Syntheses based on 1,2-Secopenicillins. Part III.[1] Hydration of 4-(3-Substituted Prop-2-ynylthio)azetidin-2-ones and a New Cephalosporin Synthesis

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Addition of secondary amines to the triple bond of 4-(3-substituted prop-2-ynylthio)azetidin-2-ones or the derived sulphoxides, followed by very ready hydrolysis of the resulting enamines, provides a convenient route to the corresponding β-oxo-sulphides and -sulphoxides. Generation of the carbonyl group in this way, followed by an intramolecular Wittig reaction to close the dihydrothiazine ring, leads to a new synthesis of cephalosporins, illustrated by the preparation of an antibacterially active isostere of cephaloridine.

A PROJECTED synthesis of cephalosporins (1) required as intermediates ketones of type (2). We describe here the preparation of such ketones by hydration [2] of the triple bond of the acetylenic precursors (3) reported in the preceding paper.[1] Utilisation of the hydration step in a synthesis of a representative cephalosporin is also described.[3]

The most usual method of adding the elements of water to the acetylenic bond is treatment with aqueous acid in the presence of mercury(II) ions. Complications were anticipated in applying such conditions to compounds containing the acid-labile tritylamino-group, so the readily available [1] model compound (4) was treated with toluene-*p*-sulphonic acid to give the primary amine (5), which with phenoxyacetyl chloride afforded the acid-stable amide (6). Treatment of the latter with mercury(II) sulphate and dilute sulphuric acid in boiling methanol for 1 h gave a 70% yield of the desired ketone (7), but this procedure failed with compounds (3) in which the acetylene function was non-terminal.

The search for a potentially more versatile procedure for hydrating the triple bond led us to try treatment with mercury(II) chloride in piperidine, previously used [4] to prepare steroidal ketones. These non-acidic conditions had the attraction of being directly applicable to tritylamino-compounds, and treatment of the acetylene (4) with mercury(II) chloride in piperidine for 1 h at room temperature gave the ketone (9a) in 90% yield. This conversion proceeded smoothly even when all moisture was excluded from the original reaction mixture, suggesting that the primary reactant was piperidine and that the resulting enamine underwent very ready hydrolysis to the ketone (9a) during work-up (which did not require the recommended [4] use of hydrogen sulphide). This reasoning led us in turn to question the role of the mercury(II) salt; experiments showed that it could in fact be omitted, although the mixture then needed to be refluxed. Alternatively, if the isomeric allene (8) [1] was used in place of the acetylene (4), reaction with piperidine occurred during 22 h at room temperature with or without mercury(II) chloride. In all these experiments pyrrolidine or morpholine could be used instead of piperidine.

Ketone formation by way of secondary amine addition also proved to be applicable to a number of non-terminal acetylenes. Thus the phenylacetylene (10b), refluxed for 2 h in piperidine, gave a high yield of the ketone (9b), and in this case inclusion of mercury(II) chloride did not permit the use of any milder conditions. Hence in the remaining experiments described here use of mercury

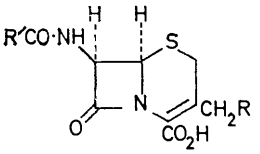
[1] Part II, M. A. Harris, I. McMillan, J. H. C. Nayler, N. F. Osborne, M. J. Pearson, and R. Southgate, preceding paper.

[2] Preliminary report, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1973, 57.

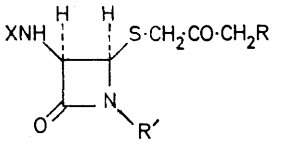
[3] Preliminary report, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1973, 58.

[4] H. B. Kagan, A. Marquet, and J. Jacques, *Bull. Soc. chim. France*, 1960, 1079.

compounds was discontinued. When the acetylene (10b) was heated in pyrrolidine and the mixture was then



(1)



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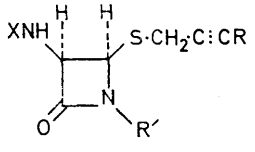

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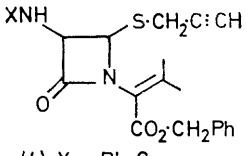
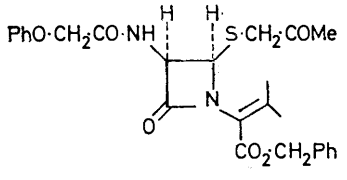


(4) X = Ph_3C
(5) X = H
(6) X = PhO·CH_2CO



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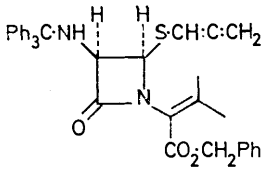

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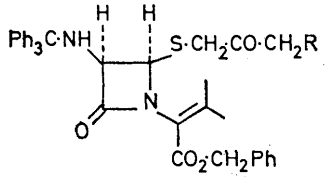

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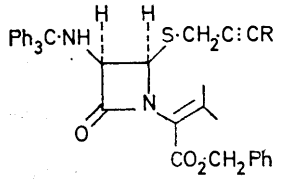


(10)

a; R = H b; R = Ph c; R = 3-pyridyl d; R = $C_6H_4CO_2Me-p$
e; R = $C_6H_4NO_2-p$ f; R = Me g; R = CH_2Ph

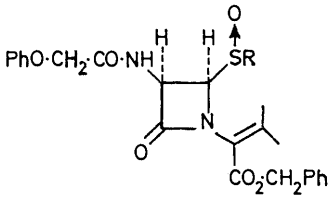
evaporated, the residue showed strong i.r. absorption at 1 560 cm^{-1} indicative of an enamine, but chromatography on silica gel sufficed to cause conversion into the ketone (9b).

