PENICILLIN SULFOXIDE THERMOLYSIS IN TRIMETHYL ORTHOACETATE

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Abstract - The thermolysis of trichloroethyl 6-phenoxyacetamido-penicillanate sulfoxide in trimethyl orthoacetate gave four -lactam cleaved products.

During the course of our studies on the 6(7)-imino ethers of penicillins and cephalosporins, it was found that although the 6-imino ether of penicillin sulfoxide can be made by reacting benzhydryl 6-aminopenicillanate sulfoxide with trimethyl orthoacetate at a temperature of 40°C, extensive decomposition took place at higher temperatures[2]. This paper describes the thermolysis of penicillin sulfoxides in the presence of trimethyl orthoacetate. 2,2,2-Trichloroethyl 6-phenoxyacetamidopenicillanate sulfoxide reacted extremely slowly with trimethyl orthoacetate in benzene under reflux. However, when trimethyl orthoacetate was used as reactent and solvent, complete reaction occurred after 16 h under reflux in an oil bath at a temperature of 115°C. The resulting residue after workup, gave the following four products after hexane-ether gradient elution chromatography on silica gel.

Product A : mp 118°C (1.2% yield), is assigned structure 1 from the following spectroscopic data :-

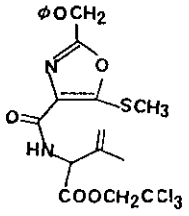
Mass spectrum[3] - m/z 494 (1.6%), corresponding with $C_{19}H_{19}Cl_3N_2O_5S$, and major fragmentation ions at 403, 402, 401 (100%), 399, 317, 269, 223, 155, 107, 99, 94, 77 and 73.

IR spectrum[4] - Absorption maxima at cm^{-1} 3367 (NH), 1759 (ester), 1639 (α,β-unsaturated amide), and 915 (cyclic ether), indicating the absence of a β-lactam ring.

PMR spectrum[5] - δ1.88(s,3H), 2.40(s,3H), 4.78 and 4.94(AB quartet,2H,J=12.2Hz), 4.96(d,1H, J=9.36Hz collapsing to a singlet after D_2O exchange), 5.02(s,2H), 5.16(d,1H,J=1.4Hz), 5.24 (s,1H), 7.05(m,3H), 7.30(d,1H,J=9.36Hz exchanged with D_2O), 7.35(m,2H).

CMR spectrum[6] - two CH_3 at 10.33 and 19.20, three CH_2 at 62.19, 74.83 and 117.06, four

CH at 61.14, 115.08, 121.96 and 129.66 (the three signals at 115.08, 121.96 and 129.66 represent the phenyl carbons), and eight tert-carbon at 94.25, 113.60, 138.60, 148.27, 155.62, 157.96, 167.90 and 185.33 ppm.



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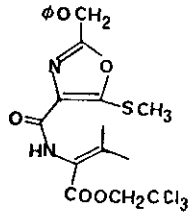
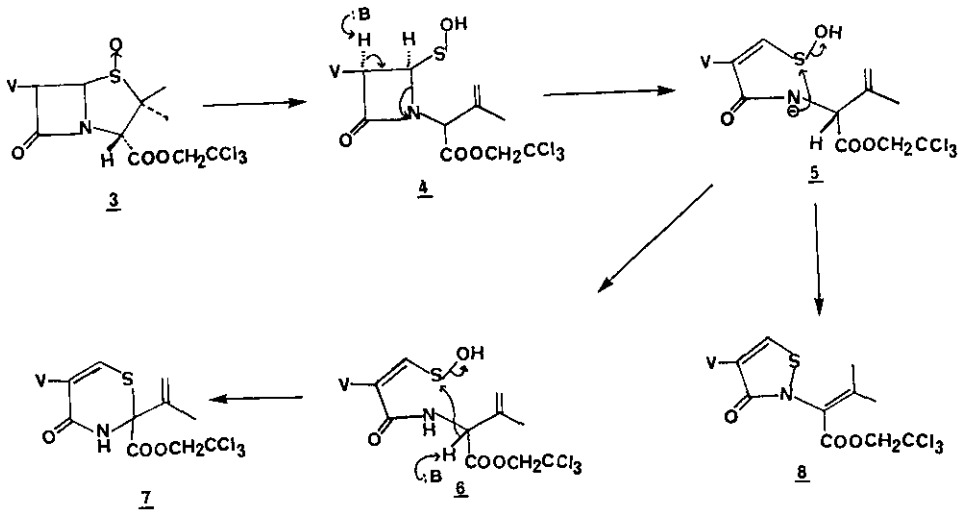


2

Treating product A with triethylamine in methylene chloride produced the α,β-unsaturated ester, 2, as was evident from the PMR spectrum[4] - δ2.00(s,3H), 2.30(s,3H), 2.40(s,3H), 4.64 (s,2H), 5.00(s,2H), 7.00(m,3H), 7.30(m,2H), and 7.72(s,1H, exchanged with D_2O).

