SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS 8*
A USEFUL METHOD FOR PREPARATION OF PENICILLIN α-SULFOXIDES

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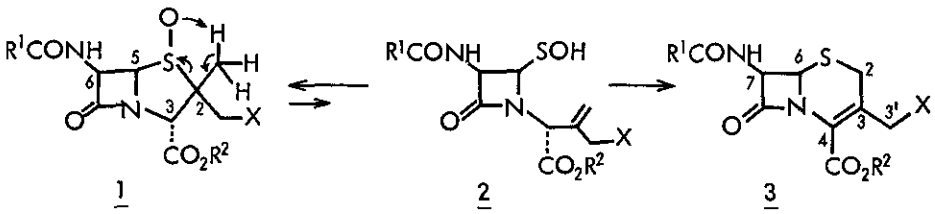
A useful method for preparation of 2β-functionalized-methyl penicillin α-sulfoxide 4 is described.

Penicillin sulfoxide has been playing an important role as a key intermediate for penicillin to cephalosporin conversion.[1] A typical example is the industrial production of deacetoxycephalosporanate 3a, a precursor of cephalexin, from penicillin sulfoxide 1a. The importance of the sulfoxide can be attributed to the fact that it is in equilibrium with the chemically reactive seco-sulfenic acid 2a via [2,3] sigmatropic shift. The seco-sulfenic acid 2a can either be cyclized to the deacetoxycephalosporin 3a in the presence of an appropriate catalyst or be intercepted with a proper reagent to give a stable seco-compound which is then transformed into various kinds of cephalosporins.[2]

The stereochemistry of the sulfoxide 1a, whether it is α(R)-

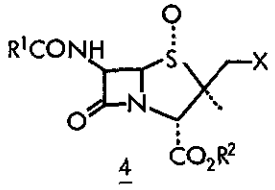
Chart 1



1 2 3

a: X = H

b: X = OAc, halogen



4

R¹: ϕCH_2 (G-), ϕOCH_2 (V-)

R²: $CH\phi_2$, $CH_2\phi$, CH_2CCl_3, etc

X: OAc, halogen

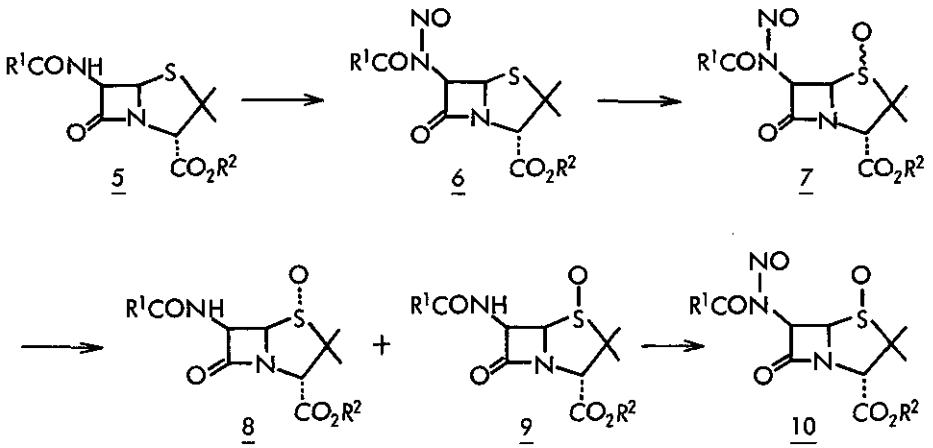
or β(S)- oriented, is not important in this instance since both compounds give the same sulfenic acid 2a. However, if one of the two methyl groups at C_2 has a functional group such as acetoxy or halogen, the sulfoxide and the 2-methyl group should be oriented in cis relationship in order to yield the desired seco-sulfenic acid 2b which could be cyclized to a 3'-functionalized cephalosporin 3b, a precursor of parenteral cephalosporin antibiotics (cephalothin, cephazolin etc.).[3] Thus, it is clear that 2β-functionalized-methyl penicillin α-sulfoxide 4 would be an important intermediate for penicillin to 3'-functionalized cephalosporin conversion. However, no efficient method for preparation of this type of compounds has hitherto been reported. In this communication we wish to report a useful method to prepare these compounds.

Oxidation of penicillins with peracids is known to give β-sulfoxides exclusively presumably owing to the hydrogen

bonding between amide NH and the reagent. We reasoned that blocking of the NH with an easily removable group followed by peracid oxidation would result in a predominant formation of the α-sulfoxide due to less hindered α-side attack by the reagent. An N-nitroso group was selected for this purpose since preparation of N-nitroso-penicillins and removal of the nitroso functionality have been known to occur in good yield.[4,5]

As a model experiment, penicillin-V benzhydryl ester 5 was converted into N-nitroso derivative 6 with N_2O_4 and the product was oxidized immediately with m-chloroperbenzoic acid to afford the unstable N-nitroso-sulfoxide 7. Nonidentity of this compound (by nmr) with the N-nitroso-β-sulfoxide 10 prepared by N-nitrosation of penicillin β-sulfoxide 9

