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STRUCTURAL STUDIES ON PENICILLIN DERIVATIVES. X. CHLORINATION OF AZETIDINONE DERIVATIVES

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ABSTRACT: The allylic methyl group of several azetidinone derivatives can be cleanly chlorinated by a mechanism which appears to be that of an ene-reaction.

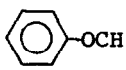
Some years ago we published a rearrangement of penicillin sulfoxide ester to the thiazoline (I).[1] This intermediate, which was produced in high yield, represented an intriguing starting point for the synthesis of various cephalosporin derivatives because, conceptually, any conversion of penicillins into cephalosporins has to entail an oxidative functionalization of the two saturated methyl groups of the pencillin. In thiazoline (I) one methyl group of the penicillin is converted into a methylene group which is convertable by many methods to the C-X functionality (where X = heteroaton). Moreover, the second methyl group is now allylic and presumably activated for further derivatization.

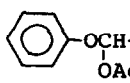
An initial attempt at functionalization of the methyl group of (I) with lead tetraacetate [$Pb(OAc)_4$, 1.2 equiv., AcOH, 80°C, 6 h] gave the acetoxy derivative (II) as a mixture of isomers.[2] Similar results were obtained with N-bromosuccinimide, indicating that this 2' position was the most sensitive to oxidation, possibly by the mechanism shown in Scheme I. Thus, we investigated the thiazoline (III) in which this sensitive position no longer existed. Reaction of (III) with chlorine (4 equiv.) in methylene chloride (25°C, 3 days) gave a good yield of the chlorinated product (IV).[3] On further investigation of solvents and chlorinating reagents, we found that the optimum method for the conversion of (III) to (IV) was the use of t-butyl hypochlorite (1.25 equiv., 25°C, 30 min) in methyl formate.

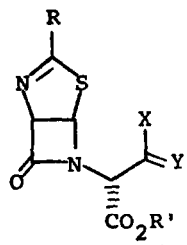
These conditions were then used on the thiazoline (I); a 60% yield of (V) resulted. It is noteworthy that the change in solvent from methylene chloride to methyl formate caused a dramatic increase in reaction rate; furthermore, when redistilled methyl formate was used, there was a decrease in the rate of the reaction. The reaction was found to be catalyzed by small amounts of acid, e.g. formic acid.[4] In an attempt to obtain further insight into the mechanism of this reaction, the deuterated thiazoline (VI) was subjected to the chlorination conditions when the product was observed to be (VII).

Mechanistically, it was intriguing to speculate that this reaction proceeded through an 'ene' process, which could explain the results obtained on the deuterated thiazoline.[5] This represented a previously unconsidered chlorination mechanism. There was, however, the alternate, more conventional, explanation that the chloronium ion was the intermediate which then on purely statistical grounds gave predominantly the observed product; the deuteration results were then explained on the basis of an isotope effect (see Scheme II).[6]

The utility of the functionalized thiazoline (V) has been recently demonstrated by a conversion to both the exomethylene cephalosporin (VIII) and the 3-hydroxycephalosporin (IX).[2]

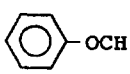
I R =  ; R' = pNB; X = CH_3; Y = CH_2

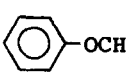
II R =  ; R' = pNB; X = CH_3; Y = CH_2

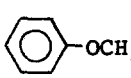


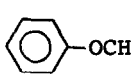
III R = EtOCO-; R'= CH_3; X = CH_3; Y = CH_2

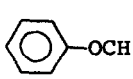
IV R = EtOCO-; R' = CH_3; X = CH_2Cl; Y = CH_2

V R =  ; R' = pNB; X = CH_2Cl; Y = CH_2

VI R =  ; R' = pNB; X = CH_3; Y = CD_2

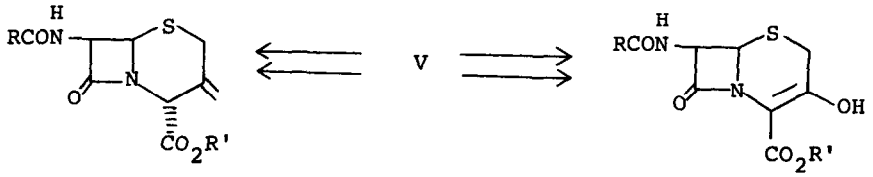
VII R =  ; R' = pNB; X = CD_2Cl; Y = CH_2

VIII R =  ; R' = pNB

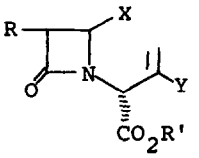
IX R =  ; R' = pNB

Because of the recent interest in new penicillin and cephalosporin type compounds in which the sulfur atom is replaced by an oxygen atom or methylene group, compounds of the type (Xb → XIIb) could represent useful intermediates for their synthesis. Consequently, we applied our previously described chlorination conditions to a series of azetidinones (Xa → XIIa) and in all

cases isolated in good yields the desired chloro compounds (Xb → XIIb). Experiments illustrating the potential utility of these compounds will be reported elsewhere.

