# Synthesis of Some 1-Oxadethiaceph-3-ems

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3-Methyl-1-oxadethiaceph-3-em-4-carboxylic acid and its 2-ethylidene analogue have been synthesised from 4-acetoxyazetidin-2-one by way of an intramolecular Wittig reaction.

INVESTIGATORS in these laboratories [1] have shown clavulanic acid, a metabolite of *Streptomyces clavuligerus* with potent β-lactamase-inhibitory and weak antibacterial activity, to have the interesting fused β-lactam structure (1). Other compounds containing the same bicyclic system were subsequently prepared in these laboratories by total synthesis.[2,3] Contemporaneously with the above synthetic studies, we decided to attempt the synthesis of compounds containing the 1-oxadethiaceph-3-em ring system (2; numbered as for cephalosporins). Our reasoning was that cephalosporins (3) show similar antibacterial properties to penicillins (5), and system (2) would stand in the same structural relationship to the basic nucleus of clavulanic acid (1) as cephalosporins (3) do towards penicillins (5).

When our work began the unsaturated bicyclic system (2) was unknown, but subsequently acylamino derivatives (4) thereof, *i.e.* 1-oxadethiacephalosporins, have been prepared [4] by total syntheses which follow different pathways from that here described.

A convenient starting material for our work was 4-acetoxyazetidin-2-one (6), which is available [5] from vinyl acetate and chlorosulphonyl isocyanate. Warming the azetidinone (6) with alcohols in the presence of magnesium powder results in nucleophilic displacement of the acetoxy group and gives 4-alkoxyazetidin-2-ones.[5] By applying a modification of this procedure, using 4 mol. equiv. of propargyl alcohol in boiling toluene as solvent, we obtained 4-(prop-2-ynyloxy)azetidin-2-one (7) which was then converted into t-butyl 3-methyl-1-oxadethiaceph-3-em-4-carboxylate (13; R = $CMe_3$) using a similar reaction sequence to that previously employed [6] to prepare cephems from 4-alkynylthioazetidin-2-ones.

The acetylene (7) was heated with t-butyl glyoxylate in benzene to give a mixture of isomeric α-hydroxy esters (8; R = $CMe_3$). Treatment with thionyl chloride then gave the mixed α-chloro esters (9; R = $CMe_3$), which with triphenylphosphine and 2,6-lutidine afforded the phosphorane (10; R = $CMe_3$). Conversion into the ketone (11; R = $CMe_3$) was brought about by treating the acetylene (10; R = $CMe_3$) with mercury(II) chloride in neat piperidine, followed by aqueous work-up. Propynyl ethers appear to be less readily hydrated than are the corresponding sulphides,[6] and the inclusion of a mercury(II) salt was essential. Completion of the 1-oxadethiacephem ring system by an intramolecular Wittig reaction occurred when the keto-phosphorane (11; R = $CMe_3$) was refluxed in dry dioxan under nitrogen for 7 h. These conditions for the formation of the cyclic compound (13; R = $CMe_3$) are surprisingly mild when compared with the temperature of 220 °C used by Bormann [7] to cyclise the sulphur analogue (12; R = Me) to an isomeric mixture of $\Delta^2$- and $\Delta^3$-cephems.