Amine addition was facilitated when the terminal substituent (R) on the propynyl group had electron-withdrawing properties. Thus only 1 h in refluxing piperidine, followed by the usual work-up, was required to convert the 3-pyridyl compound (10c) into the ketone (9c). Reaction was even easier with the *p*-methoxycarbonyl- and *p*-nitro-phenyl compounds (10d and e), occurring in piperidine at room temperature during 3 and 1 h, respectively. On the other hand, electron-releasing R groups markedly reduced reactivity, so that the but-2-ynyl and 4-phenylbut-2-ynyl sulphides (10f and g) did not react with piperidine even under forcing conditions.

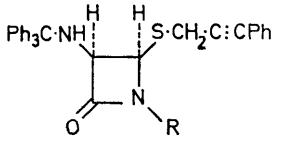
The problem of achieving addition to the triple bond even when the R group had a deactivating effect was overcome by first oxidising the sulphides to the corresponding sulphoxides with *m*-chloroperbenzoic acid. Addition of piperidine to these acetylenic sulphoxides occurred readily at room temperature, and reduction of the appropriate β-oxo-sulphoxide to the desired sulphide (9f) was effected with triphenylphosphine and acetyl chloride.

Further information on the nature of the amine addition was gained by studying the behaviour of the acetylenic sulphoxide (11) with various amines. The ketone (12) was formed most readily by using either cyclic or acyclic saturated secondary aliphatic amines or unhindered primary aliphatic amines, and more slowly with diallylamine or t-butylamine. Aniline was not satisfactory. In the case of volatile amines, work-up by simple evaporation afforded the enamine intermediates.

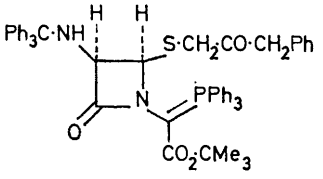
The relative slowness of the addition with t-butylamine permitted the identification of a further intermediate between the acetylene (11) and the enamine (14). The main product after a short reaction period was the allene (13), also obtained by treating the acetylene with



(11) R = $CH_2C{:}CH$
(12) R = CH_2COMe
(13) R = $CH{:}C{:}CH_2$
(14) R = $CH{:}CMe{\cdot}NH{\cdot}CMe_3$



(15) R = H
(16) R = $CH(OH){\cdot}CO_2CMe_3$
(17) R = $CHCl{\cdot}CO_2CMe_3$
(18) R = $C(:PPh_3){\cdot}CO_2CMe_3$



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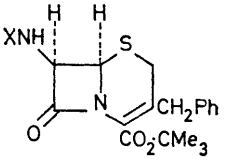
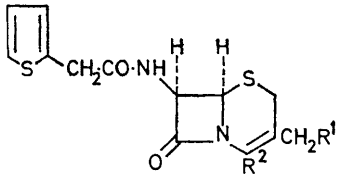


(20) X = Ph_3C
(21) X = H
(22) X = 2-thienylacetyl



(23) R^1 = Ph, R^2 = CO_2H
(24) R^1 = OAc, R^2 = CO_2H
(25) R^1 = pyridinio, R^2 = CO_2^-

triethylamine; longer reaction with t-butylamine gave the enamine (14).

The general reaction sequence for the conversion of

prop-2-ynyl sulphoxides into β-oxo-sulphoxides by treatment with primary or secondary amines therefore appears to be (i) base-promoted isomerisation to the allene, (ii) nucleophilic addition of amine to the central carbon atom of the allene system, and (iii) hydrolysis of the resulting enamine during work-up. Whether the same sequence holds for the reactive prop-2-ynyl sulphides is less certain, since we were unable to demonstrate isomerisation of such compounds to allenes by use of triethylamine. Nevertheless, simple prop-2-ynyl sulphides are converted into allenes by strong bases,[5] and participation of an allene intermediate would explain why, in both the sulphide and sulphoxide series, the carbonyl groups in our end-products were invariably β to sulphur.

With a simple method established for preparing ketones of type (2) from acetylenes (3), it remained to incorporate this key step into a new conversion of penicillins into cephalosporins. We here illustrate the procedure devised by describing the formation of a novel cephalosporin, 3-benzyl-7β-(2-thienylacetamido)ceph-3-em-4-carboxylic acid (23). In the event it proved advantageous to leave the acetylenic function intact until a late stage in the synthesis.

The azetidinone (15) [1] was accordingly subjected to a sequence of reactions used by Scartazzini and his coworkers [6,7] in a different approach to cephems lacking any 3-substituent. Thus condensation with an excess of t-butyl glyoxylate in refluxing benzene gave the α-hydroxy-ester (16), which with thionyl chloride afforded the α-chloro-ester (17), both products being mixtures of isomers. Treatment with triphenylphosphine and 2,6-lutidine then gave the stable phosphorane (18), at which point it was convenient to introduce the carbonyl function. The acetylene (18) was accordingly refluxed with piperidine to yield the readily isolable ketone (19) which, unlike a related aldehyde,[7] showed no tendency to cyclise spontaneously. Indeed the desired intramolecular Wittig condensation required refluxing in dioxan for 25 h, but then gave the cephem (20) in excellent yield. The latter was readily detritylated with toluene-*p*-sulphonic acid, and acylation of the resulting primary amine (21) then gave the amide (22). Finally, brief treatment with trifluoroacetic acid removed the t-butyl group and gave the new cephalosporin (23). The optical activity of this compound, and the characteristic ^{1}H n.m.r. pattern for *cis*-coupled β-lactam protons [8] shown by it and all its precursors, confirmed that the stereochemistry about the β-lactam ring had been maintained throughout the entire synthesis from 6-aminopenicillanic acid.

