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STRUCTURAL STUDIES ON PENICILLIN DERIVATIVES: PART VII REARRANGEMENT OF PENICILLIN SULFOXIDES WITH TRIMETHYLPHOSPHITE-ACETIC ANHYDRIDE

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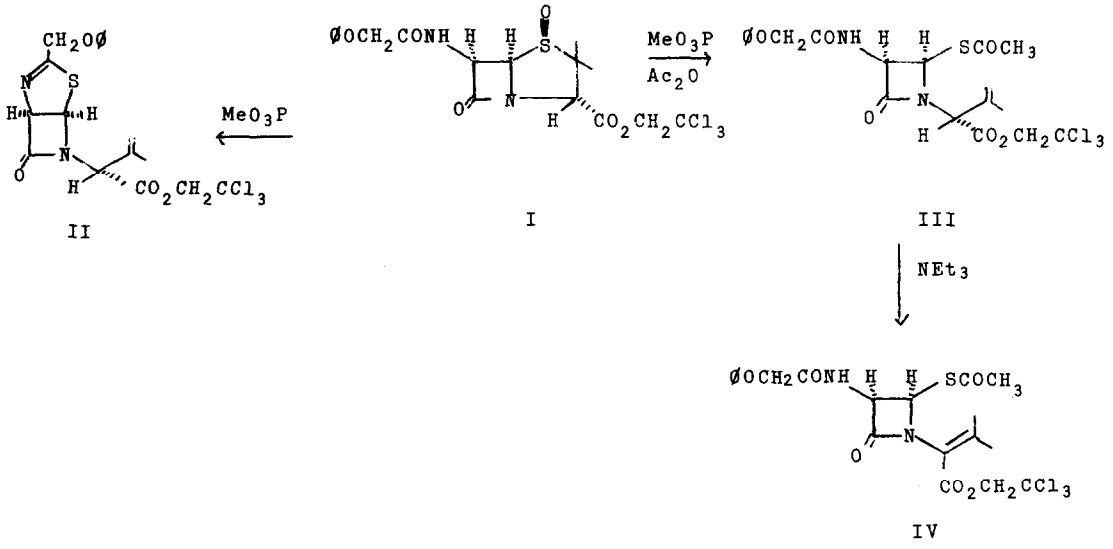
Several publications[1,2,3] in recent years have shown that the sulfenic acid obtained by a thermal sigmatropic rearrangement of penicillin sulfoxide has considerable synthetic versatility. Recently we reported[3] the rearrangement of the penicillin sulfoxide I to the thiazoline II which we believe proceeds by a reduction of the sulfenic acid to a thiol followed by intramolecular condensation with the amido side chain. We now wish to report a variation on this reaction in which the thiol intermediate is trapped intermolecularly.

When penicillin V sulfoxide trichloroethyl ester I is treated with trimethylphosphite in refluxing benzene containing a five fold excess of acetic anhydride only a small amount of the thiazoline II is obtained; the major product III after purification by chromatography on silica gel in ethyl acetate:benzene (3:7) is a colorless non-crystalline foam, $[\alpha]_D$-63° (dioxane). Compound III gives a peak in the mass spectrum at m/e 522 corresponding to $C_{20}H_{21}Cl_3N_2O_6S$[4] and major fragmentation peaks at m/e 478 (M^+,-CH_2=C=O), 464 (M^+,-$COCH_3$, -H_2O) and 447 (M^+,-$SCOCH_3$). The ir spectrum ($CHCl_3$) shows peaks at 3370 (NH), 1780 (β-lactam C=O), 1750 (sh ester), 1695 (amide I), and 1520 (amide II) indicating the presence of both β-lactam and amido side chain. The nmr spectrum[5] 1.92 (S, 3H), 2.08 (S, 3H), 4.48 (S, 2H), 4.78 (S, 1H), 4.82 (S, 2H), 5.07 (S, 2H), 5.45 (quartet, J=4.5, 8 cps, 1H), 5.95 (doublet, J=4.5 cps, 1H), 6.8-7.5 (multiplet, 5H), and 7.70 (doublet, J=8 cps, 1H) suggests III as the structure.

