(14) P. A. Levene and E. T. Stiller, J. Biol. Chem., 106, 421 (1943).
(15) N. J. Leonard and K. L. Carraway, J. Heterocycl. Chem., 3, 485 (1966).
(16) B. R. Baker in "Ciba Foundation Symposium on the Chemistry and Biology of Purines," G. E. W. Wolstenholm and C. M. O'Connor, Ed., Churchill, London, 1957, pp 120–130.
(17) R. H. Shah, H. J. Schaeffer, and D. Murray, J. Pharm. Sci., 54, 15 (1965).
(18) H. M. Kisman and B. R. Baker, J. Amer. Chem. Soc., 79, 5534 (1957).

Synthesis of 6-Hydroxypenicillanates and 7-Hydroxycephalosporanates

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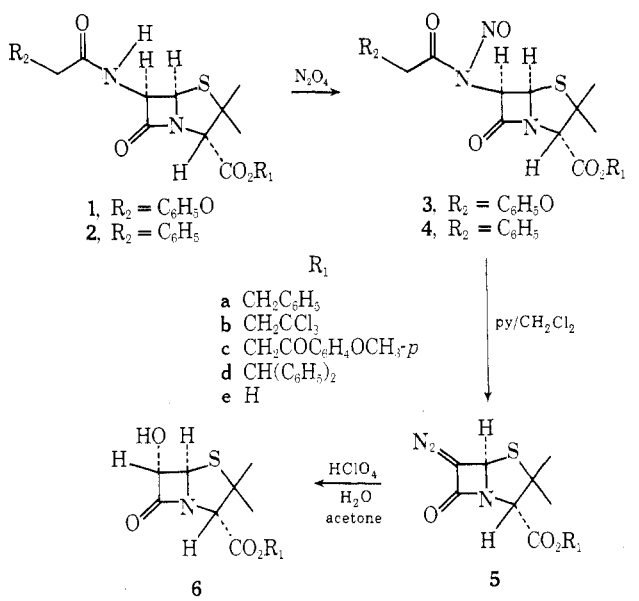
Benzyl 6-oxopenicillanate[1-3] has been shown to be a useful intermediate for the synthesis of novel β-lactam antibiotics. One precursor for this compound is benzyl 6α-hydroxypenicillanate (**6a**), derived from benzyl 6-diazopenicillanate (**5a**) (Chart I). Syntheses of **5a** have been

Chart I



1, $R_2 = C_6H_5O$
2, $R_2 = C_6H_5$

3, $R_2 = C_6H_5O$
4, $R_2 = C_6H_5$

6 5

reported by two methods: diazotization of 6-aminopenicillanic acid (Table I, a) or benzyl 6-aminopenicillanate (Table I, b) with nitrous acid and treatment of benzyl 6β-*N*-nitrosophenoxyacetamidopenicillanate with silica gel[4a] (Table I, c). The latter method especially suffers from a low yield. This method has been improved (Table I, c) and extended to make a greater variety of 6α-hydroxypenicillanates and 7α-hydroxycephalosporanates[4b] available.

In analogy to the diazomethane generating method with sodium hyroxide, the *N*-nitrosoamides (**3**, **4**, and **9**) should afford the diazo derivatives (**5** and **10**) on treatment with an appropriate base.

