Isolation of the β-Lactam Function of Penicillins

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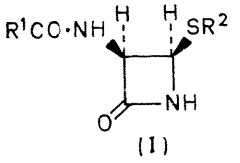
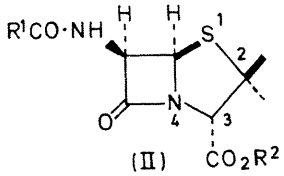
Summary A convenient method for the isolation of the β-lactam function of penicillins has been developed, involving cleavage across the thiazolidine ring.

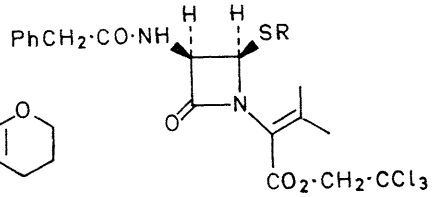
THE isolation of the β-lactam (I; R^2 = protecting group, *etc.*) from the penicillin nucleus (II) would allow considerable variation in the types of β-lactam antibiotics available



(I)

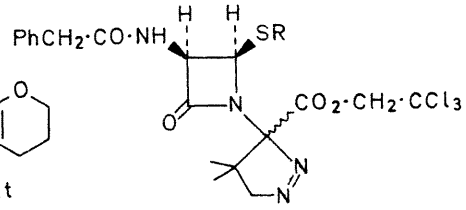


(II)



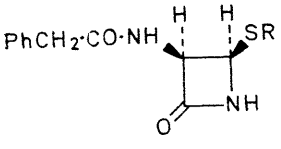
(III) R =

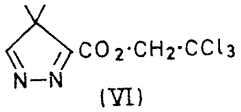
(VII) R = Et



(IV) R =

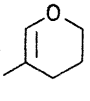
(VIII) R = Et



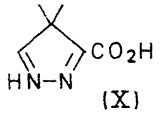


(VI)

(V) R =



(IX) R = Et

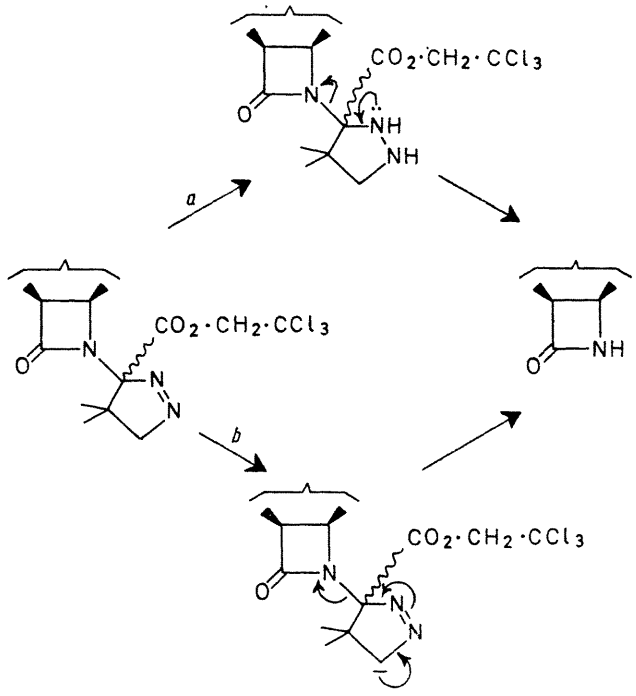


(X)

by the addition of new linkages across the S(1)–N(4) positions [see (II)]. Cleavage across the S(1)–C(2) bond of the penicillin nucleus is readily achieved by trapping the sulphenic acid intermediates produced by heating the corresponding penicillin sulphoxide.[1] In order to be able to complete the thiazolidine cleavage the remaining isopentenoyl residue attached to the β-lactam nitrogen atom has to be removed. We now describe a convenient method for this.

1,3-Dipolar addition of diazomethane[2] across the conjugated ester double bond of the dihydropyran derivative (III) proceeded slowly but quantitatively yielding two stereoisomeric adducts (IV) (ratio *ca.* 4:1). The major isomer, isolated by preparative t.l.c., had m.p. 85—86°, $[\alpha]_D^{30}$ −2° (*c* 1, $CHCl_3$)† whilst the less polar, minor component was only isolated as a non-crystalline solid, $[\alpha]_D^{29}$ −209° (*c* 1, $CHCl_3$). The pyrazoline adducts can be degraded by either of two simple procedures. Treatment of the adducts (IV), either as the stereoisomeric mixture or as individual components, with potassium t-butoxide in t-butyl alcohol at room temperature for 2 min afforded an almost quantitative yield of the β-lactam fragment (V), m.p. 152—154°, $[\alpha]_D^{28}$ −7° (*c* 1, $CHCl_3$). The other products is presumed to arise from the azine (VI).

In the alternative, and preferable, degradation method the pyrazoline adducts (IV) were reduced with zinc dust in aqueous acetic acid and again a nearly quantitative yield of the β-lactam derivative (V) was obtained. In the latter method we believe that reduction of the pyrazoline (path *a*, Scheme) would be followed by rapid elimination of (V).



SCHEME

In the former method, anion formation (path *b*, Scheme) must precede elimination.

A similar degradation sequence was also applied to the *S*-ethyl compound (VII), $[\alpha]_D^{30}$ −3° (*c* 1, $CHCl_3$) which gave, with diazomethane, a stereoisomeric mixture of adducts (VIII). As before, treatment of this adduct, either with potassium t-butoxide in t-butyl alcohol or, preferably, with

† All new compounds had satisfactory microanalytical and spectral properties.

zinc dust in aqueous acetic acid, gave the free β-lactam (IX), m.p. 168—169°, $[\alpha]_D^{28}$ + 27° (*c* 1, tetrahydrofuran). The second fragment from the reduction was the acid (X), identified as its methyl ester by comparison with an authentic sample.

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[1] D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1683; R. D. G. Cooper and F. L. José, *J. Amer. Chem. Soc.*, 1970, **92**, 2575.
[2] E. Buchner, *Annalen*, 1893, **273**, 214.