Antibacterial tests by Mr. R. Sutherland and his colleagues showed that against most Gram-positive bacteria the new product (23) possessed activity similar to those of typical marketed cephalosporins such as cephalothin (24) and cephaloridine (25). It was, however, slightly less effective than cephalothin against β-lactamase-producing staphylococci, in which respect it resembles cephaloridine, with which it is isosteric. The benzyl compound (23) was distinctly less active than both cephalothin and cephaloridine against Gram-negative bacteria.

The synthesis described here is of considerable generality and has been used to prepare cephalosporins (1) containing a variety of groups R and R′. Details of some of these are in a patent.[9]

EXPERIMENTAL

General experimental procedures were as outlined in Part I.[10]

(3R,4R)-3-*Amino*-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(*prop*-2-*ynylthio*)*azetidin*-2-*one* (5) *Toluene*-p-*sulphonate Salt*.—A solution of the 3-(triphenylmethylamino)-azetidinone (4) [1] (8.52 g) in acetone (20 ml) was cooled to −20 °C and toluene-*p*-sulphonic acid (3.03 g) in acetone (10 ml) was added during 5 min. The mixture was kept at 0° overnight and fine needles of the *toluene*-p-*sulphonate salt* were collected (6.48 g), m.p. 175—179° (from acetone–ether), $\nu_{max.}$ (Nujol) 1 780, 1 685, and 1 625 cm^{-1}, δ [$(CD_3)_2SO$] 1.98 (3 H, s), 2.21 (3 H, s), 2.3 (3 H, s), 3.16 (1 H, t, *J* 2.5 Hz), 3.5 (2 H, d, *J* 2.5 Hz), 4.95 (1 H, d, *J* 5 Hz), 5.25 (2 H, s), 5.43 (1 H, d, *J* 5 Hz), and 7.0—7.7 (9 H, m) (Found: C, 57.7; H, 5.7; N, 5.3; S, 12.6. $C_{25}H_{28}N_2O_6S_2$ requires C, 57.9; H, 5.8; N, 5.4; S, 12.4%).

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*-3-*phenoxyacetamido*-4-(*prop*-2-*ynylthio*)*azetidin*-2-*one* (6).—The toluene-*p*-sulphonate salt of (5) (2.58 g) was stirred in dry methylene chloride with cooling while triethylamine (2.2 g) was added, then phenoxyacetyl chloride (950 mg) in methylene chloride (10 ml) was added at −20 °C. After 5 min the mixture was washed with water, dried, and evaporated. Chromatography of the residue gave the *phenoxyacetamide* (6) (1.85 g), amorphous, $\nu_{max.}$ 3 375, 3 260, 1 768, 1 720, 1 690, and 1 630 cm^{-1}; δ 2.07 (3 H, s), 2.11 (1 H, t, *J* 5 Hz), 2.30 (3 H, s), 3.08 (2 H, d, *J* 2.5 Hz), 4.58 (2 H, s), 5.09 and 5.33 (2 H, ABq, *J* 12 Hz), 5.43 (2 H, m), and 6.8—7.5 (11 H, m) (Found: M^+, 478.1571. $C_{26}H_{26}N_2O_5S$ requires *M*, 478.1562).

(3R,4R)-4-*Acetonylthio*-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-(*phenoxyacetamido*)*azetidin*-2-*one* (7).—The acetylene (6) (638 mg) was dissolved in methanol (10 ml) and water (1 ml) was added. A saturated solution of mercury(II) sulphate in dilute sulphuric acid (0.4 ml) was added and the mixture refluxed with stirring for 1 h, cooled, and poured into ethyl acetate. The solution was washed with water until the washings were no longer acidic, then dried and evaporated to a gum. Chromatography gave the amorphous *ketone* (7) (449 mg), $\nu_{max.}$ 3 360, 1 770, 1 720, 1 705, 1 690, and 1 630 cm^{-1}; δ 2.07 (3 H, s), 2.10 (3 H, s), 2.28 (3 H, s) 3.12 (2 H, s), 4.58 (2 H, s), 5.1 and 5.35 (2 H, ABq, *J* 12 Hz), 5.1—5.43 (2 H, m), and 6.8—7.5 (11 H, m) (Found: M^+, 496.1686. $C_{26}H_{28}N_2O_6S$ requires *M*, 496.1668).

[5] C. J. M. Stirling, *J. Chem. Soc.*, 1964, 5856.
[6] R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, 1972, **55**, 408.
[7] R. Scartazzini and H. Bickel, *Helv. Chim. Acta*, 1972, **55**, 423.
[8] K. D. Barrow and T. M. Spotswood, *Tetrahedron Letters*, 1965, 3325; G. F. H. Green, J. E. Page, and S. E. Staniforth, *J. Chem. Soc.*, 1965, 1595.
[9] J. H. C. Nayler, M. J. Pearson, and R. Southgate, B.P. 1,405,758/1975.
[10] E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1976, 447.

(3R,4R)-4-*Acetonylthio*-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (9a).—(*a*) The acetylene (4) (586 mg) and mercury(II) chloride (544 mg) were stirred in piperidine (4.5 ml) at room temperature for 1 h. The mixture was washed through kieselguhr with ethyl acetate and water. The organic layer was separated, washed with 0.1N-hydrochloric acid and brine, dried, and evaporated. Chromatography gave the amorphous *ketone* (9a) (534 mg), $\nu_{max.}$ 1 760, 1 710, and 1 620 cm^{-1}; δ 1.98 (3 H, s), 2.02 (3 H, s), 2.22 (3 H, s), 2.53 and 2.86 (2 H, ABq, *J* 15 Hz), 2.94br (1 H, s, exch.), 4.53 (1 H, m, collapsing to d, *J* 5 Hz, on D_2O exch.), 4.65 (1 H, d, *J* 5 Hz), 5.0 and 5.25 (2 H, ABq, *J* 12 Hz), and 7.1—7.6 (20 H, m) (Found: C, 73.5; H, 6.1; N, 4.4; S, 5.1. $C_{37}H_{36}N_2O_4S$ requires C, 73.5; H, 6.0; N, 4.6; S, 5.3%).