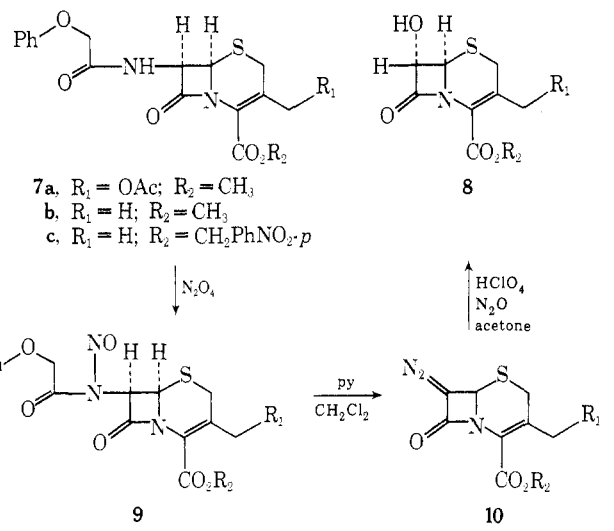
The nitrosoamides were prepared from penicillin (**1**, **2**) or cephalosporin (**7**, Chart II) derivatives according to the method of Hauser and Sigg[4a] using methylene chloride as solvent. The nitrosoamides were then treated with a base. Pyridine was found to be a better base than triethylamine for this reaction. Solvents such as ethyl acetate, methyl sulfoxide, tetrahydrofuran, and methylene chloride can be used. Refluxing methylene chloride was found to be the best solvent, resulting in the shortest reaction time and easiest removal at the end of the reaction. Table I gives the transformations to which this method has been applied and the yields. In most cases compounds **5** and **10** were hydrolyzed with perchloric acid in aqueous acetone without previous isolation.

Table I

Reaction	Yield, %
a 6-APA → **6a**	22[c]
b Benzyl 6-APA → **5a**	2.1[c]
c **1a** → **5a**	7.5[c]
d **1a** → **6a**	46
e **1b** → **6b**	30
f **1c** → **6c**	35
g **2b** → **5b**	72
h **5b** → **6b**	60
i **2b** → **6b**[a]	25
j **2e** → **6d**	7
k **7a** → **8a**	12
l **7b** → **8b**	15
m **7c** → **8c**[b]	24

[a] Without purification of **5b**. [b] Yield adjusted to account for recovered starting materials. [c] Reference 4a.

Chart II



9 10

After refluxing **4b** in methylene chloride with pyridine, a brown oil was obtained which solidified and could be recrystallized from carbon tetrachloride–petroleum ether to give β,β,β-trichloroethyl 6-diazopenicillanate (**5b**) as yellow crystals. This is the first reported isolation of an ester of 6-diazopenicillanic acid in crystalline form.[5] Pure **5b** was hydrolyzed in aqueous acetone with perchloric acid to give a 60% yield of **6b**, which was isolated by crystallization (Table I, h). Crude **5b** was hydrolyzed to give, after chromatography, **6b** in only 40% yield. Thus, working with a pure diazo compound not only resulted in a higher yield but also facilitated isolation of the product.

The *N*-nitrosocephalosporanates were found to be surprisingly resistant to rearrangement. Under the rearrangement conditions used for penicillin derivatives, 53% of the *N*-nitrosocephalosporanate **9c** was recovered. Increased reaction time or temperature resulted in loss of the β-lactam. This difference in reactivity of the nitroso derivatives **3** or **4** and **9** may be due to the steric effect of the *gem*-dimethyl group of penicillin.[6]

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were

performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Ir spectra were recorded on a Perkin-Elmer 237 spectrophotometer; only significant maxima are listed. Nmr spectra were taken on a Varian T-60 spectrometer and are reported in parts per million downfield from TMS.

β,β,β-Trichloroethyl 6β-*N*-Nitrosophenylacetamidopenicillanate (4b). Dinitrogen tetroxide (24 g) was dissolved in 250 ml of methylene chloride. A solution of β,β,β-trichloroethyl phenylacetamidopenicillanate (**2b**, 10.5 g, 22.6 mmol) in methylene chloride (100 ml) was added in 20 min with stirring at −5° to a mixture of anhydrous sodium acetate (22 g), dinitrogen tetroxide (120 ml of above solution), and methylene chloride (100 ml). The mixture was stirred below 0° for 1 hr. Additional portions of dinitrogen tetroxide (30 ml, 100 ml) were added immediately after and 30 min after addition of the penicillin derivative. Excess dinitrogen tetroxide was consumed by adding saturated sodium bicarbonate. The aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated to a yellow syrup, yield 11 g, ir (film) 1790, 1755, 1540, 1530 cm^{-1}; the NH vibration (3400 cm^{-1}) and the amide band (1690 cm^{-1}) of the parent compound were absent.

