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STRUCTURAL STUDIES ON PENICILLIN DERIVATIVES. PART III. REARRANGEMENT AND FRAGMENTATION OF PENICILLIN V

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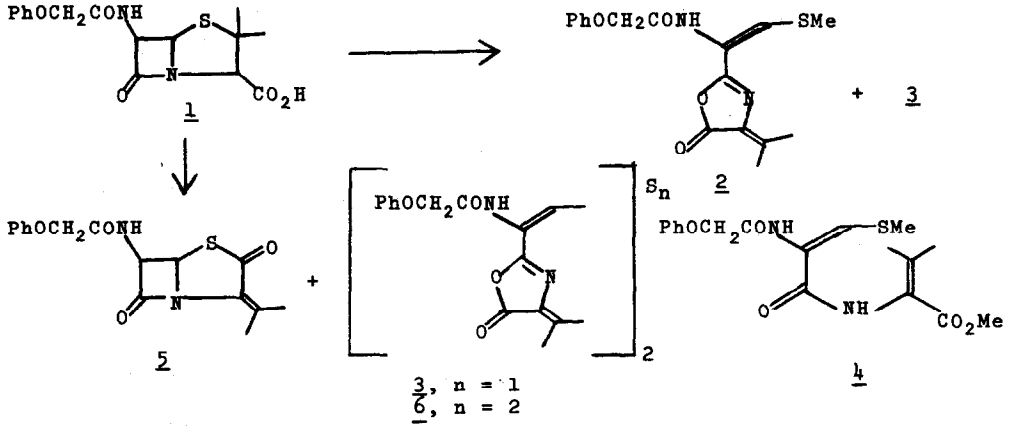
We have found that the preparation of acyl derivatives of penicillin V involving the intermediacy of an activated carboxyl group often leads to new rearrangement products containing neither the β-lactam nor the thiazolidine ring systems. In an attempt to prepare the acyl azide of penicillin V (1) by treatment with triethylamine and methylchloroformate in DMF followed by sodium azide,[1] two new products (2 and 3) were isolated.[2] We have subsequently established that these are formed solely from the reaction of triethylamine and methylchloroformate with 1 in DMF.

Compound 2, mp 114°, gives a peak in the mass spectrum at m/e 346, corresponding to $C_{17}H_{18}N_2O_4S$ (found 346.099, requires 346.099), and major fragmentation peaks at m/e 299 (M^+-SMe), 271 (M^+-SMe, -CO), 202 (M^+-SMe, -CO, $-NHC_4H_6$), 197 (M^+-$PhOCH_2CONH$), and 174 ($PhOCH_2CONHCH{=}CH^+$). The ir spectrum shows peaks at 3370, 1802 (sh), 1776, 1701, 1667, 1600, and 1492 cm^{-1} ($CHCl_3$), seemingly indicating the presence of a β-lactam ring; however the extended uv chromophore [λ_{max} (EtOH) 335, 275, and 269 mμ, ε = 30,200, 13,200, and 7,700; λ_{max} (EtOH/OH^-) 285 mμ, ε = 15,000] and nmr spectrum[3] [2.18 (s,3H), 2.32 (s,3H), 2.47 (s,3H), 4.63 (s,2H), 6.8-7.5 (m,6H), and 8.01 (s,1H)] showed no β-lactam moiety and suggested 2 as the structure. Treatment of 2 with methanolic sodium hydroxide gave the methyl ester 4, mp 153°. The mass spectrum showed a molecular ion at m/e 378 ($C_{18}H_{22}N_2O_5S$) and major fragmentation peaks at 331 (M^+-SMe), 271 (M^+-SMe, -COOMe), and 250 (M^+-NH  CO_2Me). Compound 4 had the following spectral properties: λ_{max} (EtOH) 285 (ε = 15,000); ir ν_{max}^{Nujol} 3300, 1700, 1670, and 1490 cm^{-1}; nmr 1.80 (s,3H), 2.10 (s,3H), 2.37 (s,3H), 3.67 (s,3H), 4.00 (s,3H), 6.8-7.5 (m,6H), 7.83 (s,1H, exchanges with D_2O), and 8.00 (s,1H, exchanges with D_2O). This data suggests that 4 is the structure of the

NaOH/MeOH product, thus also establishing the presence of the oxazolone ring in 2. Further evidence for the oxazolone ring was provided by the ir spectrum of 2 as it is known[4] that the ir spectra of 4-alkylidene-5(4)-oxazolones have maxima of 1795, 1764, 1667, and 1626 cm^{-1}, whereas the 4-amino substituted derivatives have peaks at 1727, 1623, and 1605 cm^{-1}.



