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REARRANGEMENT OF PENICILLIN G β-SULFOXIDE WITH CLEAVAGE OF THE C_5-S BOND, INITIATED BY VINYL CHLOROFORMATE.[1]

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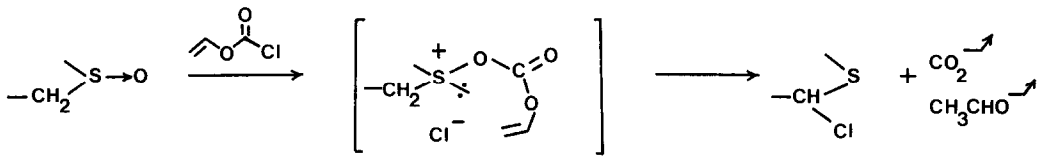
Abstract : Reaction of Penicillin G β-sulfoxide with vinyl chloroformate initiates a rearrangement by cleavage of the C_5-S bond with formation of a dihydrothiazine derivative.

We recently observed that sulfoxides react with vinyl chloroformate in inert solvents to give α-chloro sulfides with usually very good yields, according to the following scheme[1]:



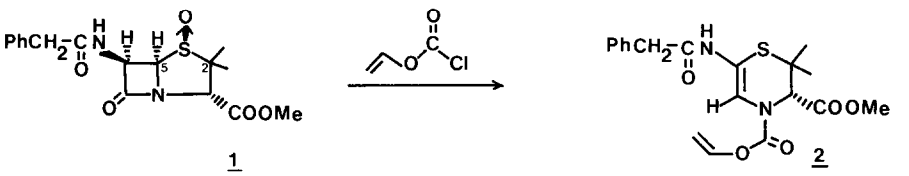
Vinyl chloroformate[2] was found to be much more reactive than other Pummerer reagents such as acetic anhydride, acyl chlorides or alkyl chloroformates. If vinyl chloroformate is much less reactive than trifluoro acetic anhydride or oxalyl chloride, one advantage over all other Pummerer reagents is that reaction conditions are totally neutral, since the by-products are carbon dioxide and acetaldehyde which furthermore are easily removed. Contrary to α-acetoxy or α-trifluoroacetoxy sulfides, α-chloro sulfides obtained by the vinyl chloroformate reaction can be used in situ for nucleophilic substitutions.[1,3]

Therefore, we examined the reaction of vinyl chloroformate with Penicillin G β-sulfoxide in order to see if this reagent, due to the mild neutral reac-

tion conditions, would give an access to the hitherto unknown 5-chloro or 5-substituted Penicillins, as all the other Pummerer reagents only yield 2-substituted penams or rearranged products.[4-7]

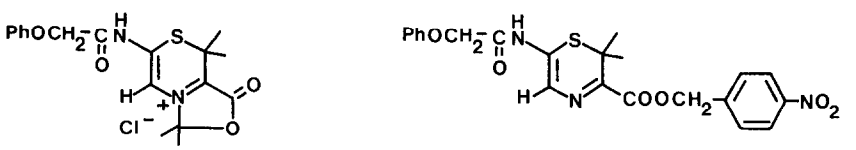
Penicillin G β-sulfoxide methyl ester[8] 1 reacts readily, at 0° or room temperature, with an excess vinyl chloroformate in anhydrous alcohol-free chloroform to give a unique compound which was isolated in 56% yield. This product is optically active $[\alpha]_D^{19°} = -74.5°$ (c=2,33 ; $CHCl_3$). Its Infra-Red spectrum[9] shows no characteristic β-lactam band and its U.V. spectrum in methanol[10] very strong absorptions.

Definite proofs of structure were obtained with ^1H and ^{13}C NMR[11], and mass spectrometry[12]. With these data, we assign structure 2 to the reaction product which results from a cleavage of the C_5-S bond and a subsequent rearrangement.



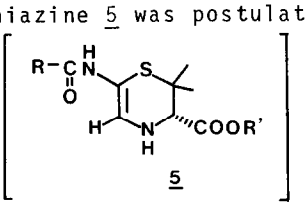
1 2

This type of structure has been observed only twice before as the result of an electrophilic activation of Penicillin sulfoxides : the thiazinium chloride 3 was obtained with phenyl acetyl chloride in acetone[13] ; N-chloro phtalimide in methylene chloride gave 4 and phenyl acetyl or phenyl sulfinyl chlorides the hydrochloride salt of 4 as transient compounds.[14]



3 4

Although the mechanism of these remarkable rearrangements has not been elucidated, the related dihydrothiazine 5 was postulated as an intermediate but never isolated.[6,13]



