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Epi-6-aminopenicillanic Acid and Epipenicillin G

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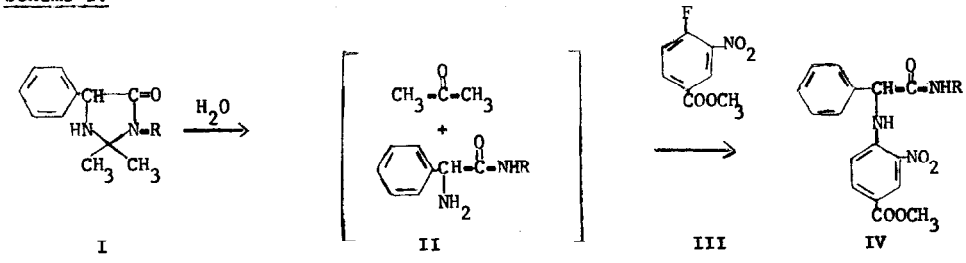
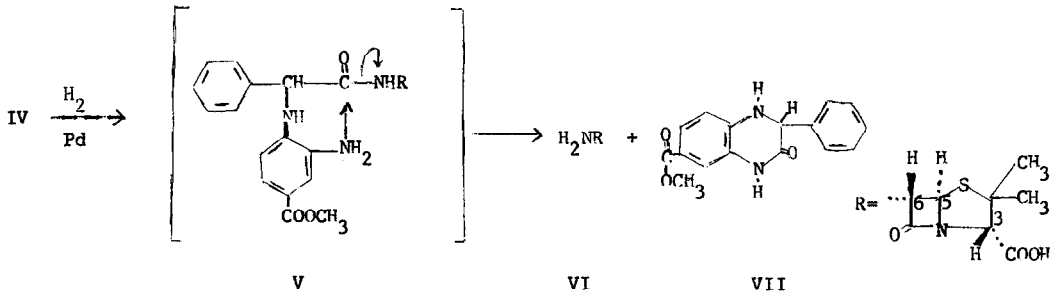
Recently we reported the first successful epimerization of an intact penicillin nucleus.[1] Our work involved the epimerization of hetacillin and methyl phthalimidopenicillanate.[1,2] Nmr studies and deuterium exchange experiments showed that the C-6 position of the penicillin nucleus had epimerized. The cis $\longrightarrow$ trans conversion of neighboring protons in β-lactams is accompanied by a numerical decrease of the coupling constant. For monocyclic β-lactams, J (cis) varies between 4.9 and 5.9 cps, J (trans) between 2.2 and 2.8 cps[3,4]; for bicyclic derivatives (penicillin and cephalosporin) the corresponding values are J (cis)=4-5 cps[5] and J (trans)=1.5-2 cps.[6-10]

We now wish to report the preparation of epi-6-APA and epibenzylpenicillin (epipenicillin G). After a few fruitless exploratory attempts to epimerize 6-APA and penicillin G, we turned our attention to a less direct but more successful route starting with the readily available epihetacillin.[1] The removal of the side chain was accomplished via a reaction sequence shown in Scheme I. This method was described by R. W. Holley and A. D. Holley[11] for the stepwise removal of amino acids from peptides. Johnson et. al.[12] adopted a slightly modified scheme for generating 6-APA from certain penicillin derivatives.

Scheme I:



