Novel Conversion of Penicillins into Cephalosporins

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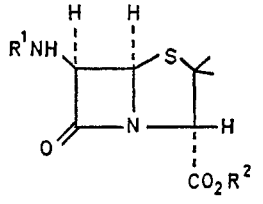
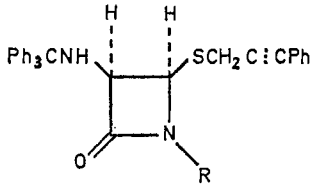
Summary A new antibacterially active cephalosporin 3-benzyl-7β-(2-thienylacetamido)ceph-3-em-4-carboxylic acid, has been prepared from the 1,2-seco-penicillin (**3**), using an intramolecular Wittig reaction to construct the dihydrothiazine ring.

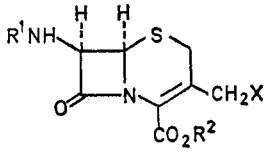
CERTAIN penicillins (**1**) are obtained by fermentation in very high yield, making their derivatives attractive intermediates for chemical conversion into cephalosporins or analogues thereof. This approach has the advantage over total synthesis that the nitrogen and sulphur substituents are already attached to the β-lactam in the desired stereochemical configuration. Deacetoxycephalosporins (**7**) are obtained by skeletal rearrangement of penicillin ester sulphoxides,[1] but several further steps are required if a substituent (X) is to be introduced into the 3-methyl group. We report an alternative approach in which part of the thiazolidine ring is removed from the penam nucleus and then replaced by a different fragment.



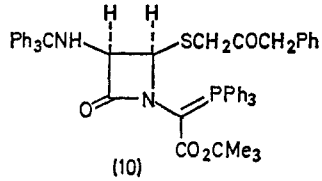
(**1**); R^1 = acyl, R^2 = H
(**2**); R^1 = Ph_3C, R^2 = CH_2Ph



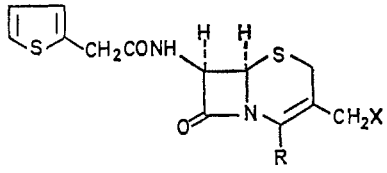
(**3**); R = C(:CMe_2)CO_2CH_2Ph
(**4**); R = H
(**5**); R = CHOH.CO_2CMe_3
(**6**); R = C(:PPh_3)CO_2CMe_3



(**7**); R^1 = acyl, R^2 = X = H
(**8**); R^1 = Ph_3C, R^2 = CMe_3, X = Ph
(**9**); R^1 = H, R^2 = CMe_3, X = Ph



(**10**)



(**11**); R = CO_2CMe_3, X = Ph
(**12**); R = CO_2H, X = Ph
(**13**); R = CO_2^-, X = pyridinium

In a typical example of the new procedure benzyl 6β-(triphenylmethylamino)penicillanate (**2**), was converted

into the 4-(3-phenylprop-2-ynylthio)azetidinone (**3**)[2] and oxidised[3] with potassium permanganate in aqueous pyridine at 0° to give the secondary amide (**4**),† m.p. 121—122°.

The next three steps parallel a sequence used by Scartazzini and his co-workers[4,5] in a different approach to cephems lacking a 3-substituent. Thus, condensation of (**4**) with an excess of t-butyl glyoxylate in refluxing benzene for 1 h gave the α-hydroxy-ester (**5**) as a mixture of isomers. Treatment of (**5**) with thionyl chloride followed by triphenylphosphine and pyridine gave the phosphorane (**6**). Hydration of the acetylenic function to give the ketone (**10**) was accomplished by refluxing (**6**) in neat piperidine[2] for 5 h. Whereas a related aldehyde prepared in a different fashion could not be isolated because an intramolecular Wittig reaction occurred spontaneously,[5] the ketone (**10**) required 25 h refluxing in dioxan to convert it into the cephem(**8**),† m.p. 160—162°, $[\alpha]^{23}$ + 1° (*c* 1, $CHCl_3$). Detritylation with toluene-*p*-sulphonic acid in acetone (overnight at 0°) gave the toluene-*p*-sulphonate salt of (**9**),† m.p. 181—182°. Reaction of (**9**) with 2-thienylacetyl chloride afforded (**11**),† m.p. 153°, $[\alpha]^{23}$ — 80° (*c* 1·1, $CHCl_3$), which on treatment with trifluoroacetic acid (1 h at 20°) gave 3-benzyl-7β-(2-thienylacetamido)ceph-3-em-4-carboxylic acid (**12**), $[\alpha]^{23}$ −63° (*c* 0·97, $CHCl_3$).

This new antibiotic had similar activity to its isostere, cephaloridine (**13**), against Gram-positive bacteria but was less active against Gram-negative organisms. We are currently exploring the scope of this route in the preparation of ceph-3-em-4-carboxylic acids with various hydrocarbon substituents in the 3-methyl group and various side-chains at position 7. All new compounds showed the expected spectroscopic properties, including the characteristic ^1H n.m.r. pattern for *cis* coupled β-lactam protons.[6]

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† Satisfactory elemental analysis.

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