β,β,β-Trichloroethyl 6-Diazopenicillanate (5b). Pyridine (3 ml) was added to **4b** (11 g) in 300 ml of methylene chloride. After refluxing for 3 hr the brown solution was washed with water, saturated sodium bicarbonate, and water, dried (Na_2SO_4), and evaporated to give 8 g of a brown syrup which slowly solidified. Recrystallization from carbon tetrachloride–petroleum ether gave **5b**, 5.85 g (72%): mp 103.5–104° dec; ir (KBr) 2100, 1760, 1740, 1525 cm^{-1}; nmr ($DCCl_3$) δ 6.15 (s, 1 H), 4.75 (s, 2 H), 4.45 (s, 1 H), 1.70 (s, 3 H), 1.55 (s, 3 H).

Anal. Calcd for $C_{10}H_{10}Cl_3N_3O_3S$ (358.64): C, 33.45; H, 2.81; N, 11.71; S, 8.94; Cl, 29.67. Found: C, 33.55; H, 2.75; N, 11.67; S, 8.87; Cl, 29.82.

β,β,β-Trichloroethyl 6β-Hydroxypenicillanate (6b). Compound **5b** (1 g) was dissolved in 50 ml of acetone. A solution of 10 ml of 1 *N* perchloric acid in 40 ml of water was added with swirling. The solution was stored overnight at 5° and then extracted with methylene chloride. The extract was washed with saturated sodium bicarbonate solution and water, dried (Na_2SO_4), and evaporated to give a pale yellow solid. Crystallization from benzene–petroleum ether gave white crystals, 0.6 g (60%): mp 107.5–108°; ir (KBr) 3470, 1770, 1755, 1160 cm^{-1}; nmr ($DCCl_3$) δ 5.30 (d, J = 1 Hz, 1 H), 4.95–4.80 (d, br, 1 H), 4.82 (s, 2 H), 4.62 (s, 1 H), 4.50 (d, J = 8 Hz, 1 H), 1.60 (s, 3 H), 1.50 (s, 3 H).

Other 6α-hydroxypenicillanates (**6c**, **6d**) and 7α-hydroxycephalosporanates (**8a**, **8b**) were made analogously.

***p*-Methoxyphenacyl 6α-hydroxypenicillanate (6c)** had R_f 0.34 (1:4 Et_2O–CH_2Cl_2); ir (film) 3400, 1770, 1745, 1690, 1600 cm^{-1}; nmr ($DCCl_3$) δ 7.90 (d, J = 9 Hz, 2 H), 6.95 (d, J = 9 Hz, 2 H), 5.50–5.25 (s over d, 3 H), 4.85 (s, br, 1 H), 4.60 (s, 1 H), 3.90 (s, 3 H), 1.60 (s, 6 H).

Benzhydryl 6β-hydroxypenicillanate (6d) had mp 125–125.5°; ir (film) 3400, 1770, 1740 cm^{-1}; nmr ($DCCl_3$) δ 7.40 (s, 10 H), 6.90 (s, 1 H), 5.30 (d, J = 1.5 Hz, 1 H), 4.95 (br, 1 H), 4.82 (d, J = 1.5 Hz, 1 H), 4.55 (s, 1 H), 1.58 (s, 3 H), 1.25 (s, 3 H).

Methyl 7α-hydroxycephalosporanate (8a) had mp 138–139°; $[\alpha]^{25}D$ +127° (*c* 1.63, $CHCl_3$); ir (KBr) 3420, 1775, 1730, 1230 cm^{-1}; nmr ($DCCl_3$) δ 5.15–4.55 (m, 5 H), 3.90 (s, 3 H), 3.48 (q, 2 H), 2.10 (s, 3 H).

Anal. Calcd for $C_{11}H_{13}NSO_6$ (287.28): C, 46.10; H, 4.57; N, 4.88; S, 11.15. Found C, 45.94; H, 4.55; N, 4.87; S, 11.27.

