6α-Substituted Penicillins

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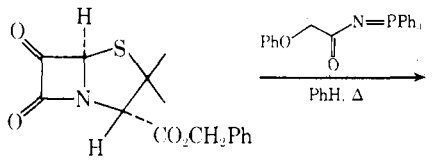
Syntheses of 6α-methoxy-6β-phenoxyacetamidopenicillanic acid and 6α-cyano-6β-phenoxyacetamidopenicillanic acid from benzyl 6-oxopenicillanate are reported. Both compounds showed weak antibacterial activities.

Syntheses of 6-methoxypenicillin have been reported[1-3] from a number of laboratories. In addition, alkyl,[4] hydroxyalkyl,[4] thioalkyl,[5] hydroxy,[1c] formyloxy,[1c] fluoro,[1c] azido,[1c] and cyano[1c] derivatives have been reported. Many of these syntheses depend on addition of the proper nucleophile to the *N*-acylimine **2** generated by halogenation and elimination.

This intermediate has been synthesized from 6-OPA (6-oxopenicillanic acid) benzyl ester **1** by a route analogous to the synthesis of the 6β-carbon analog of penicillin.[6]



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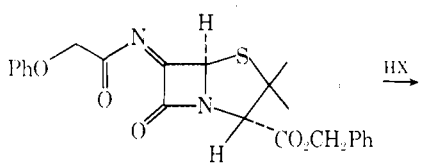

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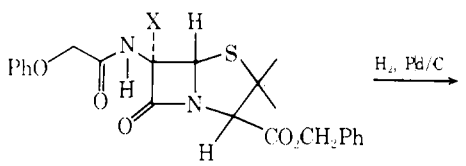
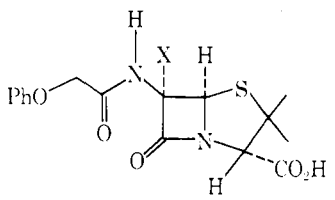


3a, X = OCH_3
b, X = CN



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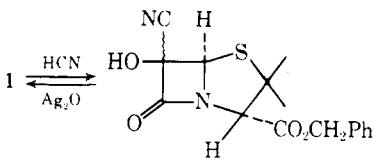
Impure 6-OPA benzyl ester is satisfactory for the syntheses of 6-carbon[6] and 6-oxygen[7] analogs of penicillins. However, condensation with a nitrogen Wittig requires a relatively pure sample of 6-OPA benzyl ester due to the high reactivity of the intermediate *N*-acylimine **2** toward nucleophiles. Purification of **1** was accomplished by forming the crystalline cyanohydrin derivative **5**. Treatment of



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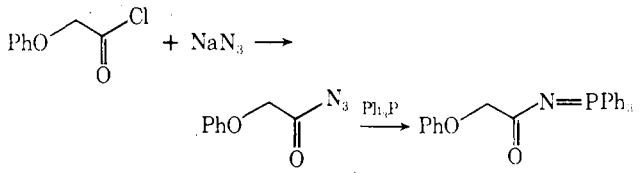
5 with silver oxide gives pure **1**. *N*-Phenoxyacetyliminotriphenylphosphorane was prepared from the azide.



Condensation of the phosphorane with **1** gave the *N*-acylimine **2** as a thermally stable compound. Comparison of the ir and nmr spectra of the reaction product mixture containing **2** with those of starting materials allowed the following signals to be assigned for the acylimine: ir (film), 1785 (β-lactam), 1735 (ester), 1715 (C=O of acylimine), 1695 cm^{-1} (imine); nmr ($DCCl_3$) δ 5.75 (s, H-5), 4.65 (s, H-3), 4.75 ppm (s, CH_2 of acylimine group).

Addition of methanol or liquid hydrogen cyanide to the cooled reaction mixture containing **2** gave the substituted penicillins **3**. In both cases, addition occurred from the less-hindered side of **2** to give the α-substituted penicillins **3**.

