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SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. 13.[1] TRANSFORMATION OF 6-EPIPENICILLINS TO 2R-{(1S, 5R)-2-OXA-6-OXO-4,7-DIAZABICYCLO[3.2.0]HEPT-3-EN-7-YL}-3-METHYLBUT-3-ENOATES

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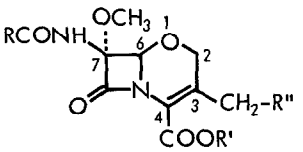
Summary Reaction of 2β-unsubstituted or functionalized-methyl 6-epipenicillin sulfoxides 2 with tervalent phosphorus compounds gave azetidinone-epi-oxazolines 3, important intermediates in synthesis of 7α-methoxy-1-oxacephems. Preparation of the 2β-functionalized-methyl substrates is described also.

A recent publication[2] from our laboratories revealed marked antibacterial activity of 7α-methoxy-1-oxacephems[3] 1 particularly against gram-negative microorganisms including β-lactamase-producing, resistant strains. This finding has urged us to find out efficient and practical synthetic routes to this new class of antibiotics 1 which are not naturally occurring



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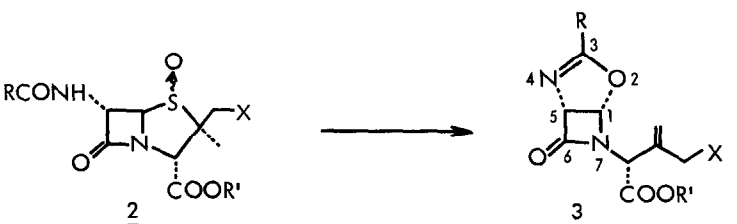
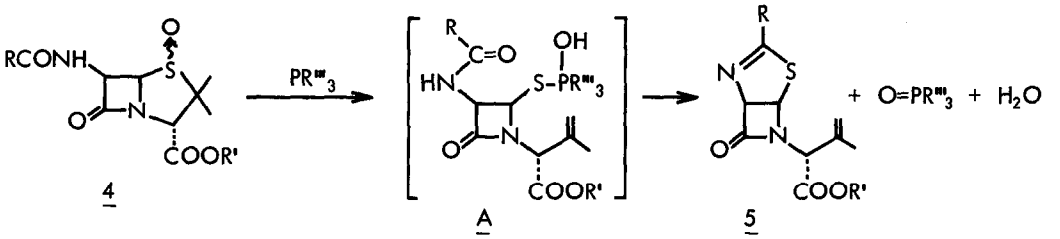
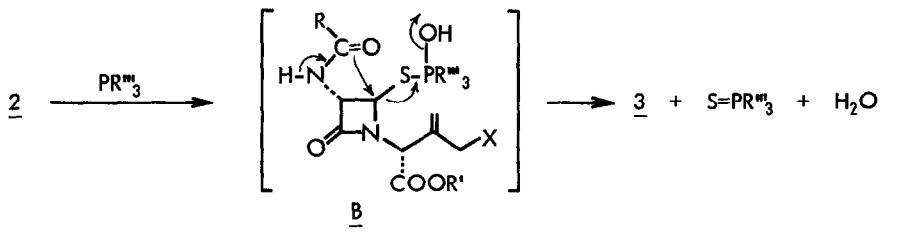
In accomplishing a straightforward synthesis of the antibiotics 1, we have needed to prepare novel azetidinone-epi-oxazolines 3 having the but-3-enoate side chain as important intermediates. We wish to report here efficient preparation of these epi-oxazolines 3 from 6-epipenicillin sulfoxides 2 and also preparation of novel 2β-functionalized-methyl substrates 2 (X ≠ H).



2 3

Our finding[4] of this oxazoline formation is based on the following consideration. Phosphoranylthioazetidinone A[6] has been suggested as an intermediate in formation of azetidinone-thiazoline 5 from penicillin sulfoxide 4. With thiazoline formation being stereochemically improbable the corresponding intermediate B from 6-epipenicillin sulfoxide 2 would undergo the C-S bond cleavage leading to the desired epi-oxazoline 3. Reasonably, the phosphoranylthio group would act as a good leaving group assisted by the facile P=S bond formation.





In fact, when 6-epipenicillin G sulfoxide ester 2a (R = $PhCH_2$, R' = $CHPh_2$, X = H) was treated with $P(OMe)_3$ (1.3 mol equiv) in refluxing dichloroethane with azeotropic removal of water for 4 hrs, epi-oxazoline 3a[7] was obtained in 67% isolated yield. Then the reaction was applied to various 2-unsubstituted-methyl 6-epipenicillin β-sulfoxides[8] 2a-f and also to 2β-functionalized-methyl 6-epipenicillin α-sulfoxides[9] 2g-k, with variation of the phosphorous reagent and the solvent.

