spectrum (20 eV) *m/e* (rel intensity) 260 (7), 259 (38), 258 (100), 257 (80), 256 (62), 255 (54).

Pyrolysis of geissovelline at 280° produced a white solid which had a uv spectrum corresponding to that of geissovelline and not a carbazole or a *N*-acetylcarbazole.

9-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole.—A mixture of 300 mg of 1,2,3,4-tetrahydro-6,7-dimethoxycarbazole, 0.5 g of anhydrous sodium acetate, and 3 ml of acetic anhydride was refluxed for 3 hr under nitrogen. The solvent was evaporated and the residue was distributed between chloroform and water. Evaporation of the chloroform gave 9-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole, which was crystallized from ether and sublimed (0.1 mm): mp (136–137° (lit.[19] mp 136°); uv max (95% EtOH) 260 nm (ε 23,500), 285 (9380); proton nmr ($CDCl_3$) δ 1.80 (m, 4, C-2 and C-3 CH_2), 2.48 (s, 3, $NCOCH_3$), 2.52 (m, 2, C-1 or C-4 CH_2), 2.77 (m, 2, C-1 or C-4 CH_2), 3.89 (s, 6, aromatic OCH_3), 6.76 (s, 1, aromatic H on C-5), 7.91 (s, 1, aromatic H on C-8).

9-Acetyl-6,7-dimethoxycarbazole.—A mixture of 200 mg of 9-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxycarbazole and 300 mg of 30% palladium/charcoal in 5 ml of *n*-hexyl ether was refluxed and stirred for 3 hr under nitrogen. The mixture was filtered hot and the cooled filtrate was diluted with petroleum ether (bp 30–60°). The product crystallized slowly. Three recrystallizations from ethanol gave colorless needles of 9-acetyl-6,7-dimethoxycarbazole: mp 123–124° after drying at 80° (0.1 mm); uv max (95% EtOH) 224 nm (ε 44,200), sh 240 (25,200), 295 (15,600), sh 303 (14,400), 324 (11,600).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.4; H, 5.6. Found: C, 71.3; H, 5.5.

(19) G. K. Hughes, F. Lions, J. J. Maunsell, and L. E. A. Wright, *J. Proc. Roy. Soc. N. S. W.*, **71**, 428 (1938).

Dehydrogenation of Deacetyldihydrogeissovelline (41).—An intimate mixture of 225 mg of deacetyldihydrogeissovelline and 225 mg of 30% palladium/charcoal was heated at 275° in a nitrogen atmosphere for 0.5 hr. The cooled mixture was extracted with methanol, the methanol was evaporated, the residue was distributed between ether and 1 *N* hydrochloric acid, the dried ethereal layer was evaporated, and the residual gum was sublimed at 140° (0.3 mm) to give 27 mg of crude 1-ethyl-6,7-dimethoxycarbazole (**35**).

Registry No.—**3**, 36954-68-4; **4**, 36950-24-0; **5**, 36954-69-5; **6**, 36950-25-1; **7**, 36950-26-2; **8**, 36950-27-3; **9**, 36950-28-4; **10**, 36950-29-5; **12**, 36950-30-8; **14**, 36950-31-9; **18**, 36954-70-8; **20**, 36954-71-9; **22**, 36954-72-0; **23**, 36950-32-0; **27**, 36954-73-1; **28**, 36954-74-2; **29**, 36954-75-3; **30**, 36954-76-4; **34**, 36994-22-6; **41**, 36994-23-7; 1,2,3,4-tetrahydro-11-methyl-6,7-dimethoxycarbazolenine, 36950-33-1; 1,2,-3,4,10,11-hexahydro-6,7-dimethoxycarbazole, 36950-34-2; 9-crotonyl-1,2,3,4,10,11-hexahydro-6,7-dimethoxycarbazole, 36950-35-3; 9-acetyl-6,7-dimethoxycarbazole, 36950-36-4.

Acknowledgment.—The authors are indebted to Mr. LeRoy F. Johnson, Varian Associates, for determining and interpreting the carbon-13 nmr spectra. The technical assistance of Mr. Lewis W. Cary, Varian Associates, in obtaining the 300-MHz proton nmr spectra is also gratefully acknowledged.