Both 6α-methoxy-6β-phenoxyacetamidopenicillanic acid (**4a**) and 6α-cyano-6β-phenoxyacetamidopenicillanic acid (**4b**) showed weak antibacterial activities.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Ir spectra were recorded on a Perkin-Elmer 237 spectrophotometer. Nmr spectra were taken on a Varian T-60 spectrometer and are reported in parts per million downfield from TMS.

Benzyl 6-Cyano-6-hydroxypenicillanate (5). Liquid hydrogen cyanide was made according to the method of Vogel.[9] It was transferred to a flask containing the oily benzyl 6-oxopenicillanate (2.04 g) and a few crystals of sodium cyanide. A solid was formed rapidly. The mixture was left at 0° for 0.5 hr and then at room temperature to evaporate excess hydrogen cyanide. Final residual hydrogen cyanide was removed at reduced pressure. The solid was collected and washed with benzene to give 1.10 g product (54% from the crude starting material). After recrystallization from methylene chloride, a white, shiny crystalline compound was obtained: mp 148–160° dec; $[\alpha]^{25}D$ +185° (c 0.545, $CHCl_3$); ir (KBr) 3300, 1790, 1730 cm^{-1}; nmr ($DCCl_3$) 7.50 (s, 5 H), 5.90 (s, 1 H), 5.35 (s, 2 H), 4.70 (s, 1 H), 3.10 (s, 1 H), 1.63 (s, 3 H), 1.50 ppm (s, 3 H).

Anal. Calcd for $C_{16}H_{16}O_4N_2S$: C, 58.00; H, 4.83; N, 8.48; S, 9.64. Found: C, 58.09; H, 4.79; N, 8.47; S, 9.59.

Benzyl 6-Oxopenicillanate (1). Benzyl 6-cyano-6-hydroxypenicillanate (3.3 g) was dissolved in 350 ml of CH_2Cl_2. Sodium sulfate (3.5 g) and silver oxide (5 g) were added with stirring at 20°. After 24 hr, charcoal was added and stirred 1 hr. Filtration and evaporation gave a brown oil which was redissolved in 300 ml of benzene and treated with charcoal for 2 hr. Filtration and evaporation gave a yellow oil: 2.89 g, 95% yield; ir (film) 1830, 1780, 1735 cm^{-1}; nmr ($DCCl_3$) 7.40 (s, 5 H), 5.85 (s, 1 H), 5.30 (s, 2 H), 4.87 (s, 1 H), 1.55 (s, 3 H), 1.48 ppm (s, 3 H).

***N*-Phenoxyacetyliminotriphenylphosphorane.** Phenoxyacetyl chloride (8.5 g) was dissolved in acetone (15 ml) and cooled. Sodium azide (4 g) in water (25 ml) was added dropwise with stirring over 45 min. Stirring was continued for an additional 30 min. A white precipitate was formed during addition. Ice–water was added to bring out more precipitate which was collected by filtration and dried in a desiccator, 8.2 g.

The dry product (5 g) in benzene (20 ml) was added dropwise to a heated, stirred solution of triphenylphosphine (9 g) in benzene (50 ml) over 20 min followed by refluxing for 30 min. After cooling,

filtering, and evaporation, a white solid was obtained which was recrystallized from benzene–petroleum ether: 11 g; mp 121–122°; ir (KBr) 3040, 1580, 1485, 1435, 1360, 1220, 1110, 820 cm^{-1}; nmr ($DCCl_3$) 7.80–6.65 (m, 20 H), 4.70 ppm (s, 2 H).

Condensation and Subsequent Addition of HX. Pure benzyl 6-oxopenicillanate and 3 equiv of *N*-phenoxyacetyliminophosphorane were refluxed in benzene for 44 hr. To the cool mixture an excess amount of HX was added rapidly. The solvent was removed to give a brown syrup which was purified by chromatography.

Benzyl 6α-methoxy-6β-phenoxyacetamidopenicillanate: 42% yield; R_f 0.41 (1:20 Et_2O–CH_2Cl_2); ir (film) 3330, 1780, 1745, 1695, 1600, 1500, 1325, 1215 cm^{-1} nmr ($DCCl_3$) 7.62 (s, br, 1 H), 7.35–6.85 (m, 10 H), 5.62 (s, 1 H), 5.17 (s, 2 H), 4.52 (s, 2 H), 4.45 (s, 1 H), 3.48 (s, 3 H), 1.40 (s, 3 H), 1.36 ppm (s, 3 H); $[\alpha]^{25}D$ +213° (*c* 0.92, $CHCl_3$).