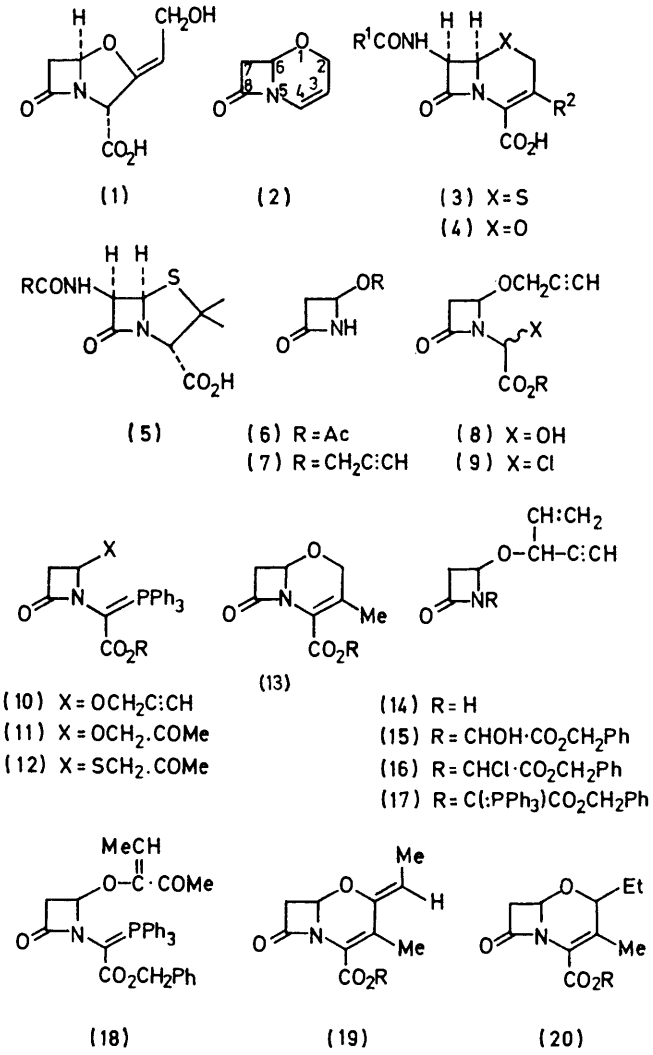
Whereas ceph-3-em-4-carboxylic acids (3) are readily obtainable by mild treatment of the t-butyl esters with trifluoroacetic acid, similar treatment of the oxa-analogue (13; R = $CMe_3$) disrupted the β-lactam. We therefore repeated the reaction sequence starting from 4-(prop-2-ynyloxy)azetidin-2-one (7) and benzyl glyoxylate, thereby obtaining benzyl 3-methyl-1-oxadethiaceph-3-em-4-carboxylate (13; R = $CH_2Ph$) in good overall yield. Hydrogenolysis in ethyl acetate using a palladium–carbon catalyst then gave the crystalline acid (13; R = H).

In order to increase the structural similarity to clavulanic acid (1) it was desirable to prepare a 2-alkylidene analogue of the acid (13; R = H). To this end 4-acetoxyazetidin-2-one (6) was treated with pent-4-en-1-yn-3-ol to give the ether (14). The condensing agent used was zinc acetate, which our colleagues [2] had meanwhile shown to be superior to magnesium powder in such displacements. The established sequence of successive treatment with benzyl glyoxylate, thionyl chloride, and triphenylphosphine then gave the phosphorane (17) by way of the intermediates (15) and (16). Hydration of the acetylene (17) with mercury(II) chloride in piperidine at room temperature overnight was accompanied by complete migration of the terminal double bond into conjugation with the newly formed carbonyl group to give the ketone (18). Cyclisation in boiling toluene then gave benzyl 2-ethylidene-3-methyl-1-oxadethiaceph-3-em-4-carboxylate (19; R = $CH_2Ph$).

Catalytic hydrogenation of the ester (19; R = $CH_2Ph$) over 10% palladium–carbon in dry tetrahydrofuran removed the benzyl group, but at the same time the exocyclic double bond was reduced and the product

[1] T. T. Howarth, A. G. Brown, and T. J. King, *J.C.S. Chem. Comm.*, 1976, 266.
[2] A. G. Brown, D. F. Corbett, and T. T. Howarth, *J.C.S. Chem. Comm.*, 1977, 359.
[3] P. H. Bentley, P. D. Berry, G. Brooks, M. L. Gilpin, E. Hunt, and I. I. Zomaya, *J.C.S. Chem. Comm.*, 1977, 748; P. H. Bentley, G. Brooks, M. L. Gilpin, and E. Hunt, *ibid.*, p. 905; E. Hunt, P. H. Bentley, G. Brooks, and M. L. Gilpin, *ibid.*, p. 906.
[4] L. D. Cama and B. G. Christensen, *J. Amer. Chem. Soc.*, 1974, **96**, 7582; S. Wolfe, J. B. Ducep, K. C. Tin, and S. L. Lee, *Canad. J. Chem.*, 1974, **52**, 3996.
[5] K. Clauss, D. Grimm, and G. Prossel, *Annalen*, 1974, 539.
[6] J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1973, 58; J. H. C. Nayler, N. F. Osborne, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1976, 1615.
[7] D. Bormann, *Annalen*, 1974, 1391.

