Sulfur-free Penicillin Derivatives. VI. Synthesis of the 1-Oxacephem Ring System

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The title compound has been synthesized by ring closure of an alkyl 2-(2′-chloro-3′-*S*-phthalimido-4′-oxo)azetidinyl-3-methyl-4-hydroxy-*trans*-2-butenoate using S_N1 experimental conditions. The required *E*-allylic alcohols were obtained in two ways starting with an alkyl 2-(2′-chloro-3′-*S*-phthalimido-4′-oxo)azetidinyl-3-methyl-2-butenoate. The first involves allylic bromination with 1 molar equiv. of *N*-bromosuccinimide, conversion of the mixed *Z*- and *E*-allylic bromides into the mixed *Z*- and *E*-allylic formates, and deformylation to a mixture of *E*-alcohol and lactone. The alcohol was separated from the lactone via its tetrahydropyranyl derivative, and then regenerated. In the second route, allylic bromination was performed with 2 molar equiv. of *N*-bromosuccinimide and the resulting dibromo compound was converted into the β,γ-unsaturated olefin with zinc in acetic acid. Epoxidation with peroxytrifluoroacetic acid followed by exposure to triethylamine again afforded a mixture of *E*-alcohol and lactone. The u.v. spectrum of a 1-oxacephem shows a maximum at 266 nm.

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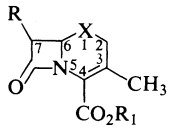
Le composé désiré a été préparé par cyclisation d'un (chloro-2′ *S*-phtalimido-3′ oxo-4′) azétidinyl-2 méthyl-3 hydroxy-4 butène-2 oate d'alkyle *trans* utilisant des conditions expérimentales S_N1. Les alcools allyliques-*E* nécessaires ont été obtenus de deux façons en partant d'un (chloro-2′ *S*-phtalimido-3′ oxo-4′) azétidinyl-2 méthyl-3 butène-2 oate d'alkyle. La première façon implique une bromuration allylique avec un équivalent molaire de *N*-bromosuccinimide, la transformation du mélange des bromures allyliques-*E* et -*Z* en un mélange de formiates allyliques -*E* et -*Z* et la déformylation pour donner un mélange d'alcool -*E* et de lactone. L'alcool est séparé de la lactone par l'intermédiaire de son dérivé tétrahydropyrannyle et est ensuite regénéré. Dans la deuxième route, la bromuration allylique est effectuée avec deux équivalents de *N*-bromosuccinimide et le composé dibromé qui en résulte est transformé en oléfine β,γ non-saturé à l'aide du zinc dans l'acide acétique. L'époxydation de cet oléfine par l'acide peroxytrifluoroacétique suivie par un contact avec de la triéthylamine conduit à nouveau à un mélange d'alcool-*E* et de lactone. Le spectre u.v. de l'oxa-1 céphem montre un maximum à 266 nm. [Traduit par le journal]

We wish to report the transformation of the thiazolidine ring of the penicillin nucleus into a dihydrooxazine ring, to form the oxygen analog (**1***a*) of a Δ^3-cephem (**1***b*).

The starting materials were the (2R)-*cis*- and (2*S*)-*trans*-chloroazetidinones **2***a–c* (Ft = phthalimido), which are obtained (1) from anhydro-6-phthalimidopenicillin (2) by chlorinolysis, hydrolysis of the derived acid chloride, and esterification with diazomethane or diphenyldiazomethane. Each of these azetidinones was monobrominated (NBS) (3, 4) to give approximately 1:1 mixtures of **3***a* + *b*, **3***c* + *d*, and **3***e* + *f*. The functionality present in the *E*-isomers **3***b*, **3***d*, and **3***f* allows two approaches to be considered for the generation of the six-membered ring, which differ in the timing of attachment of the C—O bond to the β-lactam. In the route described here, this bond has been formed in the final step of the synthesis, by cyclization of the *E*-allylic alcohols **4***a–c*.