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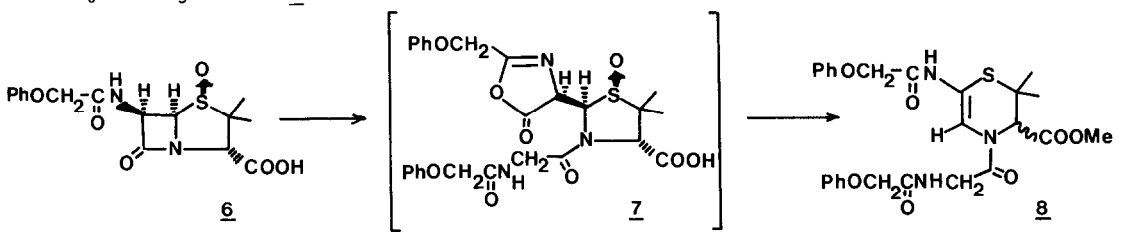
T.S. CHOU et al[14] proposed a more complex mechanism, starting by an activation of the sulfoxide, but which cannot account for a dihydrothiazine derivative

Our result would favour the involvement of the dihydrothiazine 5, because we could isolate the corresponding derivative 2, possibly due to the mild neutral conditions of the vinyl choroformate reaction.

Noteworthy, R. THOMAS probably isolated compound 8, of related structure.[15] The latter, which showed no optical activity, was isolated after derivatization of an unstable metabolite of Penicillin V β-sulfoxide 6 produced by extracellular enzymes of bacteria or Streptomycetes, PSM, the structure of which was tentatively assigned as 7.



Further work is needed to elucidate the exact mechanism of these rearrangements involving the cleavage of the C_5-S bond initiated by an electrophile on Penicillin sulfoxides, cleavage which was showed to also lead to different ring systems with other reagents, trifluoroacetic anhydride[7] and ethoxy carbonyl isocyanate.[16]

Acknowledgements. We thank Professor Andrée MARQUET for fruitful discussions and Mrs Liliane LACOMBE (Collège de France) for the ^{13}C NMR spectra. This work was supported by the CNRS (ERA 823). We also acknowledge the SNPE for a gift of vinyl chloroformate.

References and Notes

1) part of a communication presented at the Xth International Symposium on Organic Sulphur Chemistry - Abstract C 015. BANGOR (England) - September 1982.

2) vinyl chloroformate is a very stable reagent, now commercially available : SNPE (France); PCR Research Chemicals (U.S.A.); Ventron GmbH-PCR (West Germany).

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4) R.D.G. COOPER, L.D. HATFIELD, D.O. SPRY, Accounts Chem.Res. 6, 32 (1973) and references cited therein.
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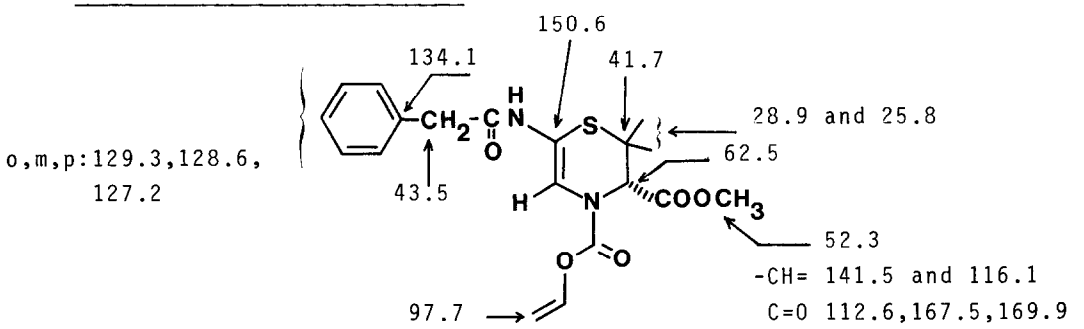
8) D.H.R. BARTON, F. COMER, P.G. SAMMES, J.Am.Chem.Soc., 91, 1529 (1969).
9) IR ($CHCl_3$) : 1650 cm^{-1}, 1680 cm^{-1}, 1730 cm^{-1}
10) U.V. (CH_3OH ; c=68.7 mg/l) : $\varepsilon_{214} = 12716$; $\varepsilon_{245} = 8249$; $\varepsilon_{270} = 8192$.
11) ^1H NMR ($CDCl_3$/TMS - 100 MHz) : CH_3 : 1.46 and 1.55 (s, 6H) ; OCH_3 : 3.70 (s, 3H); $-CH_2\varphi$: 3.60 (s, 2H); $-CH-COOCH_3$ and $-N-CH=$: 4.80 and 4.9 (s); $=CH_2$: 4.58 ^2J=1.5-2Hz, ^3J=6Hz), 4.9 (^2J=1.5-2Hz, ^3J=14Hz); $-N-\overset{O}{\overset{\|}{C}}-O-CH=$ and Ar : 7.0-7.40; NH : 6.55 (1.H, broad).
^{13}C NMR ($CDCl_3$/TMS - 20MHz) :



12) Mass Spectrometry (E.I.) : m/e 390 (M^+), 272 (M-PhCH=C=O), 244, 213, 118, 91 ($PhCH_2$).
$C_{19}H_{22}N_2O_5S$: M^+ = 390.1245 (mes.); M^+ = 390.12506 (calc.)
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