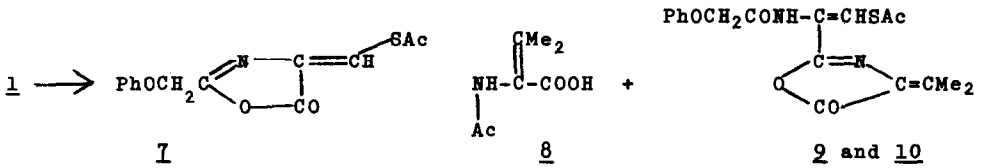
3, n = 1
6, n = 2

The second product was identical with 3, one of two substances, 3 and 6, we had isolated in a preparation of phenoxymethyl anhydropenicillin (5) according to the procedure reported for phenoxyethyl anhydropenicillin.[5] The sulfide (3), $C_{32}H_{30}N_4O_8S$, has mp 205-206.5°; λ_{max} (EtOH) 366 mμ, ε = 31,200; ir ($CHCl_3$) 1800, 1710, 1668, 1600, and 1515 cm^{-1}; and nmr ($CDCl_3$) 2.19 (s,3H); 2.34 (s,3H), 4.64 (s,2H), 7.0 (m,5H), 7.41 (s,1H), and 8.35 (s,NH). Compound 6, mp 135-138°, is tentatively identified as a symmetrical disulfide on the basis of correct analysis for $C_{32}H_{30}N_4O_8S_2$: λ_{max} (EtOH) 332, 375 mμ, ε = 15,500, 12,100; ir ($CHCl_3$) 1790, 1695, 1668, 1600, and 1515 cm^{-1}; and fragmentation in the mass spectrum.

The "dimer" reported by S. Wolfe and co-workers[5] is probably the sulfide derivative corresponding to 3. Compound 3 is often the major product in both the anhydropenicillin and the methyl chloroformate-triethylamine reaction, the yields varying with the exact experimental conditions.

The reaction of penicillin V (1) with acetic anhydride at 120-130° for 45 min afforded a mixture from which four compounds were isolated by chromatography over silica gel. The simplest of these was N-acetyl dehydrovaline (8), identi-

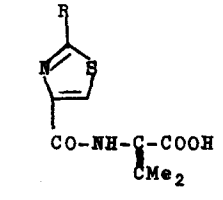
cal with a synthetic sample.[6] The second was 4-acetyl-thiomethylene-2-phenoxymethyl-5-oxazolone (7), $C_{13}H_{11}NO_4S$, mp 110-111°; structural assignment



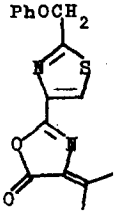
7 8 9 and 10

was made on the basis of elemental analysis and physical data [λ_{max} (EtOH) 365 and 320 mμ, ε = 11,200 and 8,400; ir ($CHCl_3$) 1803, 1720, and 1648 cm^{-1}; nmr ($CDCl_3$) 2.32 (s,3H), 4.8 (s,2H), 7.0 (m,5H), and 8.0 (s,1H).

The remaining two compounds, 9 and 10, mp 172-174° and 185-186°, were isomeric, having empirical formula $C_{18}H_{18}N_2O_5S$ (m/e 374). Structural studies were carried out primarily with the lower melting isomer 9, formed in considerably greater yield. The lack of uncoupled aliphatic and olefinic proton signals in the nmr spectrum [($TFAd_1$) 2.37 (s,3H), 2.55 (s,3H), 2.61 (s,3H), 4.88 (s,2H), 7.1 (m,5H), and 9.00 (s,1H)] and the extended uv chromophore [λ_{max} (EtOH) 230 mμ, ε = 28,800)] indicate a large degree of unsaturation. The presence of an S-acetyl group is indicated by the most predominant ion in the mass spectrum (m/e 299, M^+-SAc) and the oxazolone by the 1800 cm^{-1} (Nujol) peak in the ir spectrum.[4] Structure 9 is consistent with this data and is confirmed by acid hydrolysis to thiazole (11), $C_{16}H_{16}N_2O_4S$, mp 178-179°, and thiazole-oxazolone (13), $C_{16}H_{14}N_2O_3S$, mp 139-140°, and alkaline hydrolysis to 11 and 12, $C_{10}H_{12}N_2O_3S$, mp 198-199°.



11, R = $PhOCH_2$
12, R = CH_3



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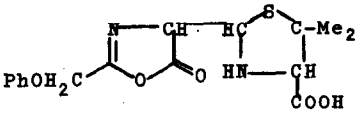

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The minor isomer has ir and mass spectra nearly identical with those of 9, an nmr spectrum similar except for the position of the olefinic proton [8.80 (s,1H)], and an uv maximum shifted somewhat to longer wave length [λ_{max} (EtOH) 332 mμ, ε = 20,200][7] A reasonable explanation would be that this is

10, the geometrical isomer of 9. This compound also gives the thiazole-acid (11) on treatment with acid. The thiazole 11 was also obtained from an acid hydrolysis of the disulfide 6.

Reaction of penicillin G with acetic anhydride was reported in the penicillin monograph,[8] and the appearance of the absorption maximum at 320 mμ was noticed. From the present work we believe that the corresponding derivative of 9 was formed. These examples indicate that the rearrangement of penicillin to oxazolones is a general reaction.

A plausible mechanism for the formation of 2 and 9 could be a double β-elimination reaction with simultaneous or subsequent methylation or acetylation of the sulfhydryl group and cyclization of the neighboring amide to the oxazolone. Compounds 3 and 6 are formed by a similar mechanism except that the sulfhydryl group is converted to the sulfide and disulfide. Phenoxymethyl anhydropenicillin is thought to derive from penicillin V by a β-elimination and cyclization to the thiolactone. Fragmentation of penicillin V with acetic anhydride to compounds 7 and 8 can be envisioned as a double β-elimination on the oxazolone-thiazolidine (14), resulting from rearrangement of penicillin V.

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

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

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7. See ref. 4, pp. 430 and 758.

8. See ref. 4, p. 168.