

NOVEL TRANSFORMATIONS OF PENICILLINS INTO 2-AZETIDINONES WITH DIAZO- AND AZIDO-COMPOUNDS AND A NOVEL SYNTHESIS OF DESACETOXYCEPHALOSPORIN

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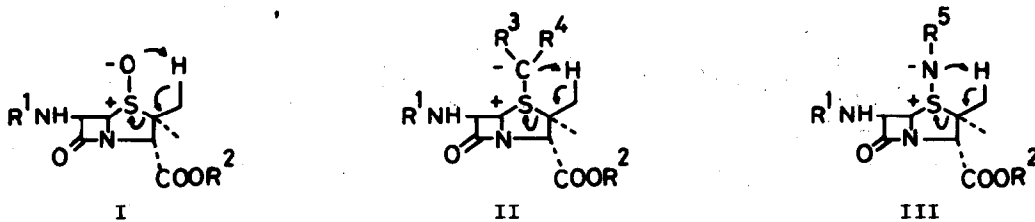
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The thermal and acid catalyzed rearrangement of penicillin sulfoxides into desacetoxycephalosporins initially discovered by Morin et al.¹⁾ has been extensively investigated and the intermediary formation of a sulfenic acid by a six-electron sigmatropic rearrangement as depicted in I has been confirmed by many methods.²⁾

Since previous studies have shown that sulfonium ylides³⁾ and sulfilimines⁴⁾ bearing β -hydrogens undergo similar rearrangements, we considered that if a penicillin sulfonium ylide (II)⁵⁾ and a sulfilimine (III) are formed they should rearrange to afford 2-azetidinones (V) and (VI), respectively, and the latter on some proper treatment might ring close to the 3-cephem system (VII).

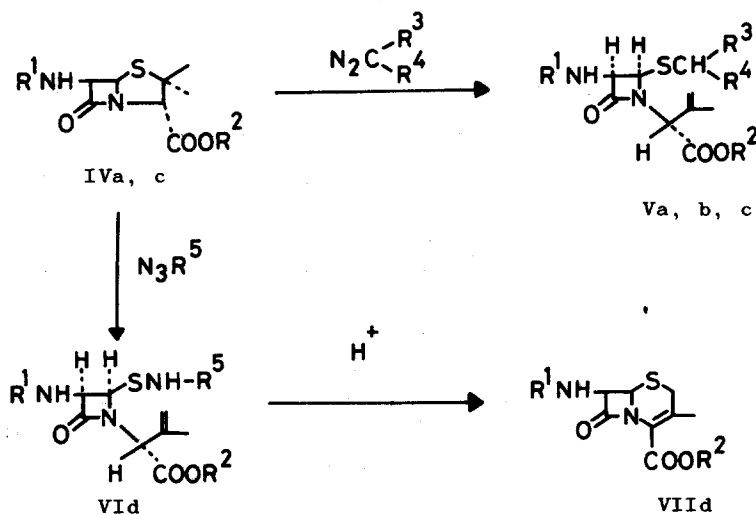


We now report evidence which supports this expectation.

Treatment of penicillin V methyl ester with 6 equiv. dimethyl diazomalonate³⁾ and 2 equiv. $\text{CuSO}_4 \cdot \text{H}_2\text{O}$ in diethyl carbonate at 110° for 30 min and chromatographic separation of the reaction mixture on silica gel impregnated with 1% oxalic acid using n-hexane-benzene as eluant afforded 2-azetidinone (Va) as a homogeneous gum in 46% yield. Va: $[\alpha]_D -77.9^\circ$ (c 0.69 in dioxane);

mass spectrum m/e 494.1368 (M, Calcd. 494.1359), 435 (M-CO₂Me), 363 (M-CH(CO₂-Me)₂), and 331 (M-SCH(CO₂Me)₂); IR (CHCl₃) 1786 cm⁻¹ (β -lactam); 100 MHz Nmr δ (CDCl₃) 1.89 (3H, s, vinylic Me), 3.67 (6H, s, 2OMe), 3.72 (3H, s, OMe), 4.14 (1H, s, SCH), 4.49 (2H, s, CH₂), 4.82 (1H, s, N₁-CH), 4.96 and 5.06 (each 1H, s, =CH₂), 5.38 (1H, dd, J 4.5 and 8 Hz, 3-H), 5.56 (1H, d, J 4.5 Hz, 4-H) and 6.8-7.4 (6H, m, phenyl and NH).