Product B ; mp 165°C (4% yield), and Product C : mp 139-140°C (38% yield), were the thiazinone, 7, and isothiazolone, 8, reported previously by Morin and co-workers[7], and are probably formed by the route (Scheme 1) suggested by Koppel and Kukolja[8], or by the mechanism proposed by Morin and co-workers[7].

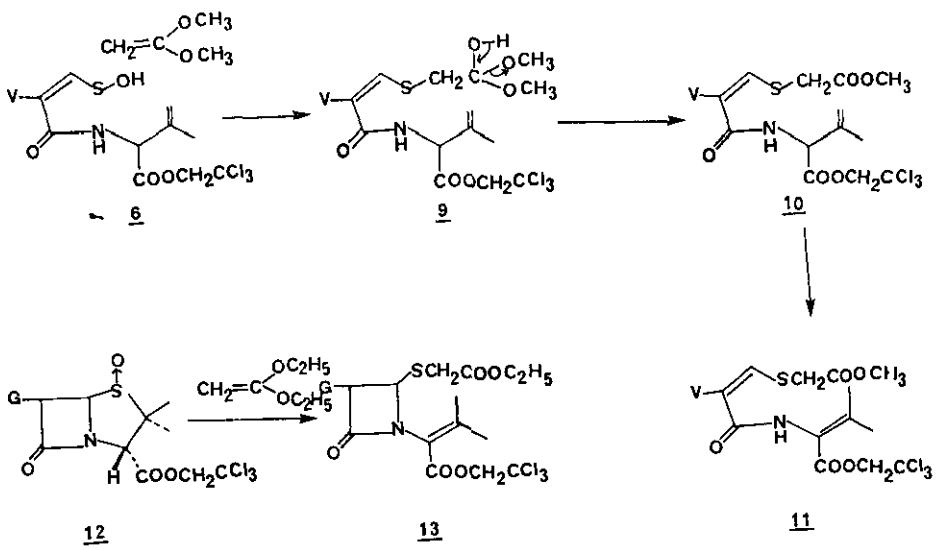
SCHEME 1



Product D : mp 78-79°C (12% yield) is assigned structure 10 from the following spectral data:-

Mass spectrum[3] - m/z 555, corresponding with $C_{21}H_{23}Cl_3N_2O_7S$, and major fragmentation ions at 451, 450, 449, 448, 447, 405, 404, 308, 300, 299 (100%), 272, 271, 202, 116, 107, 94 and 77.
IR spectrum[4] - absorption maxima at cm^{-1} 3388, 3236 (NH), 1760, 1741 (esters), 1686 (amide), and 1657 (α,β-unsaturated amide), indicating the absence of a β-lactam ring.
PMR spectrum[5] - δ1.88(s,3H), 3.58(s,2H), 3.80(s,3H), 4.68(s,2H), 4.74 and 4.96(AB quartet,2H, J=12.16Hz), 5.14(d,1H,J=1.4Hz), 5.18(s,1H), 5.20(d,1H,J=9Hz, collapsing to a singlet after D_2O exchange), 6.98(d,1H,J=9Hz, exchanged with D_2O), 7.10(m,3H), 7.40(m,2H), 7.44(s,1H) and 8.02 (s,1H, exchanged with D_2O).
CMR spectrum[6] - two CH_3 at 19.89 and 52.89, four CH_2 at 35.26, 67.45, 74.68 and 116.03, five CH at 58.06, 114.92, 122.54, 129.95, and 133.15 (the three signals at 114.92, 122.54 and 129.95 represent the phenyl carbons) and eight tert- carbon at 94.39, 124.87, 139.03, 157.03, 161.87, 167.29, 168.86 and 169.02 ppm.
The reaction of product D with triethylamine in methylene chloride produced the α,β-unsaturated ester, 11, as is evident from the PMR spectrum[4] - δ 1.95(s,3H), 2.28(s,3H), 3.65(s,2H), 3.80(s,3H), 4.68(s,2H), 4.85(s,2H), 7.12(m,3H), 7.40(m,4H) and 8.12(s,1H).

SCHEME 2



A suggested route for the formation of product D is summarized in Scheme 2. A similar type of reaction was reported by Barton and co-workers, in the thermolysis of 6-phenylacetamidopenicillanate sulfoxides with 1,1-diethoxyethene, the product being 13[9].

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3. Mass spectra were recorded on a Kratos MS-50 High Resolution Mass Spectrometer.
4. Infrared spectra were obtained on KBr discs using a Nicolet DX FTIR Spectrometer.
5. Proton magnetic resonance (PMR) spectra were recorded on a Bruker AM 300 Spectrometer using $CDCl_3$ as solvent and TMS as internal reference, and are reported as δ values.
6. CMR spectra were recorded on a Bruker AM-300 Spectrometer using $CDCl_3$ as solvent and are reported in ppm. The methyl, methylene, methyne, and tert-carbon assignments are made from INEPT experiments.
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