6-Alkyl Penicillins and 7-Alkyl Cephalosporins

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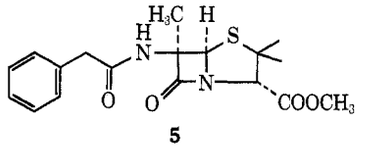
Several 6-alkyl penicillins and 7-alkyl cephalosporins have been prepared. The syntheses of two unique cephalosporins are also discussed.

Although a 6-substituted penicillin has been known for some time,[1] the first generally useful synthetic method for the preparation of 6-substituted penicillins and 7-substituted cephalosporins was published only recently.[2] Since this publication, several papers[3] have appeared describing the synthesis of other 6-alkyl penicillins[4] and 7-alkyl cephalosporins as well as of 6-methoxypenicillins and 7-methoxycephalosporins. These interesting results prompt us to describe some further work we have carried out in this area.

6α-Methylpenicillin V *p*-methoxybenzyl ester (**3**) has been synthesized by the method previously reported (Scheme I). A convenient base for generating the anion of **1** was sublimed potassium *tert*-butoxide. Hydrogenolysis of ester **3** in dioxane–water using 10% palladium on calcium carbonate liberated the free acid, **4**. The stereochemical course of this alkylation has been discussed earlier.[2] Methylation occurs from the sterically less hindered α face of the 6 anion to give the thermodynamically less favored product. The stereochemistry has already been proven by X-ray diffraction analysis on 6-amino-6-α-methylpenicillanic acid methyl ester,[2] and has been corroborated by single-crystal X-ray diffraction analysis[5] on 6α-methyl-6-phenylacetamidopenicillanic acid methyl ester (**5**).



5

In agreement with the assigned stereochemistry is the finding that double irradiation of the C_6 methyl group[6] produces a 24% nuclear Overhauser effect on the C_5 proton.

(1) R. Reiner and R. Zeller, *Helv. Chim. Acta*, **51**, 1905 (1968).

(2) E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **93**, 4324 (1971).

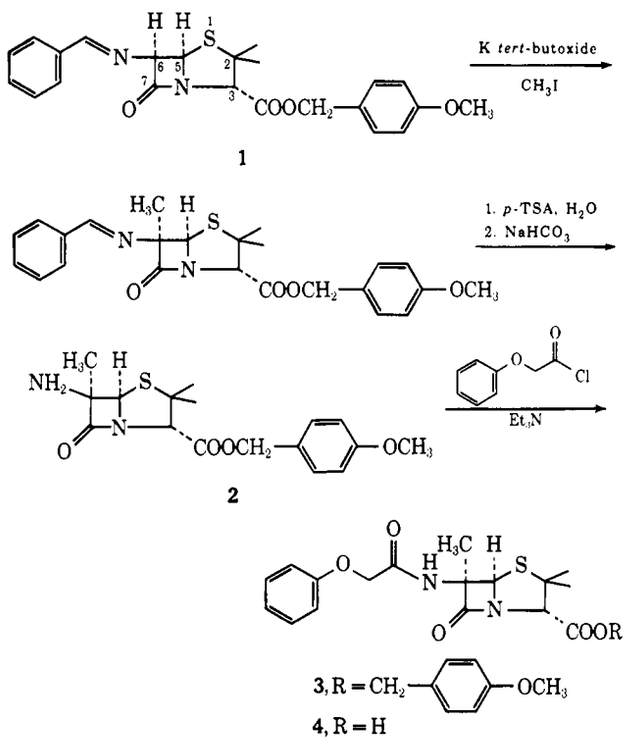
(3) (a) D. Cama, W. J. Leanza, T. R. Beatti, and B. G. Christensen, *ibid.*, **94**, 1408 (1972); (b) S. Karaday, S. H. Pines, L. M. Weinstock, F. E. Roberts, G. S. Brenner, A. M. Hoinowski, T. Y. Cheng, and M. Sletzinger, *ibid.*, **94**, 1410 (1972); (c) R. A. Firestone, N. Scheleshovv, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972).

(4) The stereospecific alkylation of a penicillin at C-6 using a nitrogen ylide has been published previously: G. V. Kaiser, C. W. Ashbrook, and J. E. Baldwin, *J. Amer. Chem. Soc.*, **93**, 2342 (1971).