Anal. Calcd for $C_{24}H_{26}N_2SO_6$ (470.54): C, 61.26; H, 5.57; N, 5.95; S, 6.81. Found: C, 61.44; H, 5.70; N, 6.04; S, 6.77.

Benzyl 6α-cyano-6β-phenoxyacetamidopenicillanate: 36% yield; R_f 0.43 (1:30 Et_2O–CH_2Cl_2); ir (film) 3300, 1795, 1740, 1695, 1600, 1500, 1315, 1215 cm^{-1}; nmr ($DCCl_3$) 7.62 (s, 1 H), 7.40–6.85 (m, 10 H), 5.88 (s, 1 H), 5.21 (s, 2 H), 4.60 (s, 2 H), 4.52 (s, 1 H), 1.38 ppm (s, 6 H); $[\alpha]^{25}D$ +179° (*c* 0.94, $CHCl_3$).

Anal. Calcd for $C_{24}H_{23}N_3SO_5$ (461.51): C, 61.92; H, 4.98; N, 9.03; S, 6.89. Found: C, 61.79; H, 5.04; N, 8.89; S, 6.76.

Hydrogenolysis of Benzyl Esters. The benzyl ester was hydrogenated in ethyl acetate over 10% palladium on charcoal for 4 hr at room temperature and 1 atm pressure. The resulting mixture was filtered and the filtrate was extracted twice with cold 1*N* potassium bicarbonate solution. The combined aqueous extracts were washed once with ether and cooled to 0°. Ether was added and the stirred mixture was acidified to pH 2 by slow addition of 12*N* hydrochloric acid. The ether layer was separated and the aqueous layer extracted three times with ether. The organic phase was washed with distilled water, dried (Na_2SO_4), and evaporated to yield an oil. This oil, after freeze-drying from benzene, gave a white solid as the product.

6α-Methoxy-6β-phenoxyacetamidopenicillanic acid: 68% yield; ir ($CHCl_3$) 3380, 1780, 1725, 1695, 1600, 1495, 1205 cm^{-1}; nmr ($DCCl_3$) 8.20 (s, br, 1 H), 7.68 (s, 1 H), 7.36–6.86 (m, 5 H), 5.60 (s, 1 H), 4.58 (s, 2 H), 4.45 (s, 1 H), 3.53 (s, 3 H), 1.55 (s, 3 H), 1.50 ppm (s, 3 H).

6α-Cyano-6β-phenoxyacetamidopenicillanic acid: 58% yield; ir ($CHCl_3$) 3380, 1795, 1725, 1695, 1600, 1490, 1235 cm^{-1}; nmr ($DCCl_3$) 8.40 (s, br, 1 H), 7.60 (s, 1 H), 7.38–6.86 (m, 5 H), 5.88 (s, 1 H), 4.62 (s, 2 H), 4.52 (s, 1 H), 1.57 (s, 3 H), 1.42 ppm (s, 3 H).

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Registry No. —1, 39126-59-5; **2**, 53198-76-8; **3a**, 35353-37-8; **3b**, 53198-77-9; **4a**, 35353-34-5; **4b**, 53198-78-0; **5**, 39486-17-4; *N*-phenoxyacetyliminotriphenylphosphorane, 53229-99-5, phenoxyacetyl chloride, 4461-31-8; sodium azide, 26628-22-8; triphenylphosphine, 603-35-0.