(*b*) The acetylene (4) (287 mg) in piperidine (5 ml) was refluxed for 2 h; work-up as in (*a*) gave the ketone (9a) (192 mg).

(*c*) The allene (8) [1] (288 mg) was stirred at room temperature in piperidine (2 ml) for 22 h; work-up as in (*a*) gave starting material (8) (26 mg) and the ketone (9a) (195 mg).

Reaction of (3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(3-*substituted prop*-2-*ynylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*ones* (10) *with Piperidine*.—(*a*) The phenylacetylene (10b) [1] (50 mg), refluxed in piperidine (2 ml) for 2 h, with work-up as before, gave the amorphous (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(2-*oxo*-3-*phenylpropylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (9b) (40 mg), $\nu_{max.}$ 1 765, 1 720, and 1 630 cm^{-1}; δ 1.97 (3 H, s), 2.2 (3 H, s), 2.56 and 3.03 (2 H, ABq, *J* 15 Hz), 2.84br (1 H, s, exch.), 3.62 (2 H, s), 4.45 (1 H, m, collapsing to d, *J* 5 Hz, on D_2O exch.), 4.65 (1 H, d, *J* 5 Hz), 5.02 and 5.22 (2 H, ABq, *J* 12 Hz), and 6.9—7.6 (25 H, m) (Found: C, 76.0; H, 6.0; N, 4.2; S, 4.9. $C_{43}H_{40}N_2O_4S$ requires C, 75.8; H, 5.9; N, 4.1; S, 4.7%).

(*b*) The pyridylacetylene (10c),[1] refluxed in piperidine for 1 h, similarly gave (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-[2-*oxo*-3-(3-*pyridyl*)*propylthio*]-3-(*triphenylmethylamino*)*azetidin*-2-*one* (9c) (48%), $\nu_{max.}$ 1 760 and 1 715 cm^{-1}; δ 2.00 (3 H, s), 2.23 (3 H, s), 2.53 and 2.94 (2 H, ABq, *J* 15 Hz), 3.02 (1 H, d, *J* 8 Hz, exch.), 3.67 (2 H, s), 4.40—4.74 (2 H, m), 5.02 and 5.25 (2 H, ABq, *J* 12 Hz), 7.2—7.7 (22 H, m), and 8.25—8.75 (2 H, m) (Found: C, 73.7; H, 6.2; N, 6.5; S, 4.9. $C_{42}H_{39}N_3O_4S$ requires C, 74.0; H, 5.7; N, 6.2; S, 4.7%).

(*c*) The *p*-methoxycarbonylphenylacetylene (10d) (0.3 g) was left in piperidine at room temperature for 3 h; work-up as before gave (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(3-p-*methoxycarbonylphenyl*-2-*oxopropylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (0.3 g), $\nu_{max.}$ 1 770, 1 720, and 1 630 cm^{-1}; δ 1.98 (3 H, s), 2.20 (3 H, s), 2.57 and 2.93 (2 H, ABq, *J* 15 Hz), 2.98 (1 H, d, *J* 7 Hz, exch.), 3.68 (2 H, s), 3.90 (3 H, s), 4.41 (1 H, dd, *J* 5 and 7 Hz, collapsing to d, *J* 5 Hz, on D_2O exch.), 4.70 (1 H, d, *J* 5 Hz), 4.98 and 5.23 (2 H, ABq, *J* 13 Hz), 7.1—7.7 (22 H, m), and 8.0 (2 H, d, *J* 8 Hz) (Found: C, 73.3; H, 5.9; N, 3.5; S, 3.8. $C_{45}H_{42}N_2O_6S$ requires C, 73.8; H, 5.7; N, 3.8; S, 4.3%).

(*d*) The *p*-nitrophenylacetylene (10e) (300 mg) was left in piperidine at room temperature for 1 h; work-up as before gave (3R,4R)-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(3-p-*nitrophenyl*-2-*oxopropylthio*)-3-(*triphenylmethylamino*)-*azetidin*-2-*one* (9e) (116 mg), $\nu_{max.}$ 1 765, 1 720br, 1 630, 1 520, and 1 350 cm^{-1}; δ 2.06 (3 H, s), 2.27 (3 H, s), 2.63 and 3.04 (2 H, ABq, *J* 15 Hz, covering exchangeable NH signal), 3.82 (2 H, s), 4.64br (1 H, s, collapsing to d, *J* 5 Hz, on D_2O exch.), 4.79 (1 H, d, *J* 5 Hz), 5.09 and 5.32 (2 H, ABq, *J* 13 Hz), 7.2—7.7 (22 H, m), and 8.27 (2 H, d, *J* 9 Hz) (Found: C, 71.3; H, 5.4; N, 5.5; S, 4.4. $C_{43}H_{39}N_3O_6S$ requires C, 71.2; H, 5.4; N, 5.8; S, 4.4%).

