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STUDIES ON β-LACTAM ANTIBIOTICS II.[1)]

A NEW SYNTHESIS OF 1,2-SECOPENICILLIN AND ITS CONVERSION TO THE CEPHAM NUCLEUS

Masafumi Yoshimoto, Sadao Ishihara, Eiji Nakayama, Emiko Shoji,
Harumitsu Kuwano, and Nobuo Soma[2)]
Central Research Laboratories, Sankyo Co., Ltd.
Hiromachi, Shinagawa-ku, Tokyo, Japan

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We have recently reported the skeletal conversion of a cephalosporin to a penicillin derivative by the reaction with a carbene.[1)] The present communication describes the reaction of a penicillin with a carbene, which resulted in the cleavage of the 1,2-bond of the penicillin ring, and the transformation of the resulting 1,2-secopenicillin to the cepham nucleus.

To a mixture of methyl 6-phenylacetamidopenicillanate (Ia) and $Cu(acac)_2$ in benzene was added dropwise ethyl diazoacetate at 80°C in a nitrogen atmosphere and the resulting mixture was heated for 2 hours. A usual work-up gave the oily 1,2-secopenicillin (IIa) as the sole β-lactam containing product in 80% yield (based on the consumed Ia (46%)), $[\alpha]_D^{27°}$ -92.3°(c=0.92, $CHCl_3$). The IR showed absorption maxima at 1765 (β-lactam), 1730 (ester), 1670 (amide), 730 (end methylene), and 3300 cm^{-1}(NH). The NMR in $CDCl_3$ exhibited the peaks at 1.23 (3H, t, J=7.0 Hz), 1.88 (3H, s), 3.08 (2H, s), 3.62 (2H, s), 3.75 (3H, s), 4.13 (2H, q, J=7.0 Hz), 4.82 (1H, s), 5.02 (1H, s), 5.12 (1H, s), 5.42 (2H, m), 7.18 (1H, d, J=6.5 Hz), and 7.26 (5H, s) ppm.

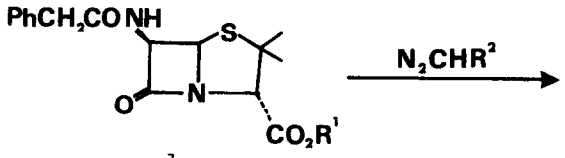
The formation of IIa evidently proceeds through the sulfonium ylide intermediate (VII). It is notable that VII is isoelectronic with the penicillin sulfoxide (VIII). The sulfoxide (VIII), upon the thermal sigmatropic rearrangement, suffers the fission of the 1,2-bond to afford the sulfenic acid (IX), which undergoes further reactions with various reagents: thus, VIII was converted into 1,2-secopenicillin derivatives when heated in the presence of trimethylphosphite,[3)] mercaptans,[4)] or vinyl ethers,[5)] and an acid-catalysed trans-

formation to a cephalosporin has been achieved by Morin.[6] The 1,2-bond cleavage of VII affords IIa, which structurally corresponds to IX, but, unlike IX, IIa did not undergo a further reaction and was isolated as the reaction product.

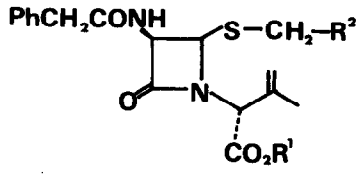
Several reports have been published concerning the fission of the thiazolidine ring of penicillins: Sheehan initially achieved the fission of the 3,4-bond via 3-penamyl carbamate,[7] Nayler obtained a 1,2-secopenicillin by the reaction with methyl iodide in the presence of a strong base,[8] and, moreover, the 1,5-bond was cleaved on the treatment with chlorine by Kukolja.[9] The present direct conversion of penicillin to a 1,2-secopenicillin having a functional group at the S-side chain will facilitate the modification of the β-lactam antibiotics. Application of the above reaction to some other diazo compounds, including diazoacetaldehyde, diazoacetonitrile, methyl diazopyruvate, or diazoacetophenone, also produced the corresponding 1,2-secopenicillins in moderate yields.

The treatment of IIa with Et_3N in CH_2Cl_2 gave the double bond isomer (IIIa), $[\alpha]_D^{27°}$-15.8° (c=1.10, $CHCl_3$) in a quantitative yield. The NMR of IIIa in $CDCl_3$ showed two singlets at 1.97 and 2.23 ppm (3H, each) assignable to the gem-dimethyl protons of the isopropylidene group.

