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SYNTHESIS AND CHEMISTRY OF CEPHALOSPORIN SULFENATE ESTERS

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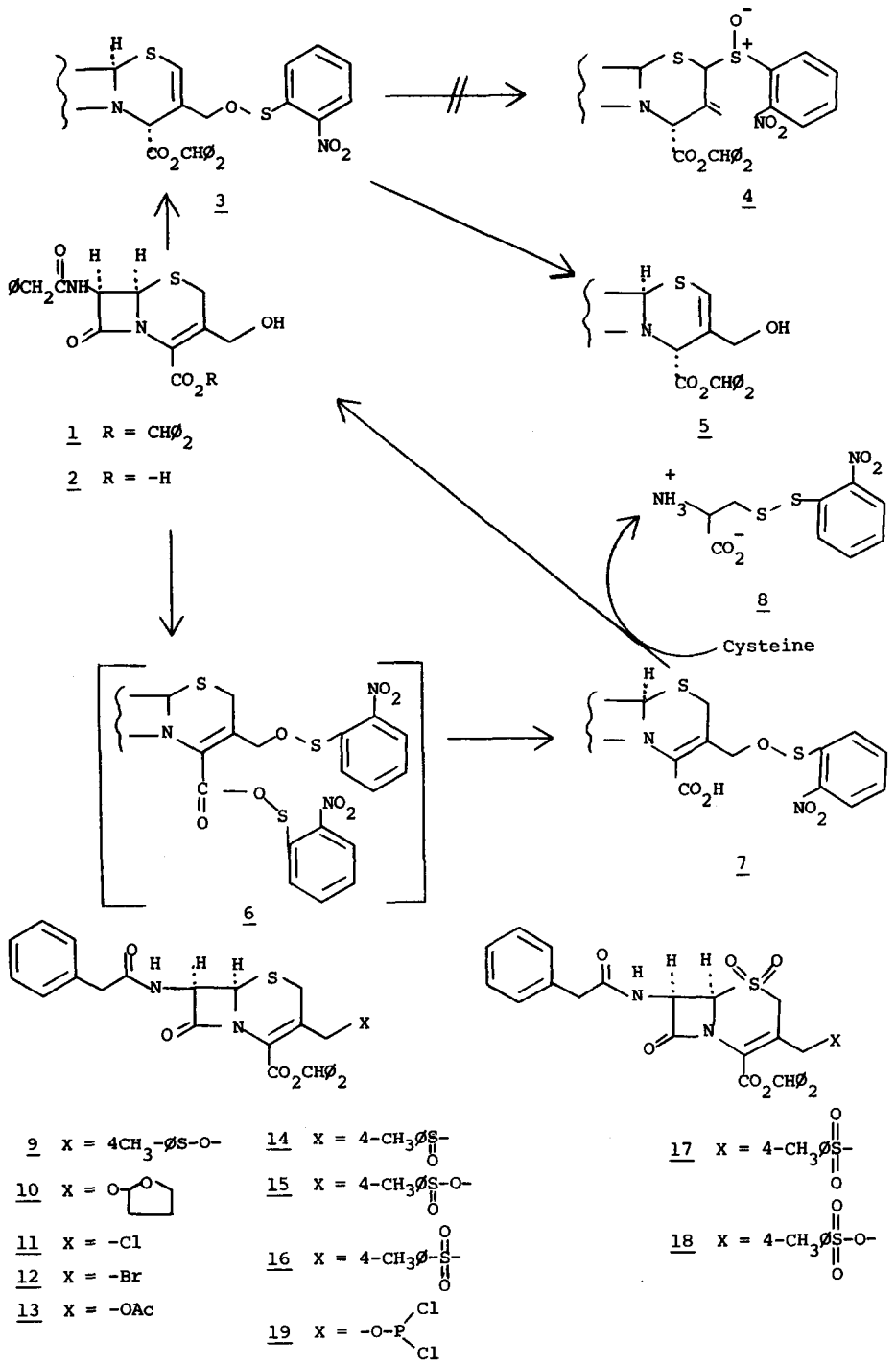
In a continuing search for improved β-lactam antibiotics, we have investigated the synthesis and properties of several C-3' sulfenate ester derivatives of cephalosporins. A priori , substances of this type would be expected to possess certain chemical features which could elicit interesting biological activities. Ejection of a C-3' substituent concerted with enzyme induced (transpeptidase, β-lactamase) β-lactam opening[1] would release reactive sulfenic acid moieties that could interact with enzyme[2] to cause "suicide" inhibition.[3] In addition, inhibition after reversible binding could also result by enzyme sulfenylation, since C-3' sulfenates would be expected to be potent sulfenyl donors.