was 2-ethyl-3-methyl-1-oxadethiaceph-3-em-4-carboxylic acid (20; R = H). When the catalyst was changed to 5% palladium–barium sulphate the exocyclic double bond was attacked before the benzyl ester function, the main product being benzyl 2-ethyl-3-methyl-1-oxadethiaceph-3-em-4-carboxylate (20; R = $CH_2Ph$). The preparation of the 2-ethylidene acid (19; R = H) was




finally achieved by base hydrolysis of the ester (19; R = $CH_2Ph$) using lithium hydroxide in aqueous tetrahydrofuran at pH 12.

Nuclear Overhauser effects (NOE) [8] were used to establish the stereochemistry of the 2-ethylidene group. Studies on the benzyl ester (19; R = $CH_2Ph$) were inconclusive owing to the similar chemical shifts of the olefinic proton and the benzylic methylene signals. However, in the acid (19; R = H) the vinyl proton signal showed a 27% increase in intensity when the 3-methyl group was irradiated, indicating that the double bond has the *Z*-configuration.

Neither the acid (13; R = H) nor its 2-ethylidene analogue (19; R = H) showed significant activity as an inhibitor of various β-lactamases, and both were devoid of antibacterial activity.

## EXPERIMENTAL

I.r. spectra were recorded for solutions in chloroform unless stated otherwise. $^1H$ N.m.r. spectra were recorded on a Varian A-60 instrument for solutions in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise. Mass spectra were determined with an A.E.I. MS9 machine. Merck silica gel GF 254 was used for t.l.c. and Merck silica gel H for column chromatography, with ethyl acetate–light petroleum as eluant. Light petroleum refers to the fraction of b.p. 60—80 °C. M.p.s were determined with a Kofler hot-stage apparatus. All the compounds are racemic.

4-(*Prop-2-ynyloxy*)*azetidin-2-one* (7).—4-Acetoxyazetidin-2-one [5] (6) (12.92 g), prop-2-ynyl alcohol (20 g), and magnesium powder (2.56 g) were stirred under reflux in dry toluene (120 ml) for 30 h. The cooled mixture was filtered through Kieselguhr and the filtrate evaporated. Chromatography afforded the *azetidin-2-one* (7) (6.1 g), which slowly crystallised, m.p. 35—36°, $\nu_{max.}$ 3 305, 3 205, and 1 770 $cm^{-1}$; δ 2.57 (1 H, t, *J* 2.5 Hz), 2.7—3.47 (2 H, m, collapses to ABq at 2.88 and 3.22, *J* 16 Hz, showing further coupling of 1.5 and 3.5 Hz, respectively, on $D_2O$ exchange), 4.3 (2 H, d, *J* 2.5 Hz), 5.28 (1 H, dd, *J* 1.5 and 3.5 Hz), and 7.1br (1 H, s, exchanges) (Found: C, 57.4; H, 5.8; N, 10.9. $C_6H_7NO_2$ requires C, 57.6; H, 5.6; N, 11.2%).

*Esters of* 1-(1-*Carboxy*-1-*hydroxymethyl*)-4-(*prop*-2-*ynyloxy*)*azetidin*-2-*one* (8).—The azetidinone (7) (930 mg) and t-butyl glyoxylate monohydrate (11 g) were refluxed in benzene (250 ml) with provision for the removal of water. After 3 h the solvent was evaporated and the product chromatographed to give the t-butyl α-hydroxy-ester (8; R = $CMe_3$) (mixture of isomers) (1.13 g), as a gum, $\nu_{max.}$ 3 420, 3 240, 1 770, and 1 735 $cm^{-1}$. The product was slightly contaminated with t-butyl glyoxylate monohydrate which could not be removed even by repeated chromatography.

Similar reaction of the azetidinone (7) (4.4 g) with benzyl glyoxylate monohydrate (14 g) afforded 1-(1-benzyloxycarbonyl-1-hydroxymethyl)-4-(prop-2-ynyloxy)azetidin-2-one (8; R = $CH_2Ph$) (10.3 g; mixed isomers) as a gum, $\nu_{max.}$ 3 420, 3 220, 1 770, and 1 745 $cm^{-1}$.