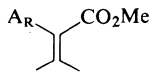
The conversion of the allylic bromides into the required allylic alcohols was achieved in two ways. In the first, the mixtures **3***a* + *b*, **3***c* + *d*, and **3***e* + *f* were treated, in chloroform or methylene chloride at room temperature, with excess tetramethylguanidinium formate to form mixtures of the formate esters **5***a* + *b* (64%),

5*c* + *d* (57%), and **5***e* + *f* (52%). The esters were obtained in each case as approximately 2:1 *Z*:*E* mixtures; **5***a–d* have been described previously (3). The n.m.r. spectrum of **5***e* + *f* showed peaks at 8.22 (0.33H, s), 8.10 (0.67H, s), 7.83 (4H, d), 7.37 (10H), 7.03 (1H, s), 6.13 (1H, d, 4.0), 5.68 (1H, d, 4.0), 5.37 (2H, br s), 2.37 (2.0H, s), 2.32 (1.0H, s). Removal of the formyl groups (HCl, MeOH–CH_2Cl_2, 0°, 1.5 h) gave the *E*-alcohols **4***a–c*, admixed with the lactones **6***a* or **6***b*. The tetrahydropyranyl ethers **7***a–c* were separated from the lactones by chromatography on silica gel to yield, from **5***a* + *b*: **6***a* (59%) and **7***a* (36%), m.p. 115–116.5°; from **5***c* + *d*: **6***b* (62%) and **7***b* (31%); from **5***e* + *f*: **6***a* (63%) and **7***c* (29%). Removal of the tetrahydropyranyl protecting groups (HCl, MeOH–CH_2Cl_2, 0°, 4 h) afforded. Compound **4***a* (93%), m.p. 134.5–135.5°; anal. found: C, 54.09; H, 4.20; N, 7.44; n.m.r.: 7.79 (4H, d), 6.17 (1H, d, 4.0), 5.71 (1H, d, 4.0), 4.75 (1H, d, 12.5), 4.25 (1H, d, 12.5), 3.82 (3H, s), 2.78 (1H, s, exchanges with D_2O), 2.38 (3H, s); **4***b* (98%), n.m.r.: 7.75 (4H, d), 6.18 (1H, d, 1.5), 5.55 (1H, d, 1.5), 4.30 (1H, d, 13), 4.27 (1H, d, 13), 3.85 (3H, s), 3.17 (1H, br s), 2.35 (3H); **4***c* (95%), n.m.r.: 7.83 (4H, d), 7.25