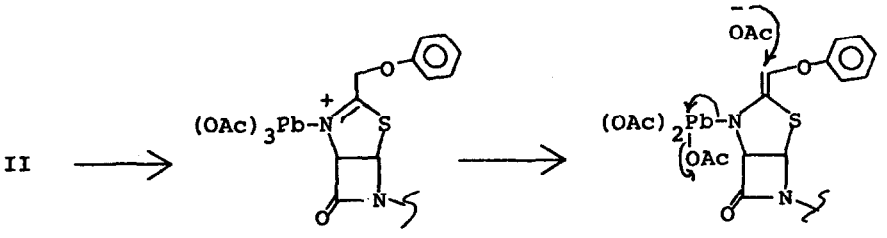


VIII V IX

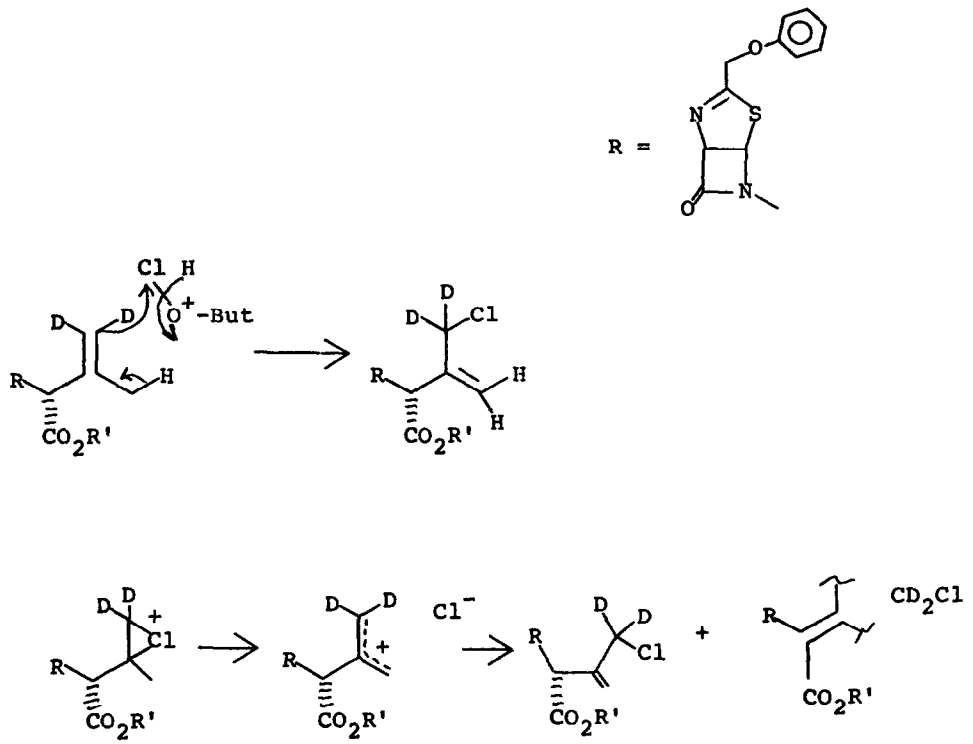


		(a)	(b)
X	R = $-OCH_2CONH-$; X = βCl; R' = $Ø_2CH-$;	Y = CH_3;	Y = CH_2Cl
XI	R = $-OCONH-$; X = βCl; R' = $Ø_2CH-$;	Y = CH_3;	Y = CH_2Cl
XII	R = $-OCONH-$; X = βOCH_3; R' = $Ø_2CH-$;	Y = CH_3;	Y = CH_2Cl

SCHEME I



SCHEME II



1. Cooper, R. D. G., and Jose, F. L. J. Am Chem. Soc., 92, 2575, 1970.
2. NMR ($CDCl_3$) 1.85 and 1.90 (s, 3H), 2.11 and 2.15 (s, 3H), 4.96 (br.s., 1H), 5.17 (br.s., 1H), 5.30 (s, 3H), 5.95 (d, 1H, J=4 Hz), 6.05 (d, 1H, J=4 Hz), 6.9-7.4 (m, 6H), 7.50 (d, 2H, J=8 Hz), and 8.20 (d, 2H, J=8 Hz).
3. Mp 105.5-107°C: NMR ($CDCl_3$) 3.9 (2H, q, J=12 Hz), 4.94 (2H, q, J=14 Hz), 5.12 (1H, s), 5.23 (1H, s), 5.46 (1H, s), 5.88 (1H, d, J=4 Hz), 6.04 (1H, d, J=4 Hz), 5.29 (2H, J=14 Hz), 6.88-7.33 (5H, m), 7.48 (2H, d, J=8 Hz), and 8.23 (2H, J=8 Hz).
4. The protonated form of t-butyl hypochlorite was a considerably more powerful electrophilic reagent. After disclosure of these results, Paquette et al. also confirmed this greatly increased electrophilic character of protonated t-butyl hypochlorite (see L. W. Hertel and L. Paquette, J. Am. Chem. Soc., in press).
5. Consideration of space filling models indicated that chlorine (or t-butyl hypochlorite) was able to form a planar ene-type transition state. Bromine, on the other hand due to its increased size, could not form a similar sterically compatible transition state and in fact will only react with the thiazoline (II) by addition to the double bond.
6. There is always a small amount of the α,β-unsaturated allylic chloride mixture of E and two isomers formed in the reaction, however, it is impossible at this stage to determine if these arise directly from the transition state or from double bond isomerization of the product.
7. Uyeo, S., Aoki, T., Itani, H., Tsuji, T., and Nagata, W. Heterocycles, 10, 99, 1978.

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