.p. 148–150 °C (30 mg, 6%); *m/e* field-desorption 298 (M^+) and 270 (M^+ − CO); *m/e* electron impact 270.104 227 (M^+ − CO; $C_{12}H_{18}N_2O_3S$ requires 270.103 805) and 255 (M^+ − CONH); $\nu_{max.}$ ($CHCl_3$) 1 780 (β-lactam) and 1 725 cm^{-1}; τ ($CDCl_3$) 8.74 and 8.72 (6 H, 2 × s, CMe), 8.2 (3 H, s, CMe), 8.08 (3 H, s, CMe) 6.32 (3 H, s, OMe), 6.1 (1 H, s, CH), 3.02 (1 H, s, br, NH, exchangeable with ^2H_2O), and 1.71 (1 H, s, CHO).

Hydrolysis of the Dipeptide (23).—0.1M Aqueous sodium hydroxide (1 ml, 0.1 mmol) was added to a solution of the dipeptide (23) (30 mg, 0.1 mmol) in methanol (10 ml). The mixture was allowed to stand at room temperature for 48 h and the solvent was removed *in vacuo* to yield an oil which was dissolved in chloroform (10 ml). The organic solution was washed with water and dried ($MgSO_4$) and the solvent

removed *in vacuo*. The product was purified by preparative t.l.c. [SiO_2; EtOAc–$CHCl_3$ (1 : 1)] to yield the starting dipeptide (10 mg, 33%) and a compound, R_F 0.7, the imine (26) which could be purified by crystallisation from pentane at −70 °C (10 mg 37%), m.p. 48—50 °C; *m/e* 270.103 005 (M^+; $C_{12}H_{18}N_2O_3S$ requires 270.103 805); $\nu_{max.}$ ($CHCl_3$) 3 360 (NH), 1 715 (ester), and 1 680 cm^{-1} (amide); τ ($CDCl_3$) 8.26 (6 H, s, Me_2C), 8.12 (3 H, s, MeC=), 7.80 (3 H, s, MeC=), 6.23 (3 H, s, OMe), 5.69 (2 H, s, CH_2), and 1.8 (1 H, br, NH).

Formylation of the Imine (26).—The imine (20 mg, 0.074 mmol) was dissolved in freshly prepared formic acetic anhydride [16] (5 ml) and the solution was left at room temperature for 48 h. The solvent was removed *in vacuo* to yield a solid which was purified by preparative t.l.c. [SiO_2; EtOAc–$CHCl_3$ (1 : 1)] followed by crystallisation from ether–pentane (15 mg, 68%). The compound m.p. 108—110 °C had identical spectra to those of the dipeptide (23) prepared above.

2,2-Dimethyl-3-thiazoline-4-carboxanilide (27).—0.1M Aqueous sodium hydroxide (1 ml, 0.1 mmol) was added to a solution of 2,2-dimethyl-3-formyl-4-thiazoline-4-carboxanilide (26 mg, 0.1 mmol) in methanol (10 ml). The solution was left overnight at room temperature and chloroform (20 ml) was added. The organic solution was washed with water and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave oil which was purified by preparative t.l.c. [SiO_2; EtOAc–$CHCl_3$ (1 : 1)]. The fraction of R_F 0.8 was crystallised from pentane at −70 °C (20 mg, 86%), m.p. 98—100 °C (Found: C, 61.15; H, 6.2; N, 11.2%; M^+, 234.083 368. $C_{12}H_{14}N_2OS$ requires C, 61.5; H, 6.0; N, 12.0%; *M*, 234.082 680); $\lambda_{max.}$ (MeOH) 275 nm (log ε 3.76); $\nu_{max.}$ ($CHCl_3$) 3 360 (NH), and 1 680 cm^{-1} (amide); τ ($CDCl_3$) 8.27 (6 H, s, Me_2C), 5.67 (2 H, s, SCH_2), 2.7 (5 H, br m, aromatics) and 1.20 (1 H, br s, NH).

We thank the M.R.C. for financial assistance.

[1/585 *Received*, 13*th April*, 1981]

REFERENCES

[1] C. J. Veal and D. W. Young, *Tetrahedron Lett.*, 1976, 2 985.
[2] P. K. Sen, C. J. Veal, and D. W. Young, *J. Chem. Soc., Chem. Commun.*, 1977, 678.
[3] O. L. Chapman and W. R. Adams, *J. Am. Chem. Soc.*, 1968, **90**, 2 333.
[4] C. J. Veal and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1975, 2 086.
[5] R. D. G. Cooper and F. L. Jose, *J. Am Chem. Soc.*, 1970, **92**, 2 575.
[6] D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc. C*, 1971, 3 540.
[7] D. C. Cook and A. Lawson, *J. Chem. Soc., Perkin Trans. 1*, 1973, 465.
[8] J. W. Cornforth in 'The Chemistry of Penicillin,' eds. H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton University Press, Princeton, N. J., U.S.A., 1949, p. 807.
[9] D. F. Corbett and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1974, 185.
[10] C. J. Veal, D. Phil. Thesis, University of Sussex, 1974.
[11] J. Cheney, C. J. Moores, J. A. Raleigh, A. I. Scott and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1974, 986.
[12] D. W. Young, D. J. Morecombe, and P. K. Sen, *Eur. J. Biochem.*, 1977, **75**, 133.
[13] P. V. DeMarco and R. Nagarajan in 'Cephalosporins and Penicillins, Chemistry and Biology,' ed. E. H. Flynn, Academic Press, New York, 1972, p. 311 *et seq.*
[14] L. A. Paquette, G. R. Allen, and M. J. Broadhurst, *J. Am. Chem. Soc.*, 1971, **93**, 4 503.
[15] E. J. Corey and J. Streith, *J. Am. Chem. Soc.*, 1964, **86**, 950.
[16] I. Muramatsu, M. Murakami, T. Yoneda, and A. Hagitani, *Bull. Chem. Soc. Jpn.*, 1965, **38**, 244.