References and Notes

(1) (a) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, **94**, 1408 (1972); (b) L. D. Cama and B. G. Christensen, *Tetrahedron Lett.*, 3505 (1973); (c) R. A. Firestone and B. G. Christensen, *J. Org. Chem.*, **38**, 1436 (1973).
(2) (a) J. E. Baldwin, F. J. Urban, R. D. G. Cooper, and F. L. Jose, *J. Amer. Chem. Soc.*, **95**, 2401 (1973); (b) G. A. Koppel and R. E. Koehler, *ibid.*, **95**, 2403 (1973).
(3) T. Jen, J. Frazee, and J. R. E. Hoover, *J. Org. Chem.*, **38**, 2857 (1973).
(4) R. Reiner and P. Zeller, *Helv. Chim. Acta*, **51**, 1905 (1968); E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **93**, 4324 (1971); R. A. Firestone, N. Schelechow, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972); W. A. Spitzer, T. Goodson, R. J. Smithey, and I. G. Wright, *Chem. Commun.*, 1139 (1972); D. B. R. Johnston, S. M. Schmitt, R. A. Firestone, and B. G. Christensen, *Tetrahedron Lett.*, 4917 (1972).
(5) W. A. Slusarchyck, H. E. Applegate, P. Funke, W. Koster, M. S. Puar, M. Young, and J. E. Dolfini, *J. Org. Chem.*, **38**, 943 (1973).
(6) Y. S. Lo and J. C. Sheehan, *J. Org. Chem.*, **38**, 3227 (1973).
(7) Y. S. Lo and J. C. Sheehan, *J. Amer. Chem. Soc.*, **94**, 8253 (1972).
(8) C. F. H. Allen and A. Bell, "Organic Syntheses," Collect Vol. IV, Wiley, New York, N.Y., 1955, p 846; H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).
(9) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, p. 182, Longmans, Green and Co., London, 1956.

Ligantrol and Ligantrol Monoacetate, Two New Linear Polyoxygenated Diterpenes from *Liatris elegans*[1]

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The geranylnerol derivative ligantrol (**1a**) and its monoacetate (**1b**) have been isolated from *Liatris elegans* (Walt.) Michx. and their structures established. The absolute stereochemistry assigned to C-11 and C-14 (11*R*, 14*S*) was deduced by degradation to a known lactone **16** of established absolute configuration.

As part of our study of the genus *Liatris* (tribe Eupatoriae, Compositae)[1a,2] which elaborates various cytotoxic and antitumor sesquiterpene lactones[3-5] we have examined *Liatris elegans* (Walt.) Michx.,[6] a species widely distributed in the Southern U.S. In the present communication we report isolation and structure determination of ligantrol (**1a**) and ligantrol monoacetate (**1b**), two highly oxygenated linear diterpenes, which are derivatives of geranylnerol. Future reports will deal with sesquiterpene lactones of this and other *Liatris* species.

Ligantrol, $C_{20}H_{36}O_5$, was obtained as a gum, $[\alpha]^{25}D$ +5.1°, and attempts to crystallize it were unsuccessful. It had ir bands at 3400, 1600, 1085, and 960 cm^{-1} and only end absorption in the uv. Ligantrol and the naturally occurring ligantrol monoacetate (**1b**), $[\alpha]^{25}D$ +25°, on acetylation with acetic anhydride–pyridine furnished the same triacetate (**1d**), $[\alpha]^{25}D$ −4.3°, which had ir bands at 3500, 1735, 1660, 1240, 1060, and 900 cm^{-1}. It was clear from these results that ligantrol had three acylable hydroxyl groups; as the ir spectrum of the triacetate still exhibited hydroxyl absorption, the other two oxygens had to be two tertiary hydroxyls or one tertiary hydroxyl and one ethereal oxygen. Since **1d** was not attacked by $CrO_3 \cdot 2Py$, the possibility of a hindered secondary hydroxyl group was ruled out.

The cmr spectrum of ligantrol (Figure 1) proved to be very helpful at this stage. The noise-decoupled spectrum accounted for all 20 carbon atoms and was also indicative of purity, as the decoupled spectrum of a mixture would have given rise to extra signals. The off-resonance decoupled spectrum displayed, in addition to ten difficult-to-disentangle signals, apparently all multiplets, in the range 23.3–32.3 ppm[9] downfield from TMS, two doublets (125.3 and 127.7) and two singlets (138.4 and 139.1 ppm)