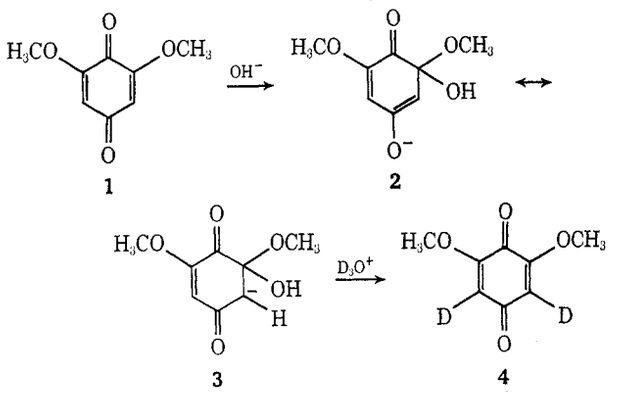
solution was extracted with chloroform, the extract dried, and the solvent removed. The pmr of the residue in $CDCl_3$ showed only a singlet at δ 3.82, indicating that the recovered product was 3,5-dideuterio-2,6-dimethoxy-1,4-benzoquinone (**4**).

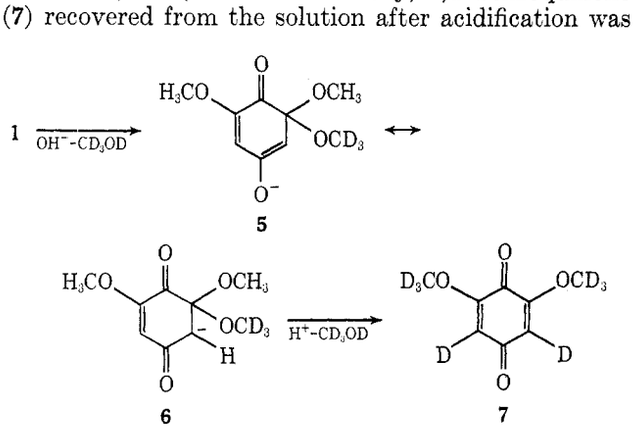
The formation of **4** can be explained as follows. In



alkaline solution, a hydroxyl ion adds on to **1** to yield an anion hitherto formulated as **2**;[4b,c,6] however, this is evidently tautomeric with the anion **3**, a form through which exchange of the ring protons can occur readily in D_2O *via* deuteration and deprotonation. Reacidification in D_2O therefore yields **4**. The original quinone **1** was re-formed from **4** by dissolution in NaOH–H_2O and acidification with HCl–H_2O. This rapid reversible deuteration therefore indicates the immediate formation in base of adducts of the type **2** ↔ **3**, which has been postulated as the first step in the alkaline decomposition of quinones.[4b,c,6]

Even for a substituted quinone, **1** is atypical in its relative stability in base. Its decomposition in alkali, as measured by the decay of the peak at 289 nm after reacidification, follows first-order kinetics with a half-life of 30 min at pH 10.5 and 20°. Other substituted quinones (1,2- and 1,4-naphthoquinone, 2-methyl-1,4-naphthoquinone, 2-methoxy-, 2,5-dimethyl-, 2,6-dimethyl-, 2,5-dichloro-, and 2,6-dichloro-1,4-benzoquinone, and 3,5-dimethoxy-1,2-benzoquinone) all decomposed within 1 min at pH 10.5. Regeneration of original quinones by acidification could not be established by uv or pmr spectroscopy. It was, therefore, impossible to establish deuterium exchange in alkaline solution.

On treatment of **1** with NaOH or CD_3ONa in CDCl–CD_3OD, both the methoxyl and proton resonances were immediately discharged from the pmr spectrum. 3,5-Dideuterio-2,6-bis(trideuteriomethoxy)-1,4-benzoquinone (**7**) recovered from the solution after acidification was



reconverted to **1** with NaOH in CH_3OH followed by acidification.