I II III IV



V VI VII

Alkylation of epihetacillin with methyl 4-fluoro-3-nitrobenzoate[13] (III) in basic aqueous tetrahydrofuran gave crude (IV) in 83% yield. Epiampicillin (II) appears to be an intermediate in this reaction. Hydrogenation of (IV) in neutral aqueous solution using 30% palladium on alumina as catalyst presumably yielded the amine (V) but no attempt was made to isolate it. Spontaneous cyclization of (V) in a moist, weakly acidic methyl isobutyl ketone extract at room temperature gave crystalline epi-6-APA in 15% yield; m.p. 168-170°, $[\alpha]_D^{25}$ + 262.4° (c 0.5, water). Anal. Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95. Found: C, 44.46; H, 5.80; N, 13.14. ν max. (KBr) 3600, 3400, 1785 (β-lactam CO) and 1620 + 1410 cm^{-1} (COO^-). The nmr spectrum of epi-6-APA (60 Mc in D_2O) shows singlets at δ 1.57 and δ 1.50 ppm (gem dimethyl), further a singlet at δ 4.39 ppm (H-3), a doublet at δ 4.67 ppm with J=1.6 cps (H-6) and a doublet at δ 5.49 ppm with J=1.6 cps (H-5). The small coupling constant is in agreement with a trans β-lactam.

The byproduct 7-carbomethoxy-3,4-dihydro-3-phenylquinoxaline-2-one (VII) was isolated from the mother liquor in 13% yield; m.p. 215°, $[\alpha]_D^{25}$ + 34.3° (c 1, methanol). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 4.99; N, 9.92. Found: C, 67.96; H, 5.19; N, 10.24. λ max. (in methanol) 219 mμ (log ε : 3.836), 241 mμ (log ε : 3.829) and 314 mμ (log ε : 3.654). ν max. (KBr) 3265, 1705 (unsat. ester) and 1687 cm^{-1} (amide). The dihydroquinoxaline derivative is identical with a sample prepared by the coupling of D(-)phenylglycine with methyl 4-fluoro-3-nitrobenzoate followed by reduction and ring closure.

In solution, compound VII oxidizes easily to the corresponding quinoxalone derivative:[14] m.p. 280°, Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.57; H, 4.31; N, 9.99. Found: C, 68.58; H, 4.33; N, 10.35. The physical data are in agreement with the structure.

Acetylation of epi-6-APA with phenylacetyl chloride yielded epipenicillin G, isolated as the crystalline potassium salt in 71% yield; m.p. 153-154°, $[\alpha]_D^{25}$ + 196.4° (c 1, water).

Anal. Calcd for $C_{16}H_{17}N_2O_3SK \cdot 1.5\ H_2O$: C, 48.29; H, 5.01; N, 7.02. Found: C, 48.29; H, 5.25; N, 7.35. ν max. (KBr): 3600-3100 (hydrate OH), 3320 (NH), 2980 + 2920 (CH_3), 1760 (β-lactam CO), 1668 + 1553 (amide), 1620 + 1540 (C=C, COO^-) and 702 cm^{-1} (phenyl). The nmr spectrum of the potassium benzylepipenicillinate (60 Mc in D_2O) shows a singlet at δ 1.50 ppm and δ 1.57 ppm (gem dimethyl), a singlet at δ 3.62 ppm ($-CH_2-$), further a singlet at δ 4.32 ppm (H-3), a doublet at δ 4.80 ppm with J=1.6 cps (H-6), a doublet at δ 5.25 ppm with J=1.6 cps (H-5) and a singlet at δ 7.32 ppm (phenyl). The low coupling constant for H-5 and H-6 indicates a trans β-lactam. Potassium benzylepipenicillinate (potassium epipenicillin G) exhibits negligible antimicrobiological activity against standard test organisms.

Esterification of benzylepipenicillin with diazomethane gave crystalline methyl benzylepipenicillinate in 83% yield; m.p. 116°, $[\alpha]_D^{25}$ + 119.1° (c 1, chloroform). Anal. Calcd for $C_{17}H_{20}N_2O_4S$: C, 58.59; H, 5.78; N, 8.04. Found: C, 58.55; H, 5.99; N, 8.13. The infrared spectrum is similar to that of methyl benzylpenicillinate. The β-lactam CO band is shifted slightly upward to 1785 cm^{-1}. The nmr spectrum (60 Mc, deuterochloroform) shows a characteristic double doublet at δ 5.01 ppm with J=1.8 cps (H-6) and a doublet at δ 5.13 ppm with J=1.8 cps (H-5).

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