*Esters of* 1-(1-*Carboxy*-1-*triphenylphosphoranylidenemethyl*)-4-(*prop*-2-*ynyloxy*)*azetidin*-2-*one* (10).—A solution of the α-hydroxy-ester (8; R = $CMe_3$) (2.16 g) in dry tetrahydrofuran (50 ml) was cooled to −15 °C and treated with dry 2,6-lutidine (2.62 g), followed during 5—10 min by thionyl chloride (2.87 g) in tetrahydrofuran (20 ml). After 15 min a precipitate was removed and the filtrate evaporated to leave the α-chloro-ester (9; R = $CMe_3$) as a gum. The latter was dissolved in freshly distilled dioxan (50 ml) and treated under nitrogen with triphenylphosphine (4.2 g) and 2,6-lutidine (1.75 g) and the mixture was heated at 50 °C for 15 h, cooled, and filtered. The filtrate was evaporated and the residue taken up in ethyl acetate and washed successively with very dilute hydrochloric acid, brine, aqueous sodium hydrogencarbonate, and brine again. The organic layer was separated, dried, and evaporated, and the

[8] F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, 1965, **87**, 5250; R. A. Bell and J. K. Saunders, *Canad. J. Chem.*, 1968, **46**, 3421; G. V. Kaiser, C. W. Ashbrook, T. Goodson, I. G. Wright, and E. M. Van Heyningen, *J. Medicin. Chem.*, 1971, **14**, 426.

residue purified by chromatography to give the *phosphorane* (10; R = $CMe_3$) as a white solid, $\nu_{max.}$ 3 225, 1 750, and 1 630br $cm^{-1}$ (Found: C, 71.9; H, 5.8; N, 2.9; P, 6.0. $C_{30}H_{30}NO_4P$ required C, 72.1; H, 6.0; N, 2.8; P, 6.2%).

Similarly the α-hydroxy-ester (8; R = $CH_2Ph$) (10 g) was converted into 1-(1-*benzyloxycarbonyl*-1-*triphenylphosphoranylidenemethyl*)-4-(*prop*-2-*ynyloxy*)*azetidin*-2-*one* (10; R = $CH_2Ph$). In this case most of the product (12.6 g) was crystallised from the crude reaction mixture. A further quantity (2.2 g) was obtained by chromatography of the mother liquors. It had m.p. 144—146° (from ethyl acetate–light petroleum), $\nu_{max.}$ 3 180, 1 753, and 1 642 $cm^{-1}$ (Found: C, 74.2; H, 5.3; N, 2.6; P, 5.9. $C_{33}H_{28}NO_4P$ requires C, 74.3; H, 5.3; N, 2.6; P, 5.8%).

*Ester of* 4-(*Acetonyloxy*)-1-(1-*carboxy*-1-*triphenylphosphoranylidenemethyl*)*azetidin*-2-*one* (11).—The acetylenic phosphorane (10; R = $CMe_3$) (499 mg) and mercury(II) chloride (544 mg) were suspended in piperidine (10 ml). The mixture was stirred at room temperature for 45 min and then the solvent was evaporated. The residue was treated with ethyl acetate–water and the residual solid removed by filtering through Kiselguhr. The organic layer was separated and washed successively with very dilute hydrochloric acid, brine, aqueous sodium hydrogencarbonate, and brine again, then dried, and evaporated. The residue was purified by chromatography to give the amorphous phosphorane (11; R = $CMe_3$) (246 mg), $\nu_{max.}$ 1 750, 1 730sh, 1 715sh, and 1 630br $cm^{-1}$.

Using the same procedure the corresponding benzyl derivative (11; R = $CH_2Ph$) (8.3 g) was converted into amorphous 4-(acetonyloxy)-1-(1-benzyloxycarbonyl-1-triphenylphosphoranylidenemethyl)azetidin-2-one (11; R = $CH_2Ph$) (7.5 g), $\nu_{max.}$ 1 750, 1 730sh, 1 710, and 1 615br $cm^{-1}$.