The exchange of the methoxyl probably involves an intermediate quinal (quinol ether) adduct (**6** ↔ **7**) analogous to the *o*-hemiquinal structure (**2** ↔ **3**). Rapid exchange of the methoxyl groups in **1** in alkaline solution by other alkoxyl groups has also been demonstrated by pmr and esr.[4c]

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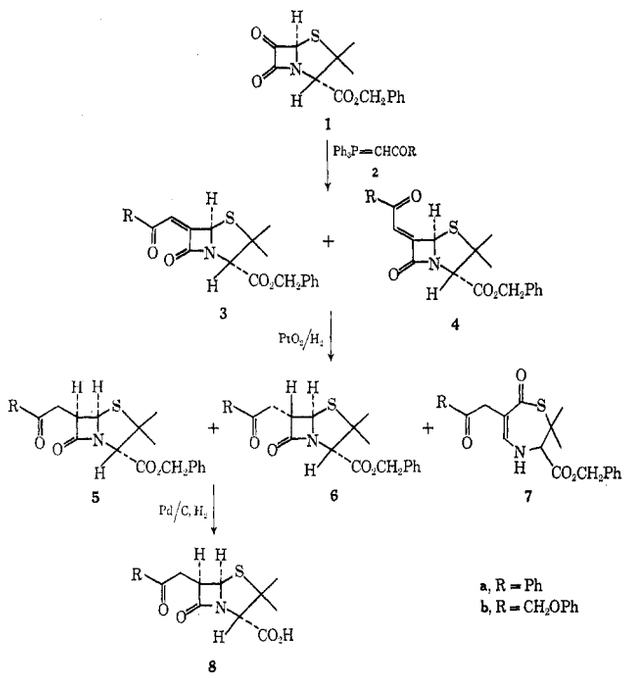
Benzyl 6-Oxopenicillanate and Derivatives. II

Summary: The amide side chain of a penicillin has been removed and the carbon analogs of penicillin V and phenylpenicillin have been synthesized stereospecifically; the penicillin V analog has antibiotic activity and penicillinase resistance.

Sir: We have reported[1] the preparation of 6β-phenoxyacetoxypenicillanic acid—a 6-oxygen analog of penicillin V, from benzyl 6-oxopenicillanate (**1**). This versatile



intermediate can also be transformed to 6β-phenoxyacetylmethylpenicillanic acid (**8b**)—a 6-carbon analog of penicillin V. Surprisingly, this relatively major change in structure resulted in a compound still containing appreciable antibiotic activity. In addition, **8b** was resistant to *Bacillus cereus* penicillinase.[2]

As a model side-chain precursor, the readily available benzoylmethylenetriphenylphosphorane (**2a**) was allowed to react with benzyl 6-oxopenicillanate (**1**) in refluxing benzene to give, after column chromatography, a yellow oily product (64%), benzyl benzoylmethylene-

(1) Y. S. Lo and J. C. Sheehan, *J. Amer. Chem. Soc.*, **94**, 8253 (1972).

(2) Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, N. Y. In the previous communication,[1] crude 6β-phenoxyacetoxypenicillanic acid was reported to be inactive. The potassium salt of this acid has since been retested and showed some antibacterial activity. Presumably the crude acid sample had decomposed before bioassay.

penicillanate:[3] R_f 0.75 (1:50 Et_2O–CH_2Cl_2); ir (film) 1770, 1740, 1690, 1635, 1595, 1450 cm^{-1}; nmr ($DCCl_3$) δ 8.07–7.30 ppm (m, 11 H), 6.12 (d, 1 H, J = 1 Hz), 5.22 (s, 2 H), 4.60 (s, 1 H), 1.60 (s, 3 H), 1.45 (s, 3 H). Presumably this oil was a mixture of the geometrical isomers **3a** and **4a**.

Hydrogenation of the oily benzyl benzoylmethylenepenicillanate in ethyl acetate in the presence of platinum oxide gave two fractions of oily products after column chromatography. The nmr spectrum of the major fraction (49%) provided good evidence for a mixture of *cis*- and *trans*-benzyl benzoylmethylpenicillanate (**5a** and **6a**). Column chromatography effected partial separation of the two epimers. An early fraction contained the cis and trans epimers in a 2:1 ratio, which increased to 19:3 in a later fraction. The overall cis:trans ratio was ~4:1. A sample containing the cis and trans epimers in a 2:1 ratio gave the following spectra: nmr ($DCCl_3$) δ 8.05–7.20 ppm (m, 30 H, aromatic protons), 5.70 (d, 2 H, J = 4.5 Hz, C-5 proton of the cis epimer), 5.20 (s, 6 H, benzylic protons), 5.10 (d, 1 H, J = 1.5 Hz, C-5 proton of the trans epimer), 4.52 (s, 1 H, C-3 proton of the trans epimer), 4.48 (s, 2 H, C-3 proton of the cis epimer), 4.30–3.25 (m, 9 H, C-6 protons and α protons to the ketone function), 1.60–1.40 (d over d, 18 H, *gem*-dimethyl protons); ir (film) 1770, 1740, 1680, 1600, 1450 cm^{-1}.