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(*but*-2-*ynylsulphinyl*)-3-(*triphenylmethylamino*)*azetidin*-2-*one*.—The sulphide (10f) [1] (1.5 g) in chloroform (25 ml) was cooled (ice-bath) and treated with *m*-chloroperbenzoic acid (0.45 g) in chloroform (10 ml), added dropwise over 20 min. After a further 20 min the solution was washed with sodium hydrogen carbonate solution and then with water. The dried solution was evaporated and the residue crystallised from ether–light petroleum to give a single isomer (n.m.r.) of the *sulphoxide* (0.94 g), m.p. 133—135°, $\nu_{max.}$ 1 770, 1 715, and 1 620 cm^{-1}; δ 1.71 (3 H, t, *J* 2.5 Hz), 2.22 (3 H, s), 2.23 (2 H, s), 3.26 (2 H, q, *J* 2.5 Hz), 3.4br (1 H, s, exch.), 4.45—4.85 (2 H, m, collapsing to d, δ 4.48, *J* 5 Hz, and d, δ 4.51, *J* 5 Hz on D_2O exch.), 4.98 and 5.20 (2 H, ABq, *J* 12 Hz), 7.0—7.6 (20 H, m) (Found: C, 73.5; H, 6.0; N, 4.4; S, 5.3. $C_{38}H_{36}N_2O_4S$ requires C, 74.0; H, 5.9; N, 4.5; S, 5.2%).

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(2-*oxobutylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (9f).—The above butynyl sulphoxide (0.6 g) in piperidine (10 ml) was left at room temperature for 4 h; work-up in the usual way gave (3*R*,4*R*)-1-(1-benzyloxycarbonyl-2-methylprop-1-enyl)-4-(2-oxobutylsulphinyl)-3-(triphenylmethylamino)-azetidin-2-one (0.436 g), $\nu_{max.}$ 1 770, 1 710 (ester and ketone), and 1 620 cm^{-1}; δ 0.97 (3 H, t, *J* 7 Hz), 2.1—2.4 (8 H, 2 Me, covering $CH_3{\cdot}CH_2$ signal), 3.33br (1 H, s, exch.), 3.23 and 3.62 (2 H, ABq, *J* 14 Hz), 4.46br (1 H, collapsing to d, *J* 5 Hz, on D_2O exch.), 4.97 and 5.25 (2 H, ABq, *J* 12 Hz), and 7.0—7.5 (20 H, m). This sulphoxide (0.3 g) in dimethylformamide (3 ml) was cooled to 0 °C and treated with triphenylphosphine (0.246 g) and acetyl chloride (111 mg). After 5 h in the refrigerator, the solution was poured into ethyl acetate and washed with sodium hydrogen carbonate solution followed by water. The dried organic layer was evaporated; chromatography of the residue gave the *oxosulphide* (9f) (0.22 g), $\nu_{max.}$ 1 760, 1 710br, and 1 625 cm^{-1}; δ 0.95 (3 H, t, *J* 7.5 Hz), 1.98 (3 H, s), 2.21 (3 H, s), 2.31 (2 H, q, *J* 7.5 Hz), 2.50 and 2.85 (2 H, ABq, *J* 14 Hz), 2.96br (1 H, s, exch.), 4.46br (1 H, collapsing to d, *J* 5 Hz, on D_2O exch.), 4.65 (1 H, d, *J* 5 Hz), 5.00 and 5.25 (2 H, ABq, *J* 12 Hz), 7.1—7.6 (20 H, m) (Found: C, 73.2; H, 6.2; N, 4.3. $C_{38}H_{38}N_2O_4S$ requires C, 73.7; H, 6.2; N, 4.5%). More (335 mg) of the same compound was obtained by similar treatment of the non-crystalline isomeric mixture of the acetylenic sulphoxide recovered from the crystallisation mother liquor.

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(4-*phenylbut*-2-*ynylsulphinyl*)-3-(*triphenylmethylamino*)*azetidin*-2-*one*.—The 4-phenylbut-2-ynyl sulphide (10 g) (676 mg) was oxidised with *m*-chloroperbenzoic acid (190 mg) as described for the but-2-ynyl analogue to give the amorphous sulphoxide (480 mg), $\nu_{max.}$ 1 775 and 1 720 cm^{-1}; δ 2.21 (3 H, s), 2.23 (3 H, s), 3.2—3.6 (5 H, m, 1 H exch. with D_2O), 4.5—4.8 (2 H, m), 4.96br (2 H, s), and 7.0—7.6 (m, ArH).

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-4-(2-*oxo*-4-*phenylbutylsulphinyl*)-3-(*triphenylmethylamino*)*azetidin*-2-*one*.—The above acetylene (150 mg) in piperidine (4 ml) was stirred at room temperature for 4 h; work-up in the usual way gave the amorphous ketone (99 mg), $\nu_{max.}$ 1 775 and 1 715 cm^{-1}; δ 2.22 (6 H, s), 2.5—2.9 (4 H, m), 3.0—3.7 (3 H, m, collapsing to 3.17 and 3.55, 2 H, ABq, *J* 14 Hz,

on D_2O exch.), 4.4—4.75 (2 H, m), 4.94 and 5.22 (2 H, ABq, *J* 12 Hz), and 7.0—7.5 (m, ArH).