(5) We wish to thank Professor Jack Z. Gougoutas and Mrs. B. Toeplitz for providing us with this data: Crystallization of **5** from dichloromethane–hexane solvent mixtures gave orthorhombic crystals of space group $P2_12_12_1$ which were used for the analysis (a = 9.75, b = 20.53, c = 9.52 Å, Z = 4, D_0 = 1.277 g/cm³). The R factor before refinement is 0.23 for the 1173 observed reflections. A full account of the refined structure will be published in a separate report.

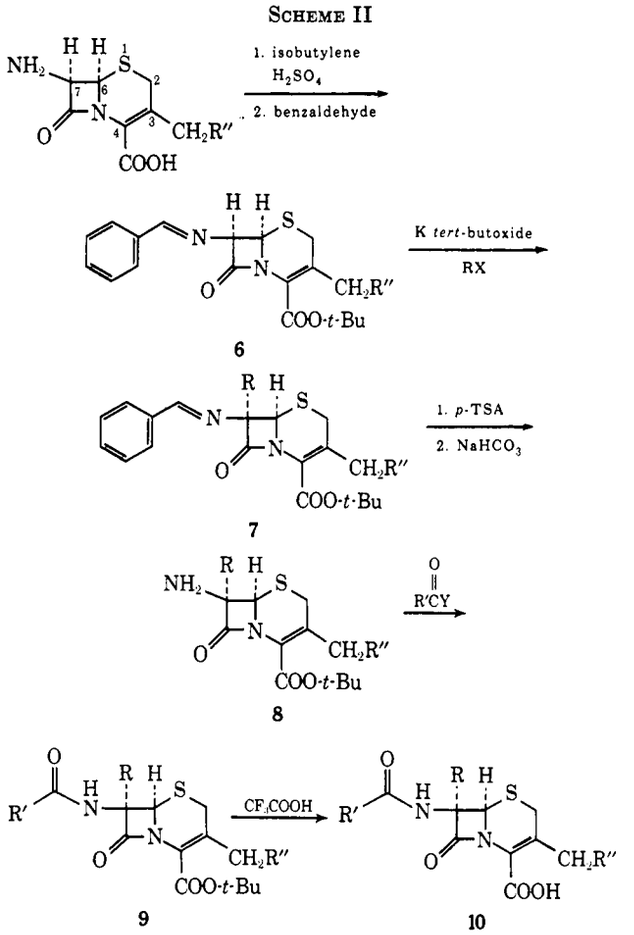
(6) This technique has been used by Firestone, *et al.*,[3c] to determine stereochemistry in a similar series of compounds.

SCHEME I

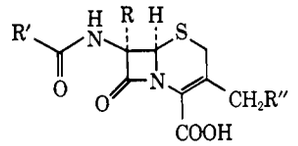


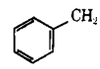
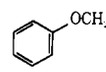
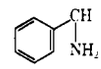
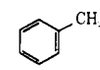
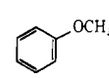
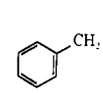
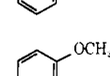
We have also synthesized several cephalosporins by the method described for 6-methylpenicillin V *p*-methoxybenzyl ester. The sequence of reactions is depicted in Scheme II.

SCHEME II



In a typical reaction sequence, the *N*-benzylidene Schiff base **6** is dissolved in anhydrous glyme and cooled to −30°. This solution is then treated with 1 equiv of potassium *tert*-butoxide before an alkylating agent, such as methyl iodide, is added. The ensuing reaction mixture is worked up to give the 7-alkylated Schiff base **7** (R = CH_3; R″ = H). The latter is then treated with excess *p*-toluenesulfonic acid (*p*-TSA) and water in ethyl acetate to give the *p*-TSA salt of the free amine **8** (R = CH_3; R″ = H). The amine is liberated with sodium bicarbonate. This amine can then be acylated in the usual manner to give compounds of type **9**. The free acid, **10**, is liberated by treating the *tert*-butyl ester with trifluoroacetic acid. Utilizing the above scheme (Scheme II), the following compounds were prepared.