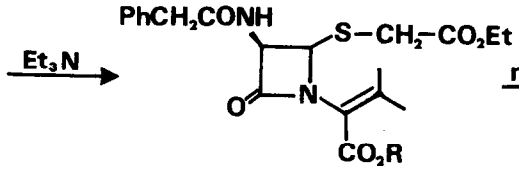
The cyclization of a 1,2-secopenicillin to the cepham nucleus was accomplished via the sulfone as described below. Repetition of the reaction on the benzyl ester (Ib) with ethyl diazoacetate afforded the corresponding oily 1,2-secopenicillin (IIb), $[\alpha]_D^{27°}$-94.4° (c=1.01, $CHCl_3$), which was isomerized to IIIb, $[\alpha]_D^{27°}$-7.46° (c=13.0, $CHCl_3$). The oxidation of IIIb with m-chloroperbenzoic acid gave the sulfone (IV), in 60% yield and the treatment of IV with 1,4-diazabicyclooctane (DABCO) in DMF at room temperature afforded the cyclized compound (V) in 35% yield. In the NMR of V in $CDCl_3$, the gem-dimethyl at C-3 showed two singlets at 0.97 and 1.50 ppm. The catalytic hydrogenolysis of V with Pd-C gave the powdery, free carboxylic acid (VI) in 82% yield, $[\alpha]_D^{27°}$-6.18° (c=0.97, $CHCl_3$). The IR showed absorption maxima at 1800 (β-lactam), 1745 (ester and carboxyl), 1668 (amide) and 3400 cm^{-1}(NH). The NMR peaks in $CDCl_3$ appeared at 1.13 (3H, s), 1.31 (3H, t, J=7.0 Hz), 1.51 (3H, s), 3.62 (2H, s), 4.23 (1H, s), 4.29 (2H, q, J=7.0 Hz), 4.46 (1H, s), 5.21 (1H, d, J=4.5 Hz), 5.95 (1H, dd,



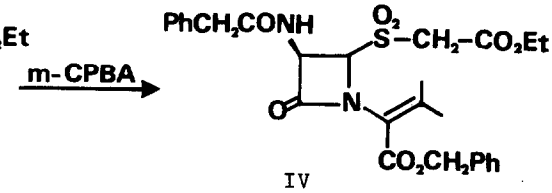
Ia: R^1=Me
Ib: R^1=$PhCH_2$



IIa: R^1=Me, R^2=CO_2Et
IIb: R^1=CH_2Ph, R^2=CO_2Et



IIIa: R=Me
IIIb: R=$PhCH_2$



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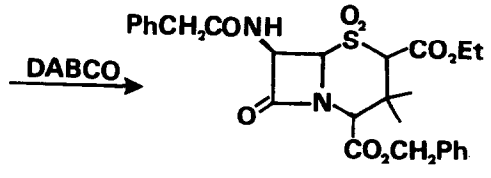
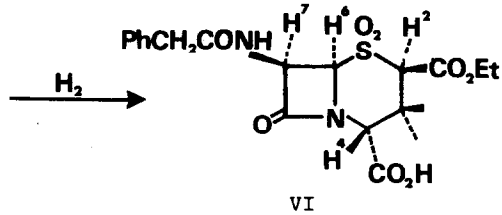
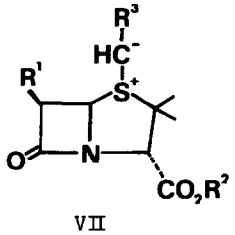


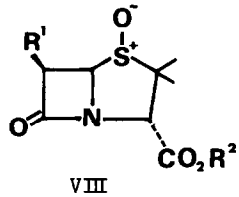
V



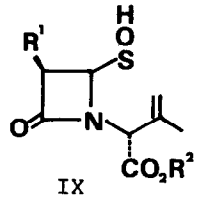
VI



VII



VIII



IX

J=4.5 and 10.5 Hz), 7.17 (1H, d, J=10.5 Hz), 7.2-7.4 (5H, m), and 8.23 (1H, br. s). The peak at 4.46 ppm disappeared by the addition of D_2O and DABCO, and was assigned to 2-H. The coupling constant, 4.5 Hz, between 6-H (5.21 ppm) and 7-H (5.95 ppm) established the cis configuration (α-orientation) of these β-lactam ring protons. Irradiation at 6α-H increased the integrated intensity of 2-H by 5%, which indicated the α-orientation of 2-H. Irradiation at methyl protons at 1.13 ppm increased the intensity of 2α-H by 10% and that at 1.51 ppm increased the intensity of 4-H (4.23 ppm) by 8%. This NOE data established the α-configuration of the methyl at 1.13 ppm and the β-configuration both of the methyl at 1.51 ppm and of 4-H.

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