Methyl 7α-hydroxydeacetoxycephalosporanate (8b) had R_f 0.45 (1:10 Et_2O–CH_2Cl_2); ir (film) 3380, 1775, 1730, 1235 cm^{-1}; nmr ($DCCl_3$) δ 4.75 (d, J = 1 Hz, 1 H), 4.65 (d, J = 1 Hz, 1 H), 3.85 (s, 3 H), 3.40 (q, 2 H), 2.20 (s, 3 H).

Benzyl 6α-hydroxypenicillanate (6a) had mp 162–163° (lit.[4a] mp 157–160°); ir and nmr were identical with those published.

***p*-Nitrobenzyl 7β-*N*-Nitrosophenoxyacetamidodeacetoxycephalosporanate (9c).** The procedure is the same as for **4b**. The product was crystallized from acetone–petroleum ether, 81%: mp 120–121° dec; $[\alpha]^{25}D$ −25.2° (*c* 0.76, $CHCl_3$); ir (CH_2Cl_2) 1790, 1745, 1725, 1535, 1350, 1225 cm^{-1}; nmr ($CDCl_3$) δ 8.28–7.50 (q, 4 H), 7.35–6.83 (m, 5 H), 5.87 (d, J = 4.5 Hz, 1 H), 5.57 (s, 2 H), 5.33 (d, J = 4 Hz, 2 H), 5.00 (d, J = 4.5 Hz, 1 H), 3.62–2.75 (q, J = 16, 2 H), 2.36 (s, 3 H).

Anal. Calcd for $C_{23}H_{20}N_4SO_8$ (512.49): C, 53.90; H, 3.93; N, 10.93; S, 6.26. Found: C, 53.82; H, 3.86; N, 10.76; S, 6.40.

***p*-Nitrobenzyl 7α-Hydroxydeacetoxycephalosporanate (8c).** Yellow crystals identified as **9c** deposited out of the hydrolysis solution (4.4 g, 41.5%). Chromatography on silicic acid of the oil left after evaporation of solvent gave an additional 1.2 g (11.3%) of **9c**, 0.6 g (6%) of **7c**, and 0.72 g (10%) of **8c**.

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Registry No.—**1a**, 1256-06-0; **1b**, 19474-19-2; **1c**, 51056-22-5; **2b**, 26774-86-7; **2e**, 61-33-6; **4b**, 51056-23-6; **5a**, 20097-92-1; **5b**, 51056-24-7; **6a**, 51056-25-8; **6b**, 51056-26-9; **6c**, 51056-27-0; **6d**, 51056-28-1; **7a**, 22266-10-0; **7b**, 10209-06-0; **7c**, 28974-31-4; **8a**, 51157-41-6; **8b**, 51056-29-2; **8c**, 51056-20-3; **9c**, 51056-21-4; dinitrogen tetroxide, 10544-72-6; 6-aminopenicillanic acid, 551-16-6; benzyl 6-aminopenicillanate, 3956-31-8.

References and Notes

(1) Y. S. Lo and J. C. Sheehan, *J. Amer. Chem. Soc.*, **94**, 8253 (1972).
(2) T. Jen, J. Frazee, and J. R. E. Hoover, *J. Org. Chem.*, **38**, 2857 (1973).
(3) Y. S. Lo and J. C. Sheehan, *J. Org. Chem.*, **38**, 3227 (1973).
(4) (a) D. Hauser and H. P. Sigg, *Helv. Chim. Acta*, **50**, 1327 (1967). (b) The synthesis of benzhydryl 7-diazocephalosporanate has been reported *via* diazotization of the amine; however, no yields were given. L. D. Cama, Q. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, **94**, 1408 (1972).
(5) Recently we also isolated *p*-nitrobenzyl 6-diazopenicillanate 1β-oxide in crystalline form, 56%, mp 83–84°. Spectral and analytical data are in agreement with this structure.
(6) For discussions of steric effects in these types of systems, see J. R. Jackson and R. J. Stoodley, *Chem. Commun.*, 647 (1971); E. H. White and D. J. Woodcock in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968; J. C. Sheehan and J. U. Piper, *J. Org. Chem.*, **38**, 3492 (1973); K. Heusler, *Helv. Chim. Acta*, **55**, 388 (1972).