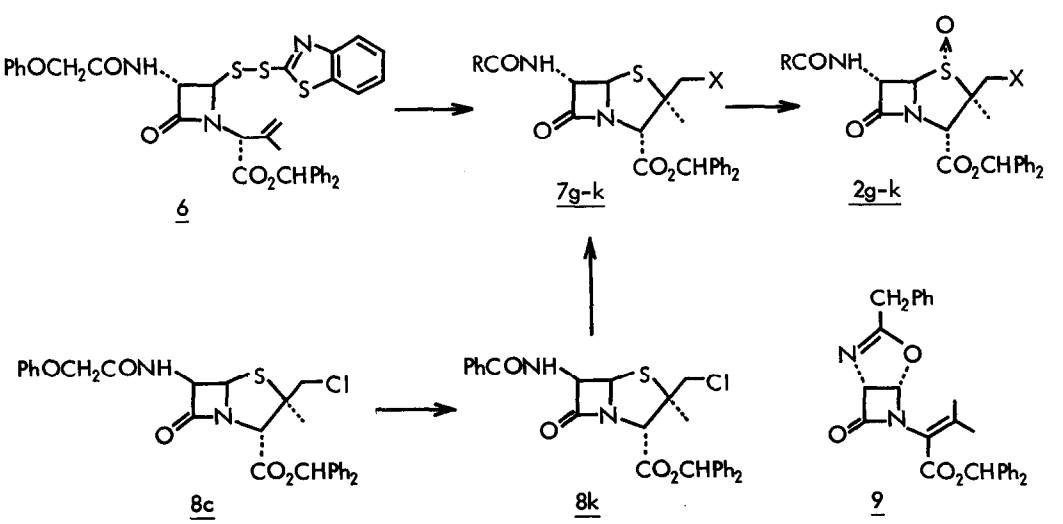
As is clear from the Table, the reaction is generally applicable to 6-epipenicillin sulfoxides having a variety of the side chain, the ester and the functionality at the C_2-methyl. The allylic chloride moiety in 2g and 2k was inert to the phosphorus reagent in accordance with our previous observation in preparation of azetidinone-thiazoline congeners.[11] It is noteworthy that the reaction of 2β-functionalized-methyl 6-epipenicillin α-sulfoxides 2g-k is significantly faster than that of β-sulfoxides 2a-f. Triphenylphosphine is generally superior to trimethyl phosphite and tributylphosphine. The reaction did not proceed smoothly with the following phosphorus compounds: $P(OPh)_3$, $P(OPh)_2Cl$ and $P(OEt)_2OH$. Suitable solvents are aromatic hydrocarbons, halogenated hydrocarbons, alcohols and their mixtures boiling in the range of 80-120°C.

Table. Transformation of Epipenicillin Sulfoxides 2 to Epi-oxazolines 3

2[i]	R	R'	X	RR''_3[ii]	Solvent[iii]	Time (hr)[iv]	3 (%)	Mp (°C)
a	$PhCH_2$	$CHPh_2$	H	$P(OMe)_3$	C_6H_6	8	55	99.5-100
a	$PhCH_2$	$CHPh_2$	H	PPh_3	DCE	5	70	
b	$PhCH_2$	CH_2Ph	H	$P(OMe)_3$	DCE	5	65	foams
c	$PhOCH_2$	$CHPh_2$	H	$P(OMe)_3$	C_6H_6	5	36	foams
d	Ph	$CHPh_2$	H	$P(OMe)_3$	DCE	5	47	117-118
d	Ph	$CHPh_2$	H	PPh_3	Tol-DCE	3.5	76	
d	Ph	$CHPh_2$	H	$P(Bu\text{-}n)_3$	Tol-BuOH-t	4	67	
e	Ph	CH_2CCl_3	H	PPh_3	Tol-DCE	4.1	71	foams
f	Ph	PNB[v]	H	PPh_3	DCE	4	52	86.5-88
g	$PhOCH_2$	$CHPh_2$	Cl	PPh_3	Tol	0.17	66	foams
h	$PhOCH_2$	$CHPh_2$	OCHO	PPh_3	Tol	0.17	60	foams
i	$PhOCH_2$	$CHPh_2$	OAc	PPh_3	Tol	0.5	38	foams
j	$PhOCH_2$	$CHPh_2$	$OCOCH_2Cl$	PPh_3	Tol-DCE	1.5	66	foams
k	Ph	$CHPh_2$	Cl	PPh_3	Tol-DCE	0.67	69[10]	105-106

[i] The stereochemistry of the sulfoxide is β in 2a-f and α in 2g-k. [ii] The molar equiv of the reagent used is 1.1-2.5; usually the 1.2 equiv is sufficient for completion of the reaction. [iii] DCE: dichloroethane; Tol: toluene; the ratio of the mixture solvents is 1:1. [iv] The reaction mixture was refluxed for the specified time with azeotropic removal of water. [v] p-Nitrobenzyl.