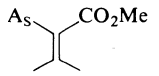


1

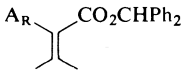
a X = O
b X = S



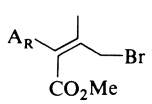
2*a*



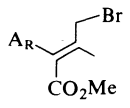
2*b*



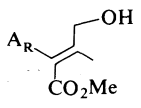
2*c*



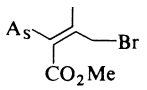
3*a*



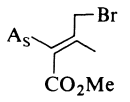
3*b*



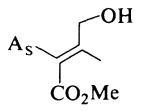
4*a*



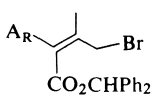
3*c*



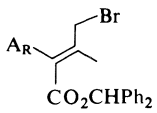
3*d*



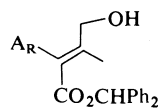
4*b*



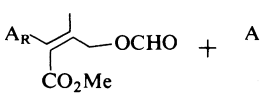
3*e*



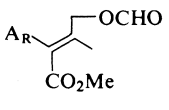
3*f*



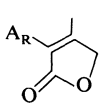
4*c*



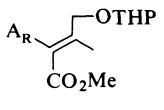
5*a*



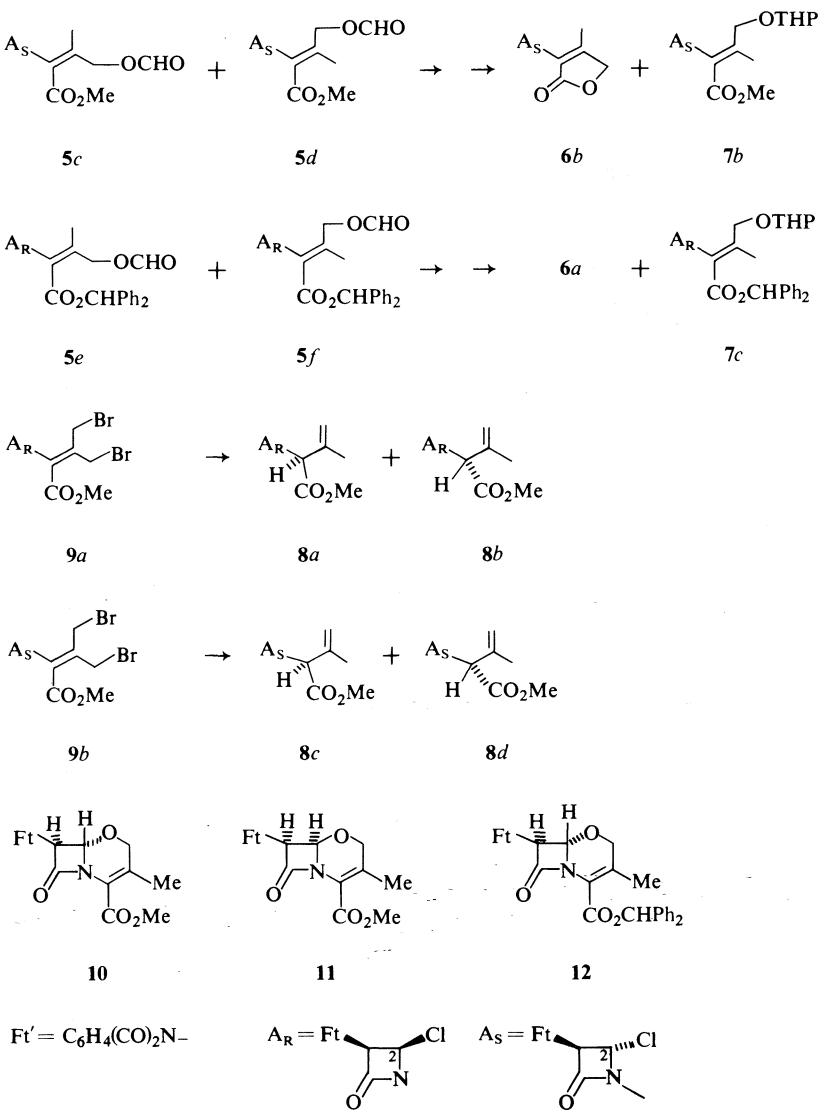
5*b*



6*a*



7*a*



(10H), 7.00 (1H, s), 6.08 (1H, d, 4), 5.80 (1H, d, 4), 4.32 (1H, d, 14), 4.08 (1H, d, 14), 2.80 (1H, br s), 2.38 (3H, s).