	R′	R	R″
11		CH_3	H
12[2]		CH_3	H
13	 (D)	CH_3	H
14	CH_3		H
15			H
16			H
17			OAc
18		CH_3	OAc

By analogy with the addition of the alkylating agent to the α side of the molecule in Schiff bases in penicillins,[2] all additions of alkylating agents to the *N*-benzylidene Schiff bases of cephalosporin esters have been assumed to yield products with similar stereochemistry. To obtain corroborative proof for the α addition of alkylating agents to these Schiff bases, the nuclear Overhauser[7] effect (NOE) of 7-amino-7α-methyldeacetoxycephalosporanic acid *tert*-butyl ester (**8**) (R = CH; R″ = H) was studied. It was found that double irradiation of the C-7 methyl group produced a 22% NOE on the C-6 proton. Similarly, when the C-7 methyl of the methyl ester of compound **11** was doubly irradiated, an NOE of 21% on the C-6 proton was observed. The magnitude of this NOE is possible only if we are dealing with the 7α-methylcephalosporins.

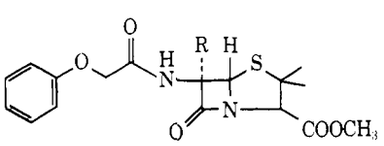
(7) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect," Academic Press, New York, N. Y., 1971.

When compounds **4**, **11–13**, and **18** were tested *in vitro*, the biological results[8] indicated that none of these new, substituted penicillin and cephalosporins were more active than their unsubstituted parent against both gram-positive and gram-negative organisms.[9] Against gram-positive organisms, the substituted compounds exhibited no more than 20% of the activity of the parent, whereas, against gram-negative organisms, these compounds were generally inactive at levels up to 200 μg/ml. Interestingly, though, 7-methoxycephalosporin C is reported to be more active toward gram-negative organisms than is cephalosporin C itself.[16] Similarly, 7-methoxycephalothin has been reported[3] to exhibit a spectrum *in vitro* that is similar to that of cephalothin, and to inhibit a number of cephalosporin-resistant organisms.

Since the biological activity in β-lactam antibiotics has been attributed[10,11] directly to an enzymatically catalyzed nucleophilic attack on the β-lactam, in the cephalosporins, a methyl group at the 7 position might tend to stabilize the β-lactam, and hence cause the substantial decrease in biological activity observed. Therefore, a C-7 substituent of greater electronegative character than methyl would make the β-lactam more susceptible to nucleophilic attack. The presence of a more reactive β-lactam might then result in greater biological activity for the whole molecule. In order to demonstrate the change in stability of the β-lactam of these types of compounds, we submitted penicillin V methyl ester,[12] 6-methylpenicillin V methyl ester, and 6-acetylpenicillin V methyl ester to basic hydrolysis[13] (Table I).

TABLE I
FIRST-ORDER RATE CONSTANTS

Compd	K, hr^{-1}, basic solutions (pH 8.0)
19	1.9×10^{-2}
20	0.5×10^{-2}
21	4.5×10^{-2}



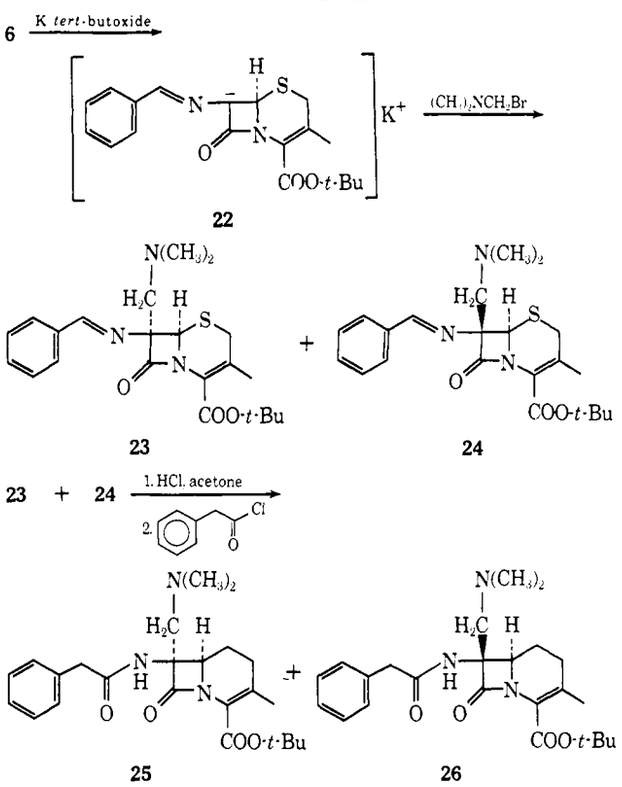
19, R = H
20, R = CH_3
21, R = $OCOCH_3$