In a similar manner penicillin V and G methyl esters were treated with methyl *p*-nitrophenyldiazoacetate⁶⁾ in the presence of CuSO₄·H₂O to afford 2-azetidiones (Vb) ($[\alpha]_D$ -62.9° (c 1 in dioxane)) and (Vc) ($[\alpha]_D$ -37.2° (c 1 in dioxane)) respectively, as foams in 70% yields. The Nmr and IR spectra of (Vb) and (Vc) were consistent with their proposed structures.



	R ¹	R ²	R ³	R ⁴	R ⁵
a	PhOCH ₂ CO-	CH ₃	-COOCH ₃	-COOCH ₃	-
b	PhOCH ₂ CO-	CH ₃	-COOCH ₃	<i>p</i> -NO ₂ -Ph-	-
c	PhCH ₂ CO-	CH ₃	-COOCH ₃	<i>p</i> -NO ₂ -Ph-	-
d	PhOCH ₂ CO-	CH ₃	-	-	-COOC ₂ H ₅

Taking precedence³⁾ into account, these results should be explicable in terms of an initial electrophilic attack of the carbenes generated from diazo-

compounds onto the sulfur atom of the penicillins to afford the sulfonium ylides (II) and a subsequent ring opening of (II) into (V) through a six-electron sigmatropic rearrangement.

In another run penicillin V methyl ester was heated with 6 equiv. ethyl azidoformate⁷⁾ in diethyl carbonate at 90-100° until 2 equiv. nitrogen had been evolved to result in 2-azetidinone (VIId) as a homogeneous gum in 12% yield.

VIId: $[\alpha]_D -38.8^\circ$ (c 1 in dioxane); mass spectrum m/e 451.1395 (M, Calcd. 451.1413), 392 (M-CO₂Me), 363 (M-NHCO₂Et) and 331 (M-SNHCO₂Et); IR (CHCl₃) 1770 cm⁻¹ (β -lactam); 100 MHz Nmr δ (CDCl₃) 1.22 (3H, t, J 8 Hz, CH₂-Me), 1.94 (3H, s, vinylic Me), 3.76 (3H, s, OMe), 4.10 (2H, q, J 8 Hz, CH₂-Me), 4.56 (2H, s, OCH₂), 4.83 (1H, s, N₁-CH), 5.01 (1H, d, J 5 Hz, 4-H), 5.06 and 5.14 (each 1H, s, =CH₂), 5.49 (1H, dd, J 5 and 8 Hz, 3-H), 5.52 (1H, s, SNH), 6.8-7.4 (5H, m, phenyl) and 7.84 (1H, d, J 8 Hz, NH).

The intermediary formation of a penicillin sulfilimine (IIIId) which underwent spontaneous ring opening to (VIId) is apparent by analogy with the foregoing results.

Retention⁸⁾ of the original stereochemistry in these 2-azetidinones is strongly indicated by the coupling constants between 3-H and 4-H, J 4.5-5 Hz, indicative of cis-orientation of the two hydrogens.

The reaction to cyclize (VIId) to a desacetoxycephalosporin (VIIId) was attained in poor yield when (VIId) was heated with diethylamine hydrochloride in N,N-dimethylacetamide at 130° for 2 hr and (VIIId) was identified by comparison with an authentic specimen.⁹⁾

We believe this is the first example of a conversion from penam into 3-cephem which does not deal with penicillin sulfoxides.

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- 10) Satisfactory combustion data were obtained for all new compounds.