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W. P. Giering, S. Raghu, M. Rosenblum*
A. Cutler, D. Ehntholt, R. W. Fish
Edison-Lecks Laboratories, Brandeis University
Waltham, Massachusetts 02154
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Synthesis of Benzyl 6-Oxopenicillanate[1] and Derivatives. I

Sir:

We wish to report the synthesis of benzyl 6-oxopenicillanate (II) and illustrate the potential of this type of substance as a source of new antibacterial agents, for example by transformation to 6β-(phenoxyacetoxy)penicillanic acid (VI)—an oxygen analog, including stereochemistry, of penicillin V.

Benzyl 6-α-hydroxypenicillanate (I) was prepared from 6-aminopenicillanic acid by the method of Hauser and Sigg.[2] Oxidation of I by diisopropylcarbodiimide in methyl sulfoxide[3] gave benzyl 6-oxopenicillanate[4] (II) which was purified by column chromatography: ir (film) 1830, 1780, 1735 cm^{-1}; nmr ($DCCl_3$) δ 7.4 (s, 5 H), 5.85 (s, 1 H), 5.3 (s, 2 H), 4.87 (s, 1 H), 1.55–1.62 (d, 6 H). The contaminant originating from diisopropylcarbodiimide was removed with difficulty. Water-soluble carbodiimides such as 1-ethyl-3-(dimethylamino)carbodiimide hydrochloride and methiodide are not promising for this oxidation. Under these conditions no benzyl 6-oxopenicillanate (II) could be isolated. Only the starting hydroxy compound I was recovered.

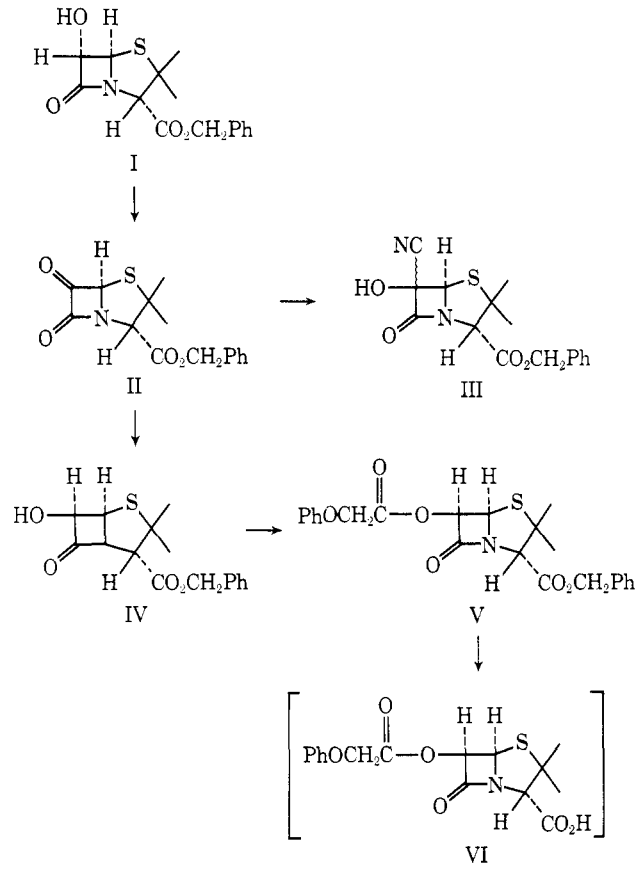
Treatment of benzyl 6-oxopenicillanate (II) with liquid hydrogen cyanide immediately gave a solid. After washing with benzene and recrystallization from methylene chloride, a colorless, crystalline cyanohydrin[4] (III) of II was obtained [mp 148–162° dec; ir (KBr) 3300, 1790, 1730 cm^{-1}; nmr (acetone-d_6) δ 7.5 (s, 5 H), 5.9 (s, 1 H), 5.35 (s, 2 H), 4.7 (s, 1 H), 3.1 (s, 1.5 H), 1.63 (s, 3 H), 1.50 (s, 3 H)].

Reduction of II by potassium borohydride in aqueous alcohol gave only one hydroxy isomer, namely, benzyl 6-β-hydroxypenicillanate (IV). The product was isolated by column chromatography and purified by recrystallization [ir (KBr) 3420, 1775, 1725 cm^{-1}]. Table I compares some of the physical properties of the 6-α- and 6-β-hydroxy isomers I and IV.

Table I. Physical Properties of I and IV

	I (lit.)[2]	IV
Mp, °C	157–160	97.5–98.5
$[\alpha]^{25}D$, deg	191 (*c* 0.53, methanol)	222 (*c* 0.87 methanol)
Nmr		
C_5	δ 5.3, d, J = 1.5 Hz	δ 5.65, d, J = 4.0 Hz
C_6	δ 4.83, m	δ 5.1–5.3, q, J = 4.0, 11.0 Hz
OH	δ 4.3, s, br	δ 3.2–3.5, d, br, J = 11.0 Hz

(1) See J. C. Sheehan, K. R. Henery-Logan, and D. A. Johnson, *J. Amer. Chem. Soc.*, **75**, 3292 (1953) for naming system.
(2) D. Hauser and H. P. Sigg, *Helv. Chim. Acta*, **50**, 1327 (1967).
(3) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **85**, 3027 (1963).
(4) All new compounds gave satisfactory analytical data.



Benzyl 6-β-hydroxypenicillanate (IV) was phenoxyacetylated to give benzyl 6-β-(phenoxyacetoxy)penicillanate[4] (V). The compound was purified by column chromatography and isolated as an oil [ir (film) 1790, 1740, 1600, 1500 cm^{-1}; nmr ($DCCl_3$) δ 7.35 (s, 5 H), 7.4–6.7 (m, 5 H), 5.8–5.6 (q, 2 H, J = 4 Hz), 5.25 (s, 2 H), 4.7 (s, 2 H), 4.55 (s, 1 H), 1.6 (s, 3 H), 1.45 (s, 3 H)].[5]

Compounds IV and VI[6] were submitted for bioassay and showed little or no bioactivity against a variety of organisms.[8]

(5) This work was assisted financially by the Sloan Basic Research Fund.
(6) Hydrogenolysis of V over 5% Pd/$BaCO_3$ in ethyl acetate for 8 hr[2] gave a pale yellow syrup containing 6-β-(phenoxyacetoxy)penicillanic acid (VI) based on spectroscopic data (ir, nmr). Attempts to remove all contaminants from this material by column chromatography were unsuccessful due to strong adsorption of the acid on the support. The acid does not readily form a crystalline *N*-ethylpiperidine salt[7] analogous to penicillin G and V.
(7) J. C. Sheehan, W. J. Mader, and D. J. Cram, *J. Amer. Chem. Soc.*, **68**, 2407 (1946).
(8) Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, N. Y.

Young S. Lo, John C. Sheehan*
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received July 24, 1972

Negatively Charged Electrophiles. Acylation of Strong Nucleophiles by Enolate Salts of β-Keto Esters

Sir:

Poly-β-carbonyl compounds are presently of interest because their reactions bear a relationship to the biosynthesis of phenolic natural products.[1] We have de-

(1) For a review, see T. Money, *Chem. Rev.*, **70**, 553 (1970).