*Esters of* 3-*Methyl*-1-*oxadethiaceph*-3-*em*-4-*carboxylic Acid* (13).—A solution of the ketone (11; R = $CMe_3$) (235 mg) in dry dioxan (10 ml) was refluxed under nitrogen for 7 h, cooled, and evaporated. Chromatography of the residue gave the *oxacephem* (13; R = $CMe_3$) (85 mg), m.p. 103—104° (from light petroleum), $\nu_{max.}$ (Nujol) 1 765, 1 715, and 1 642 $cm^{-1}$; δ 1.56 (9 H, s), 1.95 (3 H, s), 2.76 and 3.35 (2 H, ABq, *J* 18 Hz, each arm showing further coupling of *ca.* 1 and *ca.* 3 Hz, respectively), 4.24 (2 H, s), and 4.95 (1 H, dd, *J ca.* 1 and *ca.* 3 Hz) (Found: C, 60.3; H, 7.4; N, 5.9. $C_{12}H_{17}NO_4$ requires C, 60.3; H, 7.1; N, 5.9%).

Similar treatment of the keto-phosphorane (11; R = $CH_2Ph$) (7.5 g) provided *benzyl* 3-*methyl*-1-*oxadethiaceph*-3-*em*-4-*carboxylate* (13; R = $CH_2Ph$) (2.7 g), m.p. 96—97° (ethyl acetate–light petroleum), $\lambda_{max.}$(EtOH) 262 nm (ε 5 265); $\nu_{max.}$ (Nujol) 1 764, 1 718, and 1 638 $cm^{-1}$; δ 2.00 (3 H, s), 2.87 and 3.40 (2 H, ABq, *J* 15 Hz, each arm showing further coupling of *ca.* 1 and *ca.* 3 Hz, respectively), 4.33 (2 H, s), 4.99 (1 H, dd, *J ca.* 1 and *ca.* 3 Hz), 5.35 (2 H, s), and 7.4—7.7 (5 H, m) (Found: C, 65.8; H, 5.5; N, 5.0. $C_{15}H_{15}NO_4$ requires C, 65.9; H, 5.5; N, 5.1%).

3-*Methyl*-1-*oxadethiaceph*-3-*em*-4-*carboxylic Acid* (13; R = H).—(a) The t-butyl ester (13; R = $CMe_3$) (25 mg) was dissolved in anhydrous trifluoroacetic acid (0.5 ml). After 5 min the solution was evaporated, the residue treated with toluene, and the mixture re-evaporated (× 2). The i.r. spectrum of the total product showed complete loss of β-lactam.

(b) The benzyl ester (13; R = $CH_2Ph$) (0.30 g) was dissolved in ethyl acetate (25 ml) and hydrogenolysed over 10% Pd–C (0.03 g) to give the required *acid* (13; R = H) (0.19 g), m.p. 163—165° (ethyl acetate–light petroleum); $\lambda_{max.}$(EtOH) 258 nm (ε 8 100); $\nu_{max.}$ (Nujol) 3 000br, 1 766br, 1 695, and 1 630 $cm^{-1}$; δ[$CDCl_3$–$(CD_3)_2SO$] 2.01 (3 H, s), 2.85 and 3.45 (2 H, ABq, *J* 16 Hz, each arm coupled by *ca.* 1 and 3.5 Hz, respectively), 4.36 (2 H, s), 5.04 (1 H, dd, *J ca.* 1 and 3.5 Hz), 8.30br (1 H, s, exchanges) (Found: C, 52.2; H, 5.2; N, 7.7. $C_8H_9NO_4$ requires C, 52.5; H, 4.9; N, 7.7%).

4-(1-*Vinylprop*-2-*ynyloxy*)*azetidin*-2-*one* (14).—4-Acetoxyazetidin-2-one (6) (2.58 g), pent-4-en-1-yn-3-ol (4.8 g), and powdered zinc acetate dihydrate (2.2 g) were stirred under reflux in benzene (20 ml), with provision for the removal of water. After 16 h the cooled mixture was filtered through Kieselguhr and the filtrate evaporated. Chromatography gave the *azetidin*-2-*one* (14) (2.4 g) as a gum, $\nu_{max.}$ (film) 3 280, 1 762, and 1 642 $cm^{-1}$; δ 2.67 (1 H, m), 2.76 and 3.11 (2 H, ABq, *J* 15 Hz, each arm of higher field part shows further coupling of *J* 1.5 Hz; each arm of lower field part shows further coupling of *J* 3 and 2.5 Hz, but only *J* 3 Hz on $D_2O$ exchange), 4.74 (2 H, m), 5.2—6.1 (3 H, m, typical 'vinyl' system), 7.3br (1 H, s, exchanges) (Found: C, 63.4; H, 6.2; N, 9.1. $C_8H_9NO_2$ requires C, 63.6; H, 6.0; N, 9.3%).