The minor portion [16%; ir (film) 3300, 1735, 1680, 1625, 1560–1500, 1200, 1000, 910 cm^{-1}; nmr ($DCCl_3$) δ 8.05–7.20 ppm (m, 10 H), 6.85–7.75 (d, 1 H, J = 8 Hz), 6.55–6.30 (m, 1 H, J = 5, 8 Hz), 5.15 (s, 2 H), 4.40–4.30 (d, 1 H, J = 5 Hz), 4.18–3.40 (q, 2 H, J = 17 Hz), 1.50 (s, 3 H), 1.40 (s, 3 H)] has tentatively been assigned the structure of 2,2-dimethyl-3-carbobenzyloxy-6-benzoylmethyl-7-oxo-2,3,4,7-tetrahydro-1,4-thiazepine (**7a**)[3] based on similar spectral data and the same nmr coupling pattern as the 1,4-thiazepine derivatives reported by Sjöberg, *et al.*,[4] and Clayton, *et al.*[5]

Condensation of phenoxyacetylmethylenetriphenylphosphorane (**2b**) with benzyl 6-oxopenicillanate (**1**) gave, after column chromatography, benzyl 6-phenoxyacetylmethylenepenicillanate[3] (62%) as a yellow oil: R_f 0.65 (1:25 Et_2O–CH_2Cl_2); ir (film) 1775, 1735, 1715, 1595, 1490 cm^{-1}; nmr ($DCCl_3$) δ 7.40–6.70 ppm (m, 11 H), 6.05 (d, 1 H, J = 1 Hz), 5.15 (s, 2 H), 4.70 (s, 2 H), 4.65 (s, 1 H), 1.55 (s, 3 H), 1.40 (s, 3 H). This oil may contain both geometrical isomers **3b** and **4b**.

Hydrogenation of benzyl 6-phenoxyacetylmethylenepenicillanate gave, after column chromatography, three product fractions. The first fraction contained a 29% yield of a mixture of the cis and trans epimers, **5b** and **6b**, in a 4:1 ratio. The second fraction contained the pure cis epimer **5b** in ~1% yield. The third fraction contained 2,2-dimethyl-3-carbobenzyloxy-6-phenoxyacetylmethyl-7-oxo-2,3,4,7-tetrahydro-1,4-thiazepine (**7b**, yield 7.5%). Benzyl 6β-phenoxyacetylmethylpenicillanate (**5b**)[3] was isolated as a pale yellow oil: R_f 0.75 (1:10 Et_2O–CH_2Cl_2); ir (film) 1770, 1735, 1595, 1490 cm^{-1}; nmr ($DCCl_3$) δ 7.50–6.80 ppm (m, 10 H), 5.65 (d, 1 H, J = 4.2 Hz), 5.20 (s, 2 H), 4.60 (s, 2 H), 4.45 (s, 1 H), 4.30–3.85 (m, 1 H), 3.25–3.12 (d, 2 H, J = 8 Hz), 1.58 (s, 3 H), 1.42 (s, 3 H).

The free acid, **8b**, was obtained by hydrogenating a 8:1 cis:trans mixture of benzyl 6-phenoxyacetylmethylpenicillanate in ethyl acetate in the presence of palladium on charcoal (10%) at 25° and 1 atm pressure. The acid, **8b**,[3] was purified by crystallization from benzene: yield 43%; mp 101.5–102°; ir (KBr) 3440, 1785, 1765, 1750, 1730, 1720, 1700, 1595, 1490, 1225 cm^{-1}; nmr ($DCCl_3$) δ 11.15 (s, 1 H), 7.50–6.85 (m, 5 H), 5.65 (d, 1 H, J = 4.5 Hz), 4.65 (s, 2 H), 4.50 (s, 1 H), 4.30–3.95 (m, 1 H), 3.35–3.20 (d, 2 H, J = 8 Hz), 1.65 (d, 6 H). Compound **8b** was found to be resistant to *Bacillus cereus* penicillinase and showed the following MIC's: *Diplococcus pneumoniae*, 1; *Streptococcus pyogenes*, 2; *Staphylococcus aureus* Smith, 32.

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(4) O. K. J. Kovas, B. Ekstrom, and B. Sjöberg, *Tetrahedron Lett.*, 1863 (1969).
(5) J. P. Clayton, R. Southgate, B. G. Ramsey, and R. J. Stoodley, *J. Chem. Soc.*, 2089 (1970).