As predicted, compound **21** was found to be more susceptible to basic hydrolysis than were the other two. However, when compounds **14–17** were submitted to *in vitro* assay, the biological results[8] indicated that, rather than enhancement of microbiological activity for these 7-acetylcephalosporins over the corresponding 7-methylcephalosporins, a pronounced decrease of activity was observed.

An alkylation with a Mannich-type[14] base was also carried out (Scheme III). Dimethylbromomethylamine[15] was added to the anion **22** in solution and allowed to react for 45 min at room temperature. An approximate 1:1 mixture of α and β isomers of the substituted Schiff bases **23** and **24** resulted. This mixture was then treated with aqueous hydrochloric acid–acetone to give the corresponding free amines. These were acylated to give both the α and β isomers of 7-dimethylaminomethyl-7-phenylacetamidodeacetoxycephalosporanic acid *tert*-butyl ester (**25** and **26**). At this point, the mixture was separated into its two components. As has been shown previously, the C-7 substitutions occur almost stereospecifically from the α face of the molecule. In this case, however, we are dealing with a "reversible alkylation"[14] and, hence, a 1:1 mixture of α and β isomers is not an unlikely result. We were able to make stereochemical assignments to the two components by studying their NOE's. The values for the NOE observed for both **25** and **26** are depicted in Chart I. Because of hindered rotation, the two methylene protons of the dimethylaminomethyl side chain had different chemical shifts and, hence, NOE's could be assigned for each of the two protons.

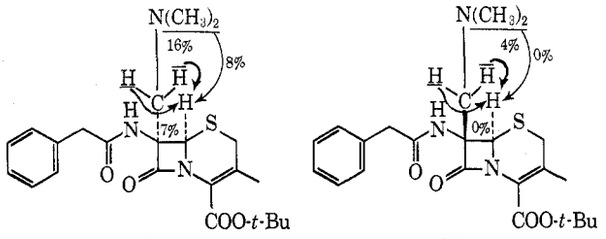
In the course of studying these 7-substituted cephalosporins, we obtained two new and chemically unique structures. The first, **27**, arose when we attempted

SCHEME III



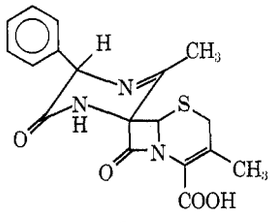
(8) The full *in vitro* spectra of these compounds will be reported elsewhere.
(9) F. Pansy, H. Basch, W. Tambor, G. Maestone, R. Semar, and R. Donovick, *Antimicrob. Ag. Chemother.*, 399 (1966).
(10) J. L. Strominger and D. J. Tipper, *Amer. J. Med.*, **30**, 708 (1965).
(11) J. L. Strominger, K. Izaki, M. Matsuhasi, and D. J. Tipper, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **26**, 9 (1967).
(12) G. Gomis, M. Isquierdo, and A. Turado, *Bull. Soc. Chim. Fr.*, 420 (1968).
(13) The lability of β-lactams toward nucleophiles has been studied before: R. J. Washkuhn and J. R. Robinson, *J. Pharm. Sci.*, **60**, 1168 (1971); R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, **71**, 2124 (1949); **72**, 2771 (1950); **73**, 3172 (1972).
(14) R. O. C. Norman, "Principles of Organic Synthesis," Methuen London, 1968, p 248.
(15) H. Bohme, E. Mundles, and O. E. Herboth, *Chem. Ber.*, **90**, 2003 (1957).