Chart 2



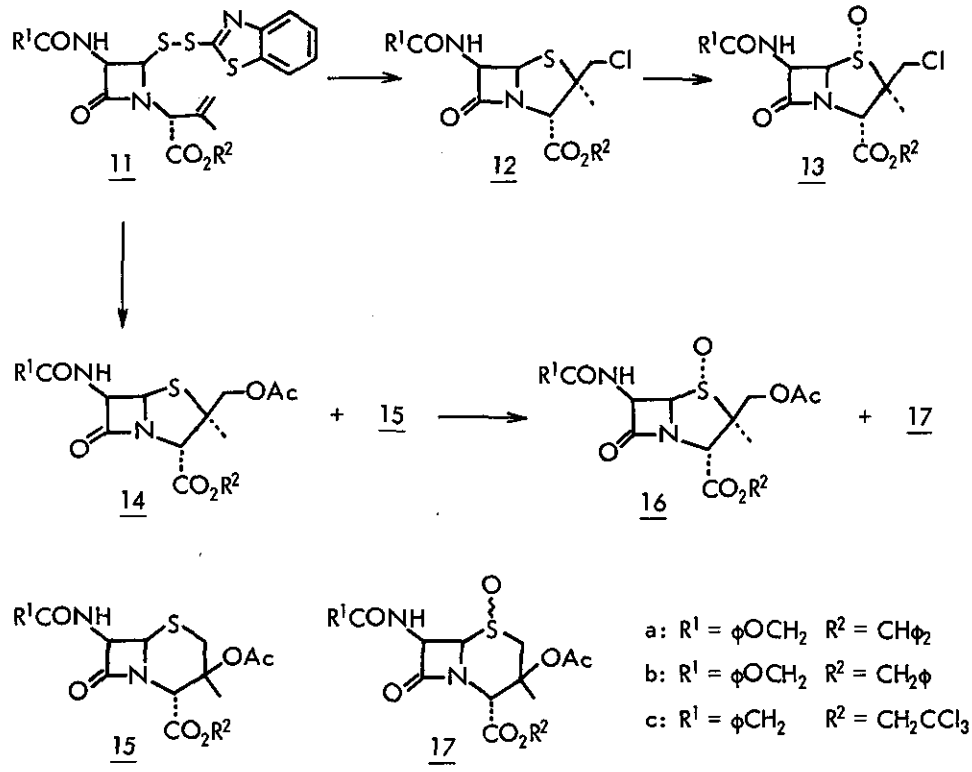
R^1: ϕOCH_2

R^2: $CH\phi_2$

suggested that α-sulfoxidation occurred predominantly as expected. In fact, treatment of the N-nitroso-sulfoxide 7 with zinc and acetic acid in methylene dichloride at 0°C gave a mixture of the α- and β-sulfoxides 8 and 9 at the ratio of 5 to 1 in favor of the former. Additional experiments using other substrates showed that application of this procedure to various 2β-functionalized-methyl penicillins was successful in producing the α-sulfoxides exclusively and that most of the carboxylic acid protective groups commonly used for β-lactam antibiotics were not affected during the operation except for the p-nitrobenzyl group.

Thus, 2β-chloromethyl penicillin-V benzhydryl ester 12a, prepared from the disulfide 11a,[6] gave the α-sulfoxide 13a in 66% yield, while the 2β-acetoxymethyl derivative 14a, which was prepared also from 11a[6] and contaminated with the difficultly separable 3-acetoxycepham derivative 15a, gave the α-sulfoxide 16a in 50% yield from 11a after simple chromatographic separation from the cepham sulfoxide 17a which was formed from 15a. Other 2β-functionalized-methyl penicillin α-sulfoxides 13b (60%), 13c (66%), 16b (50%) and 16c (62%) were prepared similarly. On heating in toluene, these α-sulfoxides were rearranged to the more stable 2α-functionalized-methyl penicillin β-sulfoxides in high yields.[7] A following example illustrates a general experimental procedure for the present new method.

Chart 3



To a suspension of 2β-chloromethyl penicillin benzhydryl ester 12a (9.6 g) and an anhydrous sodium acetate (5.0 g) in methylene dichloride (25 ml) was added dinitrogen tetroxide (ca. 2 ml) under ice-cooling and the mixture was stirred for 1 hr at the same temperature and then poured into an aqueous sodium bicarbonate solution. The product was extracted with methylene dichloride and the organic layer was washed with water and dried with anhydrous magnesium sulfate. The drying agent was filtered off and the filtrate (ca. 100 ml) was treated with m-chloroperbenzoic acid (80%) (4.50 g) under

ice-cooling for 1 hr. Acetic acid (5 ml) and activated zinc powder (8 g) were added to the reaction mixture and the resulting mixture was stirred for 1 hr under ice-cooling. Usual work-up and chromatography of the crude product on silica gel (deactivated with 10% W/W H_2O) using a benzene-ethyl acetate mixture (9:1) as the eluting solvent gave the α-sulfoxide (6.32 g) 13a as a foam.

ir ($CHCl_3$): 1800, 1750, 1695 cm^{-1}

nmr ($CDCl_3$): δ 1.10 s 3H, 3.90 s 2H, 4.50 s 2H, 4.76 d
J = 4 cps 1H, 4.86 s 1H, 5.25, 5.38 dd
J = 4 cps 1H, 6.93 s 1H, 6.8-7.6 m 15H.

Conversion of these α-sulfoxides to cephalosporins will be discussed in a separate paper.

REFERENCES

* Dedicated to Prof. T.Nozoe on the occasion of his 77th birthday.

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