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STUDIES ON β-LACTAM ANTIBIOTICS I.
SKELETAL CONVERSION OF CEPHALOSPORIN TO PENICILLIN

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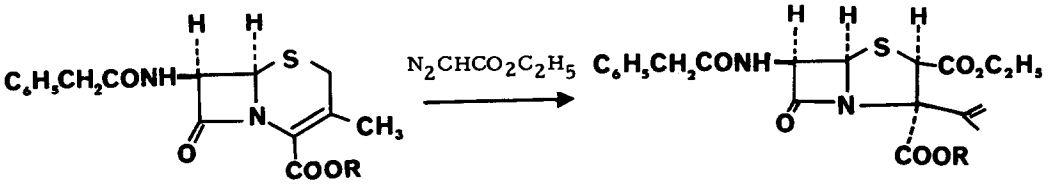
The transformation of a penicillin to a cephalosporin was first accomplished by Morin and co-workers.[1] The present communication is concerned with the first skeletal conversion of a cephalosporin to a penicillin achieved by the reaction with a carbene, which involves a [2,3]-sigmatropic rearrangement of a sulfonium ylide intermediate. It is known that the electrophilic addition of carbenes to allyl sulfides forms sulfonium ylids and these undergo two types of reactions, Stevens and [2,3]-sigmatropic rearrangements.[2] In cyclic allyl sulfonium ylids, however, the latter rearrangement has been reported only on a simple, fundamental system.[3]

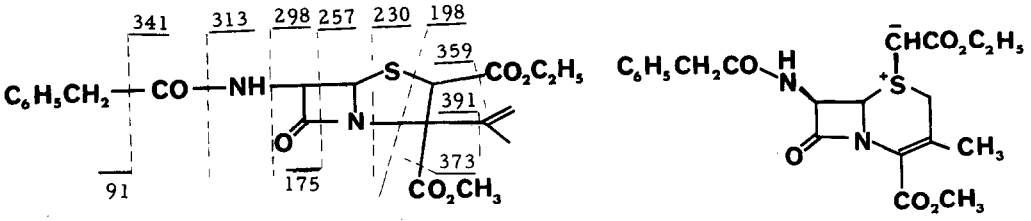
To a mixture of methyl 3-methyl-7-phenylacetamido-3-cephem-4-carboxylate (Ia) and copper powder in xylene was added dropwise ethyl diazoacetate at 130° in a nitrogen atmosphere and the resulting mixture was heated for 3 hours. A usual work-up including purification by dry column chromatography gave the penam



Ia: R=CH_3
Ib: R=CH_2Ph
Ic: R=CH_2CCl_3

IIa: R=CH_3
IIb: R=CH_2Ph
IIc: R=CH_2CCl_3
IId: R=H

compound (IIa) as the sole β-lactam containing product in 53% yield (based on the consumed Ia (50%)): mp 111-112° (recryst. from MeOH), $[\alpha]_D^{20°}$ +252° (c=1.00, $CHCl_3$). The molecular formula, $C_{21}H_{24}O_6N_2S$, was determined by the combustion analysis and M^+ (m/e=432) in the MS. The UV maximum of Ia, 260 nm(log ε=3.82), disappeared in IIa and the IR showed absorption maxima at 1796 (β-lactam), 1740 (ester), 1698 (amide), and 3400 (NH) cm^{-1}. The NMR peaks appeared at 1.23 (3H, t, J=7.0 Hz), 2.06 (3H, dd, J=1.6 and 0.7 Hz), 3.62 (2H, s), 3.77 (3H, s), 4.00 (2H, q, J=7.0 Hz), 4.60 (1H, s), 5.17 (1H, q, J=1.6 Hz), 5.28 (1H, q, J=0.7 Hz), 5.34 (1H, d, J=4.0 Hz), 5.64 (1H, dd, J=4.0 and 9.5 Hz), 6.77 (1H, d, J=9.5 Hz), and 7.28 (5H, s) ppm.[4] Irradiation at H^5 (5.34 ppm) increased the integrated intensity of H^2 (4.60 ppm) by 20% and that at olefinic methyl protons (2.06 ppm) increased the intensity of the olefinic proton at 5.17 ppm by 7%. The above NOE observed between H^2 and H^5 indicated the same orientation of the two protons, and the coupling constant, 4.0 Hz, between H^5 and H^6 established the cis configuration of these protons on the β-lactam ring. The MS fragmentation pattern shown below was also consistent with the structure.



III

With respect to the configuration at C-3, the spectral data did not provide any definitive information; however, the following considerations permitted the assignment of the carbomethoxy group as having α-orientation, that is, the same as natural penicillins. The preferential formation of β-S-oxides in the oxidation of penicillin derivatives in non-polar solvents with various oxidizing agents has been explained as the result of the hydrogen bond formation between

the 6-β-amide proton and the oxidants.[5] Moreover the same argument was applied to the predominant formation of β-S-oxides in the cephalosporin field.[6] Considering our reaction with these data as background, the carbethoxycarbene arising from ethyl diazoacetate would be expected to approach the sulfide function of Ia from the β-side by the interaction between the carbethoxy group and the 7-β-amide moiety of Ia to afford the β-orientated ylid intermediate (III). The [2,3]-sigmatropic rearrangements of allylic ylids are now recognized as a process of great facility and widespread occurrence, and Baldwin proved that the rearrangements proceed suprafacially with respect to both fragments with stereochemical evidence illustrating the concerted Wittig rearrangement.[7] The [2,3]-sigmatropic rearrangement of III via a doubly suprafacial transition state would result in the α-orientation of the carbomethoxy group in IIa. Thus, the structure of IIa including all stereochemistry has been deduced. The unambiguous determination of the structure was due to a X-ray diffraction study carried out in this Laboratories and the details will be published in a full paper.

Repetition of the above reaction on the benzyl ester (Ib) and trichloroethyl ester (Ic) afforded the corresponding oily penam compounds, IIb and IIc, respectively. The catalytic hydrogenolysis of IIb, and preferably, the treatment of IIc with zinc dust in aqueous acetic acid gave the free carboxylic acid IId: mp 168-170° (recryst. from 50% MeOH), $[\alpha]_D^{20°}$ +294° (c=1.02, $CHCl_3$), IR ν_{max}^{nujol} 1802 (β-lactam), 1728 (ester and carboxyl), 1638 (amide) cm^{-1}.

Contrary to our expectation, IId did not show a significant antimicrobial activity.

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4) All coupling constants except the ethyl ester were confirmed by the n.m.d.r. measuring.

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