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EPIHETACILLIN

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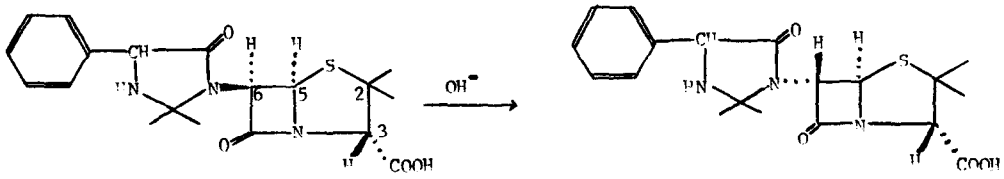
Recently the synthesis and structure of the antibiotic hetacillin* has been published.[2] We wish to report its epimerization at the C-6 position. This is the first reported epimerization of an intact penicillin nucleus.

Treatment of crystalline hetacillin (I) with aqueous sodium hydroxide (pH 11.5) for 30 min. at room temperature, followed by acidification to pH 2 with dilute hydrochloric acid gave crystalline epihetacillin (II) in 85% yield; m.p. 164-165°, $[\alpha]^{23}_{D}$ +232° (c 1, pyridine). Anal. Calcd for $C_{19}H_{23}N_3O_4S$: C, 58.60; H, 5.94; N, 10.79; S, 8.23. Found: C, 58.60; H, 6.03; N, 10.44; S, 8.44.



I II

Esterification with diazomethane gave methyl epihetacillinate in 91% yield; m.p. 156-158°, $[\alpha]^{23}_{D}$ +202° (c 1, pyridine). Anal. Calcd for $C_{20}H_{25}N_3O_4S$: C, 59.54; H, 6.25; N, 10.42; S, 7.92; mol wt 403. Found: C, 59.04; H, 6.32; N, 10.67; S, 7.68; mol wt (osmometric), 392.

While very similar, the infrared spectra of hetacillin and epihetacillin show the

* Hetacillin is a semisynthetic penicillin having the chemical name 6-[D-(-)-2,2-dimethyl-5-oxo-4-phenyl-1-imidazolidinyl]penicillanic acid.

following important differences: the β-lactam band at 1775 cm^{-1} is shifted to 1800 cm^{-1} for epihetacillin. The band at 1728 cm^{-1} in hetacillin becomes two bands at 1700 and 1740 cm^{-1} in epihetacillin. The methyl ester shows bands at 3340 (NH), 2980 (CH_3), 1780 (CO β-lactam), 1745 (CO ester), 1685 (CON), 735 and 705 cm^{-1} (phenyl).

The foregoing data indicated that epihetacillin was isomeric with hetacillin, possibly differing only in configuration. The sharp drop in the specific rotation from $[\alpha]_D^{23}$ +343° in hetacillin to $[\alpha]_D^{23}$ +232° in epihetacillin accompanied by loss of ~ 90% of the biopotency suggested that inversion at one or more asymmetric carbon atoms occurred. It was thought at first that the tertiary proton adjacent to the phenyl group might have been epimerized. Since acid hydrolysis of epihetacillin gave D(-)-phenylglycine, however, no epimerization at this carbon atom could have taken place.

The nmr spectrum of epihetacillin [60 Mc in deuterochloroform-DMSO (3:1), tetramethysilane as standard] shows singlets at δ 1.47, 1.52, 1.58 ppm integrating for four methyl groups, singlets at δ 4.45 and 4.70 ppm for the tertiary proton at C-3 and adjacent to the phenyl group respectively, a multiplet at δ 7.40 ppm integrating for five protons (phenyl) and doublets at δ 4.50 and 5.44 ppm (J=1.5 cps) for the coupled protons at C-6 and C-5 respectively. Methyl epihetacillinate (60 Mc in deuterochloroform, tetramethylsilane as standard) shows singlets at δ 1.47, 1.55, 1.62 ppm integrating for four methyl groups, further a singlet a 3.75 ppm (OCH_3) integrating for three protons, a singlet at δ 4.56 and 4.69 ppm for the tertiary protons at C-3 and adjacent to the phenyl group respectively, a multiplet at δ 7.40 ppm (phenyl) integrating for five protons and doublets at δ 5.49 and 4.67 ppm (J=1.5 cps) for the coupled protons at C-5 and C-6 respectively.

The nmr spectrum of epihetacillin is identical in most respects with that of hetacillin. However, hetacillin shows doublets for the C-5 and C-6 protons with a coupling constant of J=4.5 cps in agreement with a *cis* β-lactam. Since reported *trans* β-lactam ring protons show coupling constants of 2.2-2.8 cps[3-6] while *cis* β-lactam ring protons have coupling constants of 4.5-5.9 cps[7] a *trans* relationship is indicated for epihetacillin and the corresponding methyl ester. This shows that an inversion occurred at C-5 or C-6.

Finally, a deuterium exchange experiment proved that only the proton at C-6 epimerized. Treatment of I in D_2O with sodium deuteroxide (pH 11.5) followed by deuterium chloride (pH 2.0) gave deuteroepihetacillin in 79% yield. In the nmr the doublet at 4.50 ppm (C-6 proton) is absent and a singlet at δ 5.42 ppm (C-5 proton) has replaced the doublet formerly at δ 5.44 ppm in epihetacillin. This proves that H-6, as the more acidic proton, was exchanged by deuterium and that epimerization occurred at C-6. Since deuteroepihetacillin shows signals for the proton at C-3 and the proton adjacent to the phenyl group, these positions have not been epimerized.

Epimerization can also proceed with amines in non-aqueous systems. Treatment of methyl hetacillinate in DMSO with triethylamine for 5.5 hours gave methyl epihetacillinate, which is in every respect identical with an esterified (diazomethane) sample of epihetacillin.[8]

References

1. To whom correspondence should be addressed.
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8. Methyl 6-phthalimidopenicillanate was epimerized under similar conditions. This reaction was independently observed by Dr. Saul Wolfe and co-workers (Chem. Commun., in press).