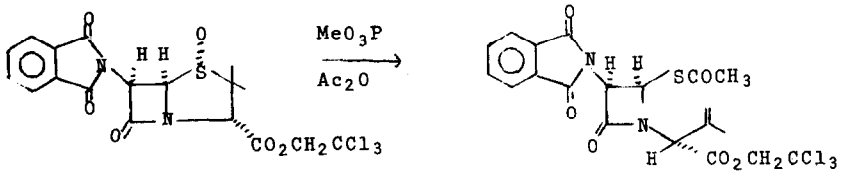
Compound III on treatment with triethylamine in methylene chloride gives an isomer IV as a colorless foam, $[\alpha]_D$-12° (dioxane). The mass spectrum and ir are very similar to those of III. The nmr spectrum has peaks at 2.13 (S, 3H), 2.27 (S, 3H), 2.30 (S, 3H), 4.55 (S, 2H), 4.80 (quartet, J=2 cps, 2H), 5.20 (quartet, J=4.5, 11 cps, 1H), 6.13 (doublet, J=4.5 cps, 1H), 6.8-7.5

(multiplet, 5H), and 7.60 (doublet, J=11 cps, 1H). Precedence[3,6] and changes in the nmr spectrum suggest structure IV for the isomer.



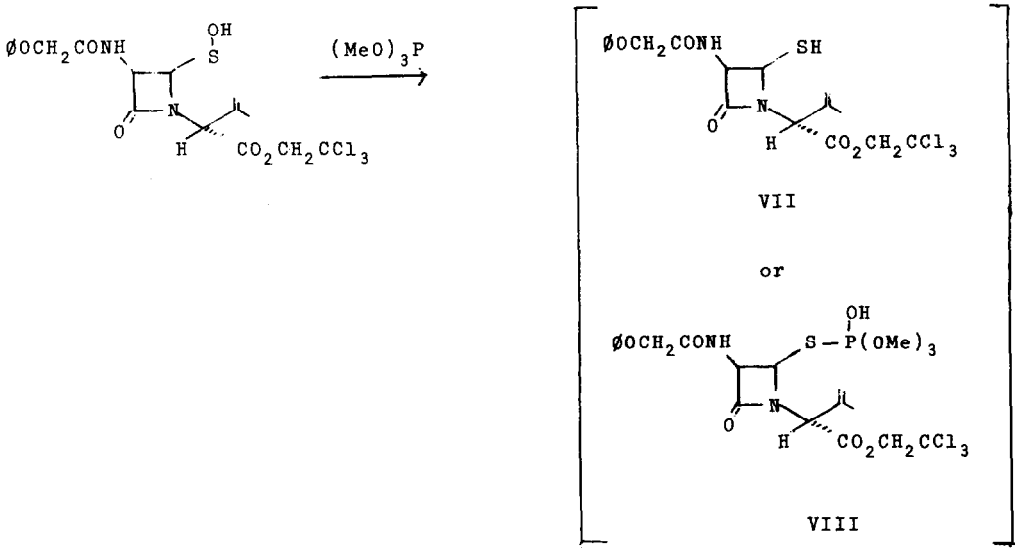
II I III IV

Repeating this reaction on phthalimidopenicillin (R)-sulfoxide trichloroethylester V where an intramolecular condensation is not possible, the -S acetyl derivative VI is obtained as a colorless foam, $[\alpha]_D$-144° (dioxane) in >90% yield.



V VI

The isolation of compounds such as III and VI presents strong evidence for the intermediacy of a thiol VII, or alternatively a phosphorus intermediate VIII which could also give rise to the same reaction products.



The possible existence, albeit transient, of an intermediate of the type VIII may be inferred by analogy with the reaction of alkyl phosphites and dialkyl peroxides. The initial product at low temperatures has been characterized[7] as the penta-alkoxy addition product IX, indicating the first stage of the reaction is a nucleophilic attack of phosphorus on oxygen to give an essentially

$$RO\text{-}OR + (RO)_3P \longrightarrow (RO)_5P$$

IX

co-valent alkoxyphosphonium alkoxide. By analogy, the reaction of an alkyl phosphite with a sulfenic acid would be by a nucleophilic attack of phosphorus on sulfur to give an intermediate such as VIII.

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4. Satisfactory analytical data were obtained for all new compounds.

5. Nmr spectra were recorded on a Varian A60 in deutero chloroform using TMS as internal reference and are reported as δ values.

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