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-(*phenoxyacetamido*)-4-(*prop*-2-*ynylsulphinyl*)*azetidin*-2-*one* (11).—The sulphide (6) (3.2 g) in chloroform (70 ml) at 0 °C was treated during 5 min with *m*-chloroperbenzoic acid (1.26 g). Usual work-up followed by careful chromatography on silica gel H (150 g) gave the two pure isomeric sulphoxides as amorphous solids. The *faster-running isomer* (1.12 g) had $\nu_{max.}$ 3 320, 3 250, 1 788, 1 725 sh, 1 625, and 1 065 cm^{-1}; δ 2.12 (1 H, t, *J* 3 Hz), 2.32 (6 H, s), 3.58 (2 H, t, *J* 3 Hz), 4.62 (2 H, s), 5.18 and 5.43 (2 H, ABq, *J* 14 Hz), 5.5 (1 H, d, *J* 4 Hz), 6.05 (1 H, dd, *J* 4 and 10 Hz), 6.87—7.67 (10 H, m), and 7.95 (1 H, d, *J* 10 Hz) (Found: N, 5.4; S, 6.7. $C_{26}H_{26}N_2O_6S$ requires N, 5.7; S, 6.5%). The *slower-running isomer* (1.57 g) had $\nu_{max.}$ 3 260, 1 795, 1 724, 1 695, 1 627, and 1 062 cm^{-1}; δ 2.25 (1 H, s, *J* 3 Hz), 2.2 (3 H, s), 2.35 (3 H, s), 3.47 (2 H, t, *J* 3 Hz), 4.63 (2 H, s), 5.1 and 5.23 (2 H, ABq, *J* 12 Hz), 5.18 (1 H, d, *J* 5 Hz), 6.12 (1 H, dd, *J* 5 and 10 Hz), 6.87—7.6 (10 H, m), and 8.75 (1 H, d, *J* 10 Hz) (Found: C, 62.5; H, 5.5; N, 5.3; S, 6.7. $C_{26}H_{22}N_2O_6S$ requires C, 63.1; H, 5.3; N, 5.7; S, 6.5%).

(3R,4R)-4-*Acetonylsulphinyl*-1-(1-*benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-(*phenoxyacetamido*)*azetidin*-2-*one* (12).—*Method* 1. The acetylene (11; mixed isomers) (10 mg) was dissolved in the minimum volume of a secondary or primary amine (*ca.* 0.2 ml). Work-up by addition of ethyl acetate and washing with dilute hydrochloric acid (×2) and brine gave the *ketone* (12; mixed isomers) essentially quantitatively, $\nu_{max.}$ 3 350, 1 780, 1 720sh, 1 690, and 1 625 cm^{-1} (Found: C, 60.6; H, 5.4; N, 5.3; S, 6.5. $C_{26}H_{28}N_2O_7S$ requires C, 60.9; H, 5.1; N, 5.5; S, 6.3%).

With the following amines the reaction was worked up after 2—3 min: dimethylamine (33% in EtOH), ethylamine (33% in EtOH), n-butylamine, benzylamine, cyclohexylamine, diethylamine, pyrrolidine, piperidine, and morpholine. Diallylamine and t-butylamine each required *ca.* 5—10 min.

Use of the individual acetylenic sulphoxide isomers gave the separate isomers of the β-oxo-sulphoxide (12) as amorphous solids. The product from the faster-running isomer of the acetylene (11) had δ 2.12 (3 H, s), 2.27 (6 H, s), 3.52 and 3.85 (2 H, ABq, *J* 15 Hz), 4.6 (2 H, s), 5.25 (1 H, d, *J* 5 Hz), 5.28 (2 H, s), 5.92 (1 H, dd, *J* 5 and 10 Hz), 6.82—7.6 (10 H, m), and 7.88 (1 H, d, *J* 10 Hz). That from the slower-running isomer of the acetylene (11) had δ 2.17 (6 H, s), 2.33 (3 H, s), 3.65 (2 H, s), 4.67 (2 H, s), 5.0 (1 H, d, *J* 5 Hz), 5.17 and 5.4 (2 H, ABq, *J* 12 Hz), 6.1 (1 H, dd, *J* 5 and 10 Hz), 6.7—7.7 (10 H, m), and 8.58 (1 H, d, *J* 10 Hz).

Method 2. The acetylene (11) (25 mg) was dissolved in benzene (0.2 ml) and treated with a secondary or primary amine (5 equiv.) at room temperature. Work-up as in method 1 gave the ketone (12) quantitatively. The more reactive amines previously mentioned required *ca.* 10 min, diallylamine 1 h, and t-butylamine 6 h.

In the case of volatile amines, alternative work-up by evaporation gave enamines. That from diethylamine had $\nu_{max.}$ 3 260, 1 775, 1 710, 1 685, 1 620, and 1 550 cm^{-1} (enamine). That from n-butylamine had $\nu_{max.}$ 3 360, 3 270, 1 775, 1 718, 1 685, 1 620, and 1 588 cm^{-1} (enamine).

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-(*phenoxyacetamido*)-4-(2-*t-butylaminoprop*-1-*enylsulphinyl*)-*azetidin*-2-*one* (14).—(*a*) The faster-running isomer of the acetylene (11) (43 mg) in dry benzene (0.5 ml) was treated with t-butylamine (30 mg) for 6 h, then the mixture was evaporated and the product dried under high vacuum to leave a single isomer of the enamine (14) (48 mg), $\nu_{max.}$ 3 350, 3 280, 1 775, 1 715, 1 685, 1 620, 1 590 (enamine), and 1 060 cm^{-1}; δ 1.2 (9 H, s), 1.97 (3 H, s), 2.30 (3 H, s), 2.40 (3 H, s), 4.17br (1 H, s, exch.), 4.60 (2 H, s), 4.95 (1 H, d, *J* 5 Hz), 5.03 (1 H, s), 5.10 and 5.34 (2 H, ABq, *J* 12 Hz), 5.87 (1 H, dd, *J* 5 and 10 Hz), 6.9—7.7 (10 H, m), and 8.42 (1 H, d, *J* 10 Hz).