Hydroxy acid 2 was easily prepared directly from 7-ACA on a large scale by a modification of the procedure of H. Nomura, et al.[4] Diphenyldiazomethane (DDM) converted 2 to 1 which reacted instantly with o-nitrobenzene sulfenyl chloride (acetonitrile, Et_3N, 26°) to afford sulfenate 3 as orange crystals; m.p. 136-137°d, IR ($CHCl_3$) 1775, 1735, 1680 cm^{-1}; NMR ($CDCl_3$) δ 3.66 (s, 3H), 4.33 (d of d, 2H, J = 12), 5.26 (d, 1H, J = 4), 5.63 (d of d, 1H, J = 4,9), 6.40 (d, 1H, J = 9), 6.46 (s, 1H) 6.93 (s, 1H), 7.2 → 8.2 (m, 14H).

The well-documented [2,3] sigmatropic interconversion of allylic sulfoxides and sulfenates was not observed.[5] Thus, sulfoxide 4 could not be detected (80°, ØH). Sulfenate 3 could be reductively cleaved by trimethylphosphite to afford Δ^2-hydroxy ester 5, identical with an authentic sample.[6]

In order to extend this methodology and obtain materials suitable for biological testing, hydroxy acid 2 was treated with two equivalents of o-nitrobenzene sulfenyl chloride (acetonitrile, pyridine, -50°). The bisadduct 6 formed but was unstable above 0°. Selective cleavage at low temperature of the reactive sulfenic anhydride in preference to the C-3' sulfenate ester, by a stoichiometric amount of trimethyl phosphite, led directly to sulfenate


3
4
5
1 R = CHØ2
2 R = -H
8
Cysteine
6
7
9 X = 4CH3-ØS-O-
10 X = O
11 X = -Cl
12 X = -Br
13 X = -OAc
14 X = 4-CH3ØS-
15 X = 4-CH3ØS-O-
16 X = 4-CH3Ø-S-
19 X = -O-P
17 X = 4-CH3ØS-
18 X = 4-CH3ØS-O-

acid 7; m.p. 124-126°d; IR (KBr) 1770, 1710, 1670 1640 cm^{-1}; NMR [$(CD_3)_2C = O$] 3.65 (s, 2H), 3.72 (s, 2H), 4.85 (s, 2H), 5.18 (d, 1H, J = 5), 5.80 (d of d, 1H, J = 5, 8). Sulfenates such as 7 are novel types of cephalosporins. Interestingly, 7 is a reactive thiolating agent, and thus interacts readily with cysteine (acetone/water, pH 8, 26°) to form disulfide 8 and reform 2. Glycine, serine, diaminobutyric acid and cystine did not react with 7 under these conditions.

Sulfenate esters such as 7 are relatively stable due to a strong inductive effect by the nitrophenyl substituent. To probe the generality of the above chemistry preparation of a less stable sulfenate was undertaken. Allylic alcohol 1 reacted with p-toluene sulfenyl chloride[7] in a variety of nonhydroxylic solvents containing non-nucleophilic bases (N-methylmorpholine) to form sulfenate 9 (tlc, nmr). In the conversion of 1 → 9, if unpurified THF was employed as solvent, a major co-product was found to be 10. Acetal 10 likely derives via peroxide catalyzed homolysis of the S-O bond in sulfenate 9. The resulting radicals interact with solvent to form 10.

Although stable at low temperature, 9 was slowly converted at 26° to a new substance ("A"). Use of excess p-toluene sulfenyl chloride favored this process. Substance "A" was inert to phosphite in refluxing methanol, but reaction with phosphorous trihalides afforded C-3'-halomethyl compounds (11, 12), while acetyl chloride/stannous chloride treatment afforded mixtures of 11 and acetoxy ester 13.

NMR evidence indicated that "A" was likely a mixture of diastereomeric materials. Sulfoxides 14 and sulfinate esters 15 were considered as the most probable structures. The former class was discounted by the following experiments. Cephalosporin G sodium salt reacted with sodium p-toluene-sulfinate (water, 47°),[7] to give a sulfone acid which was esterified (DDM) yielding 16. Interestingly, this compound in the presence of $CD_3OD/(CD_3)_2SO$ underwent facile proton exchange at C-3'. Oxidation of sulfone ester 16 with m-chloroperbenzoic acid gave disulfone ester 17 in which proton exchange at both C-2 and C-3' was rapid ($CD_3OD/(CD_3)_2CO$). Exhaustive oxidation of "A" afforded a solid which was different (IR, NMR, TLC) from 17 and for which we assign structure 18. The most likely alternative for "A", therefore, is sulfinate ester 15, which, bearing a chiral sulfur, can exist as a diastereomeric mixture. Hydroxy ester 1 reacted with p-toluene sulfinyl chloride[9] to afford a pro-

duct which was similar to "A" in all respects,[10] and we conclude that 15 is indeed the structure of "A". Attempts at de-esterification of sulfinate ester 15 (trifluoroacetic acid/anisole, 0°) led to extensive decomposition.

The interesting conversion of 15 to 3-halomethyl cephems 11 and 12 apparently does not proceed via the hydroxy ester 1, since this substance cannot be converted to 11 or 12 under similar reaction conditions. The product derived from reaction of 1 and phosphorous trichloride is probably dichlorophosphoryl ester 19.

Compound 7 did not inhibit a β-lactamase enzyme,[11] and showed weak antimicrobial activity against gram positive organisms.

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