The 2β-functionalized-methyl substrates 2g-k are prepared in the following way. Disulfide 6[12] obtained from 6-epipenicillin V sulfoxide 2c in 62% yield was reacted respectively with $CuCl_2$ in CH_2Cl_2 and with an excess of formic, acetic or chloroacetic acid in the presence of silver acetate in AcOEt by applying Kamiya's method[13] to give 2β-chloromethyl 6-epipenam 7g



(X = Cl) in 50% yield and 2β-acyloxymethyl compounds 7h-j (X = OCHO, OAc or $OCOCH_2Cl$) in 40-50% yields. Oxidation of 7g-j with iodobenzene dichloride in aqueous pyridine[8] exclusively gave the corresponding α-sulfoxides[9] 2g-j in 50-60% yields. Since the disulfide formation from the benzoylamino derivative 2d did not proceed well, the 2β-chloromethyl benzoylamino substrate 2k was prepared in 46% overall yield from the corresponding penicillin V ester 8c[13] by the known one-pot, acyl exchange process (8k)[14] followed by epimerization (7k)[8] and oxidation.

Our ealier synthesis[1] of 7α-methoxy-1-oxacephems 1 has been much improved by convenient preparation of an important intermediate 9 by facile base-catalyzed isomerization of the epi-oxazoline 3a. A further improved, straightforward synthesis of the important β-lactam compounds 1 via compounds 3 will be reported soon.

References and Notes

1. For Part 12 in this series see S. Uyeo, I. Kikkawa, Y. Hamashima, H. Ona, Y. Nishitani, K. Okada, T. Kubota, K. Ishikura, Y. Ide, K. Nakano and W. Nagata, submitted to J. Am. Chem. Soc.
2. M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani and W. Nagata, J. Med. Chem. in press.
3. We use the trivial name of 1-oxacephem(s) for 1-oxa-1-dethiacephalosporin(s).
4. While our procedure was submitted to the patent literature two years ago [see Y. Hamashima, M. Yoshioka, S. Uyeo, T. Tsuji, I. Kikkawa and W. Nagata, Japan Patent Kokai 78-87388. Aug. 1, 1978 (Application date, Jan. 10, 1977)], preparation of an epi-oxazoline 3 (R = CH_2Ph, R^1 = Me, X = H) was reported very recently.[5]
5. R. Busson, E. Roets and H. Vanderhaeghe, J. Org. Chem. 43, 4434 (1978).
6. L. D. Hatfield, J. Fisher, F. L. Jose and R. D. G. Cooper, Tetrahedron Lett. 4897 (1970).
7. 3a: NMR ($CDCl_3$) δ 1.70 bs 3 H, 3.52 s 2 H, 4.82 s 1 H, 4.96 s 1 H, 5.10 bs 1 H, 5.08 d 1 H (3.8 Hz), 5.73 d 1 H (3.8 Hz), 6.92 s 1 H, 7.25 s 5 H, 7.32 s 10 H; IR ($CHCl_3$) 1784, 1752, 1647, 1171 cm^{-1}.
8. A. Vlietinck, E. Roets, P. Claes, G. Janssen and H. Vanderhaeghe, J. Chem. Soc. Perkin I 937 (1973).
9. The sulfoxide and the 2-methyl group in 3 should be cis in order to yeild the sulfenic acid intermediate via [2.3] sigmatropic shift. See S. Uyeo, T. Aoki and W. Nagata, Heterocycles 11, 305 (1978).
10. 3k: NMR ($CDCl_3$) δ 4.13 s 2 H, 5.17 s 1 H, 5.35 s 1 H, 5.62 s 1 H, 5.38 d (3 Hz) 1 H, 6.03 d (3 Hz) 1 H, 6.93 s 1 H, 7.2-8.1 m 15 H; IR ($CHCl_3$) 1784, 1751, 1633 cm^{-1}.
11. S. Uyeo, T. Aoki, H. Itani, T. Tsuji and W. Nagata, Heterocycles 10, 99 (1978).
12. 6: m.p. 83-86°; NMR ($CDCl_3$) δ 1.92 bs 3 H, 4.47 s 2 H, 5.01 s 1 H, 4.9-5.3 m 3 H, 5.17 d (2 Hz) 1 H, 6.93 s 1 H, 6.8-8.1 m 15 H; IR ($CHCl_3$) 3430, 3005, 1785, 1745, 1700 cm^{-1}.
13. T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi and T. Oku, Tetrahedron Lett. 3001 (1973).
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