1-(1-*Benzyloxycarbonyl*-1-*hydroxymethyl*)-4-(1-*vinylprop*-2-*ynyloxy*)*azetidin*-2-*one* (15).—Treatment of the azetidinone (14) (3 g) with benzyl glyoxylate (7.0 g) as described for (8; R = $CH_2Ph$) provided the α-hydroxy-ester (15) (7.4 g), $\nu_{max.}$ 3 400, 3 250, 1 770, and 1 745 $cm^{-1}$.

1-(1-*Benzyloxycarbonyl*-1-*triphenylphosphoranylidenemethyl*)-4-(1-*vinylprop*-2-*ynyloxy*)*azetidin*-2-*one* (17).—The α-hydroxy-ester (15) (7.4 g) was converted into the phosphorane (17) (6.5 g) as described for (10; R = $CH_2Ph$), $\nu_{max.}$ 3 250, 1 756, and 1 618br $cm^{-1}$.

1-(1-*Benzyloxycarbonyl*-1-*triphenylphosphoranylidenemethyl*)-4-[(Z)-1-*ethylideneacetonyloxy*]*azetidin*-2-*one* (18).—Reaction of the phosphorane (17) (4.5 g) with mercury(II) chloride (4.6 g) in piperidine (50 ml) at room temperature for 17 h as described for (11; R = $CH_2Ph$) gave the αβ-unsaturated ketone (18) (2.4 g), $\nu_{max.}$ 1 755, 1 678 (αβ-unsaturated CO), and 1 620br $cm^{-1}$.

*Benzyl* (Z)-2-*Ethylidene*-3-*methyl*-1-*oxadethiaceph*-3-*em*-4-*carboxylate* (19; R = $CH_2Ph$).—A solution of the keto-phosphorane (18) (2.4 g) in dry toluene (150 ml) was refluxed under nitrogen for 9.5 h, cooled, and evaporated. Chromatography of the residue provided the *oxacephem* (19; R = $CH_2Ph$) (977 mg), m.p. 105° (ethyl acetate–light petroleum), $\lambda_{max.}$(EtOH) 310 nm (ε 19 400); $\nu_{max.}$ 1 778, 1 708, and 1 620 $cm^{-1}$; δ 1.75 (3 H, d, *J* 7 Hz), 2.14 (3 H, s), 2.92 and 3.33 (2 H, ABq, *J* 16 Hz, showing further coupling of *ca.* 1.5 and 3 Hz respectively), 5.05 (1 H, d d, *J ca.* 1.5 and 3 Hz), 5.25 (2 H, s), 5.39 (1 H, q, *J* 7 Hz), and 7.2—7.5 (5 H, m) (Found: C, 68.2; H, 5.7; N, 4.4. $C_{17}H_{17}NO_4$ requires C, 68.2; H, 5.6; N, 4.7%).

2-*Ethyl*-3-*methyl*-1-*oxadethiaceph*-3-*em*-4-*carboxylic Acid* (20; R = H).—The lactam (19; R = $CH_2Ph$) (220 mg) was hydrogenated over 10% Pd–C (72 mg) in tetrahydrofuran (10 ml) for 10 min. The catalyst was removed by filtration through Kieselguhr and the filtrate evaporated. Trituration of the residue with ether afforded the *acid* (20; R = H) (60 mg), m.p. 124—125° (ether–light petroleum), $\lambda_{max.}$(EtOH) 257 nm (ε 6 800); $\nu_{max.}$ (Nujol) 1 765, 1 713, and 1 629 $cm^{-1}$; δ 0.97 (3 H, t, *J* 7 Hz), 1.5—2.1 (2 H, m), 2.05 (3 H, s), 2.93 and 3.43 (2 H, ABq, *J* 16 Hz, showing further coupling of 1 and 3.5 Hz, respectively), 4.4 (1 H, m), 5.1 (1 H, dd, *J* 1 and 3.5 Hz), and 10.8 (1 H, s, exchanges) (Found: C, 56.3; H, 6.4; N, 6.5%; $M^+$, 211.086 3.