A second synthesis of the alcohols **4***a* and **4***b* proceeded via the β,γ-unsaturated olefins **8***a–d*. These were prepared by zinc dust debromination (2 equiv. zinc/mol, HOAc, 0°, 4 min) of the monobromo compounds **3***a* + *b* and **3***c* + *d* or, better, by debromination of the dibromo compounds **9***a* and **9***b* (4.4 equiv. zinc/mol, HOAc, 0°, 4 min). The β,γ-isomers were obtained as 1:1 mixtures of epimers in each case; n.m.r. of **8***a* + *b* (78% from **9***a*): 7.92 (4H, d), 6.43 (0.5H, d, 4.0), 6.05 (0.5H, d, 4.0), 5.76 (0.5H, d, 4.0), 5.74 (0.5H, d, 4.0), 5.27 (2H, br s), 5.14 (0.5H, s), 4.76 (0.5H, s), 3.85 (3H, s), 2.05 (3H, br s); n.m.r. of **8***c* + *d* (90% from **9***b*): 7.77 (4H), 5.95 (0.5H, d, 2), 5.88 (0.5H, d, 2), 5.57 (0.5H, d, 2), 5.47 (0.5H, d, 2), 5.25 (1H, br s), 5.15 (1H, br s), 4.83 (0.5H, s), 4.22 (0.5H, s), 3.83 (1.5H, s), 3.80 (1.5H, s), 2.00 (3H, br s). Each of the β,γ-isomers rearranged rapidly to the α,β-isomer upon exposure to triethylamine (5). Oxidation of the mixture **8***a* + *b* (CF_3CO_3H, CH_2Cl_2, 20°, 1.5 h), afforded a mixture of four epoxides which, without purification, was rearranged (triethylamine–methanol) to a 3:1 mixture of **6***a* and **4***a*. These were separated as described above. The

mixture **8***c* + *d* similarly afforded a 2:1 mixture of the lactone **6***b* and the *E*-allylic alcohol **4***b*.

Depending on the experimental conditions (4, 6), substitution at C-2 of these azetidinones may proceed by S_N1 or S_N2 pathways. When S_N2 conditions are employed, the rate of the reaction depends upon the nature of the C-3 substituent in the order H_2N > acylamino > phthalimido (1). The alcohols **4***a–c* contain a phthalimido substituent at C-3 and did not cyclize under a variety of S_N2 conditions (Et_3N, NaH, LiH). Unimolecular conditions were therefore necessary, with the result that the oxacephems **1***a* were obtained as epimeric mixtures at C-6, upon treatment of **4***a–c* with stannous chloride in dimethoxyethane or tetrahydrofuran or, in the case of the crystalline alcohol **4***a*, upon heating to the melting point.

Cyclization proceeded smoothly to give oxacephems in yields of 80–92% and, under identical conditions, the same mixture of epimers was formed from **4***a* and *b*, indicative of a common intermediate (4, 6). Some variation in the proportions of these epimers could be achieved by systematic variation of the experimental conditions. Thus, treatment of **4***a* (229 mg) at room temperature with 1.38 molar equiv. of $SnCl_2$ in dimethoxyethane (15 ml) yielded 176 mg (86% after recrystallization from chloroform–hexane) of **10**, m.p. 170–171°, $[\alpha]_D$ −16.9 (*c* 0.3, $CHCl_3$).

Anal. Calcd. for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12; N, 8.18. Found: C, 59.78; H, 3.94; N, 8.42.

The i.r. (KBr): 5.61, 5.65, 5.79μ; n.m.r.: 7.80 (4H, d), 5.33 (1H, d, 1.8), 5.27 (1H, d, 1.8), 4.37 (2H, s), 3.90 (3H, s), 2.03 (3H, s). The u.v. spectrum of 10 shows λ_{max} (EtOH) 266 (12 500), 226 (40 000). The presence of a maximum at 266 nm supports conclusions (7, 8) that the Δ^3-cephem chromophore near 260 nm is not associated with the presence of sulfur. Repetition of the above experiment with 1.67 molar equiv. of $SnCl_2$ in dimethoxyethane (30 ml) afforded, in 90% yield, a 1:1 mixture of **10** and **11**, which possesses the natural configuration at C-6; $[\alpha]_D$ 52.5 (*c* 0.3, $CHCl_3$); M^+, 342; n.m.r.: 7.80 (4H, d), 5.56 (1H, d, 3.8), 5.10 (1H, d, 3.8), 4.30 (2H), 3.90 (3H, s), 2.03 (3H, s). The n.m.r. spectrum of the oxacephem **12** showed peaks at 7.68 (4H, d), 7.23 (10H), 6.83 (1H), 5.20 (1H, d, 1.5), 5.13 (1H, d, 1.5), 4.26 (2H), 1.97 (3H).

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