(*b*) The slower-running isomer of the acetylene (11) (95 mg) was dissolved in t-butylamine (1 ml). After 5 min the amine was evaporated off, the residue dissolved in toluene, and the mixture re-evaporated. Drying under high vacuum then gave an amorphous solid consisting of a mixture (*ca.* 1 : 1) of two further (*E*- and *Z*-) isomers of the enamine (14); $\nu_{max.}$ 3 360, 3 260, 1 775, 1 715, 1 685, 1 620sh, 1 590, and 1 060 cm^{-1}; δ 1.15 and 1.2 (9 H, two s, lower field signal slightly more intense), 2.07 (3 H, s), 2.28 (3 H, s), 2.35 (3 H, s), 4.37br (>1 H, s, exch.), 4.59 and 4.60 (2 H, two s, lower field signal slightly more intense), 4.80 (1 H, d, *J* 5 Hz), 5.10 and 5.49 (2 H, ABq, *J* 12 Hz), 5.24 and 5.30 (1 H, two s, olefinic CH), 6.10 (1 H, dd, *J* 5 and 10 Hz, collapsing to d, *J* 5 Hz, on D_2O exch.), 6.8—7.6 (10 H, m), and 9.27 (1 H, d, *J* 10 Hz, exch.).

(3R,4R)-1-(1-*Benzyloxycarbonyl*-2-*methylprop*-1-*enyl*)-3-(*phenoxyacetamido*)-4-(*propa*-1,2-*dienylsulphinyl*)*azetidin*-2-*one* (13).—(*a*) The acetylene (11; mixed isomers) (342 mg) was dissolved in dry benzene (2.5 ml) and treated with t-butylamine (0.37 ml) for 15 min; then the mixture was evaporated. Chromatography of the residue gave the *allene* (13; mixed isomers), an amorphous solid, $\nu_{max.}$ 3 360, 1 950w and 1 930w (allene), 1 780, 1 720, 1 690, 1 620, and 1 068 cm^{-1} (Found: N, 5.4; S, 6.8. $C_{26}H_{26}N_2O_6S$ requires N, 5.7; S, 6.5%).

(*b*) Each isomer of the acetylene (11) (95 mg) in benzene (3 ml) was treated with triethylamine (0.5 ml) for 30 min; then the mixture was evaporated to give the allene (13) (95 mg). The isomer from the faster-running acetylene (11) had δ 2.33 (6 H, s), 4.6 (2 H, s), 5.0—5.4 (5 H, m), 5.48—5.8 (1 H, m), 5.95 (1 H, dd, *J* 5 and 10 Hz), 6.8—7.6 (10 H, m), and 7.95 (1 H, d, *J* 10 Hz). The isomer from the slower-running acetylene (11) had δ 2.22 (3 H, s), 2.35 (3 H, s), 4.62 (2 H, s), 4.88 (1 H, d, *J* 5 Hz), 4.95—5.45 (5 H, m), 5.87 (1 H, m), 6.12 (1 H, dd, *J* 5 and 10 Hz), 6.8—7.58 (10 H, m), and 8.65 (1 H, d, *J* 10 Hz).

(3R,4R)-1-(1-t-*Butoxycarbonyl*-1-*hydroxymethyl*)-4-(3-*phenylprop*-2-*ynylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (16).—The azetidinone (15) [1] (966 mg) and t-butyl glyoxylate monohydrate (1.5 g) were refluxed in benzene (25 ml) with provision for removal of water. After 75 min the solution was cooled, washed with water (×5), dried, and evaporated. Chromatography gave the amorphous α-hydroxy-ester (16) (940 mg) as a mixture of isomers, $\nu_{max.}$ 3 450, 1 770, and 1 735 cm^{-1}; δ 1.78 and 1.80 (9 H, two s), 3.17 and 3.35 (2 H, two s), 3—3.8vbr (2 H, exch.), 4.43—4.88 (2 H, m), 5.08 and 5.22 (1 H, two s), and 7.1—7.7 (20 H, m).

(3R,4R)-1-(1-*Chloro*-1-*t-butoxycarbonylmethyl*)-4-(3-*phenylprop*-2-*ynylthio*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (17).—A solution of the α-hydroxy-ester (16) (606 mg) in dry tetrahydrofuran (25 ml) was cooled to −15 °C and treated with dry 2,6-lutidine (315 mg), followed during 1—2 min by thionyl chloride (357 mg) in tetrahydrofuran (5 ml). After 15 min a precipitate was removed and the filtrate

evaporated to leave the α-chloro-ester (17) as an amorphous solid (629 mg), $\nu_{max.}$ 1 780 and 1 745 cm^{-1}.

(3R,4R)-4-(3-*Phenylprop*-2-*ynylthio*)-1-(1-*t*-*butoxycarbonyl*-1-*triphenylphosphoranylidenemethyl*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (18). The α-chloro-ester (17) (626 mg) was dissolved in freshly distilled dioxan (15 ml) and treated under nitrogen with triphenylphosphine (525 mg) and 2,6-lutidine (210 mg), and the mixture was heated at 55—60 °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 hydrogen carbonate, and brine again. The organic layer was separated, dried, and evaporated, and the residue purified by chromatography to give the phosphorane (18) as a white solid (827 mg), $\nu_{max.}$ 1 755 and 1 640 cm^{-1}.