$C_{10}H_{13}NO_4$ requires C, 56.9; H, 6.2; N, 6.6%; *M*, 211.084 4).

*Benzyl 2-Ethyl-3-methyl-1-oxadethiaceph-3-em-4-carboxylate* (20; R = $CH_2Ph$).—(a) The lactam (19; R = $CH_2Ph$) (220 mg) was hydrogenated over 10% Pd–C (72 mg) as previously described. The total crude product was dissolved in dry dimethylformamide (5 ml) containing benzyl bromide (250 mg) and anhydrous potassium carbonate (140 mg). The mixture was stirred at room temperature for 24 h and then poured into ethyl acetate–brine. The organic layer was separated, washed with water, dried, and evaporated. Chromatography gave the dihydrobenzyl ester (20; R = $CH_2Ph$) (120 mg) as a gum, $\nu_{max.}$ 1 782, 1 720, and 1 627 $cm^{-1}$; δ 0.93 (3 H, t, *J* 7 Hz), 1.43—2.03 (2 H, m), 1.93 (3 H, s), 2.83 and 3.33 (2 H, ABq, *J* 16 Hz, showing further coupling of 1 and 3.5 Hz, respectively), 4.28 (1 H, m), 5.0 (1 H, dd, *J* 1 and 3.5 Hz), 5.33 (2 H, s), and 7.4 (5 H, s) (Found: $M^+$, 301.134 0. $C_{17}H_{19}NO_4$ requires *M*, 301.131 4).

(b) The lactam (19; R = $CH_2Ph$) (224 mg) was hydrogenated over 5% Pd–$BaSO_4$ (78 mg) in tetrahydrofuran (10 ml) for 20 min. The catalyst was removed by filtration through Kieselguhr and the filtrate evaporated. The residue (183 mg) was triturated with ether to give the dihydro-acid (20; R = H) (30 mg). Chromatography of the mother liquors afforded the dihydrobenzyl ester (20; R = $CH_2Ph$) (111 mg), identical to that obtained in (a).

(Z)-2-*Ethylidene*-3-*methyl*-1-*oxadethiaceph*-3-*em*-4-*carboxylic Acid* (19; R = H).—The benzyl ester (19; R = $CH_2Ph$) (60 mg) dissolved in dry tetrahydrofuran (20 ml) was added to water (20 ml) in a pH stat, to give a homogeneous solution. The pH was raised to 9.5 using 1M-lithium hydroxide but no reaction took place. However when the pH was increased to 12, uptake of base slowly commenced. The titration was stopped when an excess of base had been consumed (0.26 ml). The tetrahydrofuran was evaporated, ethyl acetate added, and the mixture shaken. The organic layer was discarded and the aqueous solution layered with ethyl acetate. The mixture was cooled to *ca.* 5 °C and vigorously stirred. The pH was lowered to *ca.* 2 using 0.1N-hydrochloric acid and the organic layer separated, washed with brine, dried, and evaporated. The residue was triturated with ether to give the *acid* (19; (R = H) (8 mg), m.p. 152—154°, $\lambda_{max.}$(EtOH) 296 nm (ε 14 600); $\nu_{max.}$ 2 400—3 500br, 1 780, 1 700br(sh), and 1 630 $cm^{-1}$; δ 1.75 (3 H, d, *J* 8 Hz), 2.19 (3 H, s), 2.98 and 3.36 (2 H, ABq, *J* 17 Hz, showing further coupling of *ca.* 1 and 3 Hz), 5.06 (1 H, dd, *J* *ca.* 1 and 3 Hz), 5.43 (1 H, q, *J* 8 Hz), and 7.91br (1 H, s, exchanges) (Found: $M^+$, 209.069 4. $C_{10}H_{11}NO_4$ requires *M*, 209.068 8).

Rebenzylation of another sample (19; R = H) (20 mg) in dimethylformamide (1 ml) containing benzyl bromide (34 mg) and anhydrous potassium carbonate (27 mg) gave the benzyl ester (19; R = $CH_2Ph$), identical in all respects with an authentic sample.

[8/048 *Received*, 12*th January*, 1978]