(3R,4R)-4-(2-*Oxo*-3-*phenylpropylthio*)-1-(1-*t*-*butoxycarbonyl*-1-*triphenylphosphoranylidenemethyl*)-3-(*triphenylmethylamino*)*azetidin*-2-*one* (19).—The acetylenic phosphorane (18) (445 mg) in piperidine (13 ml) was refluxed under nitrogen for 5½ h; the mixture was cooled and poured into ethyl acetate, and the solution was washed with dilute hydrochloric acid (×2) and brine (×2), dried, and evaporated. Chromatography gave the ketone (19) (331 mg), $\nu_{max.}$ 1 755, 1 720, and 1 635 cm^{-1}.

t-Butyl 3-*Benzyl*-7β-*triphenylmethylaminoceph*-3-*em*-4-*carboxylate* (20).—A solution of the ketone (19) (331 mg) in dry dioxan (15 ml) was refluxed under nitrogen for 25 h, cooled, and evaporated. Chromatography of the residue gave the *cephem* (20) (141 mg), m.p. 161—162° (from acetone), $[\alpha]_D$ +1° (*c* 1 in $CHCl_3$), $\nu_{max.}$ 3 480, 1 775, 1 710, and 1 630 cm^{-1}; δ 1.50 (9 H, s), 2.92 (1 H, d, *J* 10 Hz, exch.), 2.85 and 3.20 (2 H, ABq, *J* 18 Hz), 3.48 and 3.97 (2 H, ABq, *J* 15 Hz), 4.25 (1 H, d, *J* 5 Hz), 4.70 (1 H, dd, *J* 5 and 10 Hz, collapsing to d, *J* 5 Hz, on D_2O exch.), and 7.1—7.7 (20 H, m) (Found: C, 75.3; H, 6.2; N, 4.8; S, 5.4. $C_{37}H_{36}N_2O_3S$ requires C, 75.5; H, 6.2; N, 4.8; S, 5.5%).

Toluene-p-*sulphonic Acid Salt of t-Butyl* 7β-*Amino*-3-*benzylceph*-3-*em*-4-*carboxylate* (21).—A solution of the tritylaminocephem (20) (929 mg) in acetone (2 ml) was cooled to −20 °C and treated dropwise during 3 min with toluene-*p*-sulphonic acid (330 mg) in acetone (2 ml). The mixture was left at 0 °C for 18 h, then the crystalline *amine toluene*-p-*sulphonate salt* (493 mg) was collected, washed with a little cold acetone, and dried; m.p. 181—182°, $\nu_{max.}$ (Nujol) 1 778, 1 720, and 1 640 cm^{-1} (Found: C, 57.6; H, 5.8; N, 5.6; S, 12.3. $C_{25}H_{28}N_2O_6S_2$ requires C, 57.9; H, 5.8; N, 5.4; S, 12.4%).

t-Butyl 3-*Benzyl*-7β-(2-*thienylacetamido*)*ceph*-3-*em*-4-*carboxylate* (22).—The amine toluene-*p*-sulphonate salt (258 mg) was suspended in dry methylene chloride (15 ml) at −20 °C and treated with dry triethylamine (200 mg), followed dropwise by 2-thienylacetyl chloride (90 mg) in dry methylene chloride (1 ml). After 10 min, the mixture was washed with water, dried, and evaporated. Chromatography afforded the *amide* (22) (129 mg), m.p. 153° (from ethyl acetate–light petroleum), $[\alpha]_D^{23}$ −80° (*c* 1.1 in $CHCl_3$); $\lambda_{max.}$ (EtOH) 237 (ε 13 900) and 266 nm (9 000); $\nu_{max.}$ (Nujol) 3 250, 1 780, 1 718, 1 665, and 1 640 cm^{-1}; δ 1.54 (9 H, s), 3.04 and 3.43 (2 H, ABq, *J* 19 Hz), 3.77 and 4.05 (2 H, ABq, *J* 13 Hz), 3.85 (2 H, s), 4.98 (1 H, d, *J* 5 Hz), 5.83 (1 H, dd, *J* 5 and 10 Hz), 6.38 (1 H, d, *J* 10 Hz), and 6.98—7.3 (8 H, m) (Found: C, 61.0; H, 5.5; N, 5.8; S, 13.7. $C_{24}H_{26}N_2O_4S_2$ requires C, 60.9; H, 5.6; N, 6.0; S, 13.6%).

3-*Benzyl*-7β-(2-*thienylacetamido*)*ceph*-3-*em*-4-*carboxylic Acid* (23).—The t-butyl ester (22) (97 mg) was dissolved in anhydrous trifluoroacetic acid (2 ml). After 5 min the solution was evaporated, the residue treated with toluene, and the mixture re-evaporated (×3). The residue was dissolved in ethyl acetate and extracted (×2) with saturated sodium hydrogen carbonate solution. The combined extracts and aqueous washings were covered with ethyl acetate, cooled to 0 °C, and treated with 20% hydrochloric acid (to pH 2.8), and the layers were separated. The solvent layer was washed with brine, dried, and evaporated to leave the amorphous cephalosporin (23) (64 mg), $[\alpha]_D^{23}$ −63° (*c* 0.97 in $CHCl_3$); $\lambda_{max.}$ (EtOH) 237 (ε 11 600) and 265.5 nm (6 900); $\nu_{max.}$ 2 500—3 400br, 1 780, 1 720sh, 1 680, and 1 630sh cm^{-1}; δ 3.02 and 3.40 (2 H, ABq, *J* 20 Hz), 3.57 and 4.13 (2 H, ABq, *J* 15 Hz), 3.81 (2 H, s), 4.97 (1 H, d, *J* 5 Hz), 5.75 (1 H, m, collapses to d, *J* 5 Hz, on D_2O exch.), 6.75 (1 H, d, *J* 9 Hz, exch.), 6.86—7.4 (8 H, m), and 7.73br (1 H, s, exch.).

[6/343 *Received*, 18*th February*, 1976]