CHART I



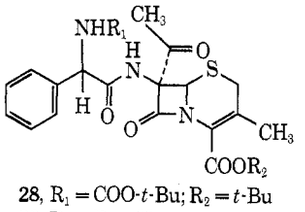
25 26

to deprotect 7α-acetyl-7-*tert*-butoxycarbonyl-D-phenylglycylaminodeacetoxycephalosporanic acid *tert*-butyl



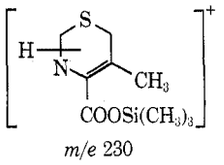
27

ester (**28**) with trifluoroacetic acid in order to prepare 7α-acetyl-7-phenylglycylaminodeacetoxycephalosporanic acid (**29**). Evidence for structure **27** was



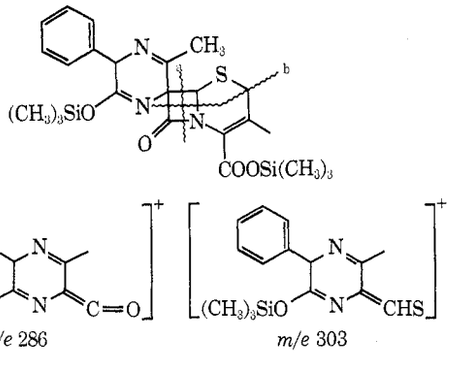
28, R_1 = COO-*t*-Bu; R_2 = *t*-Bu
29, $R_1 = R_2$ = H

obtained by submitting its trimethylsilyl derivative to mass-spectral analysis. The low-resolution spectrum yielded a molecular ion at *m/e* 515 corresponding to the ditrimethylsilylation of **27**. The typical β-lactam type fragmentation at *m/e* 230 corresponding to the following fragment is observed.



m/e 230

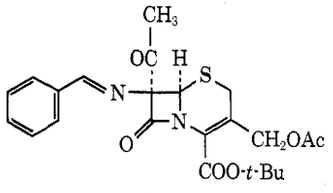
The β-lactam can be cleaved in two ways to give, *via* fragmentation a, the ion *m/e* 286 and, *via* fragmentation b, the ion *m/e* 303. Both of these ions are present



m/e 286 *m/e* 303

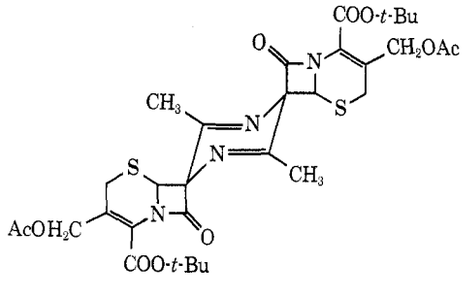
in the spectrum. Electrophoretic studies of compound **27** indicated that it was monoacidic, as evidenced by its charge of −1 at pH 4.0.

The second new and interesting material was formed when *N*-benzylidene-7-α-acetyl-7-aminocephalosporanic acid *tert*-butyl ester (**30**) was treated with dilute,



30

aqueous hydrochloric acid. Instead of the expected free amine, the following dimer (**31**) was the major



31

component of the reaction mixture. The nuclear magnetic resonance spectrum of this compound agreed with the structure assigned. Furthermore, electrophoretic studies showed **31** to be a neutral compound.

From the preceding observations, it is apparent that, in the presence of simple alkyl groups adjacent to the β-lactam carbonyl, the antimicrobial activities of these compounds are lowered and their overall microbiological spectra of inhibition are limited. Also it is apparent that the mere presence of an electron-withdrawing group at that position is not, *per se*, sufficient to improve or maintain the activity of the parent, unsubstituted compound. Whether the methoxy group has a unique effect[16] not generally shared by other electronegative groups is a point which must be established.

Experimental Section

Melting points (corrected) were taken on a Kofler hot stage. Proton nmr spectra were recorded on a Varian T-60 spectrometer. Nuclear Overhauser effects were studied on a Varian XL-100-15 spectrometer on deoxygenated, sealed $CDCl_3$ solutions. Chemical shifts are relative to TMS. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. Elemental analyses were performed at the Squibb Institute. Preparative thin layer chromatography was carried out on Quantum PQlF silica gel plates.

***N*-Benzylidene-6-aminopenicillanic Acid *p*-Methoxybenzyl Ester** (1).—6-Aminopenicillanic acid *p*-methoxybenzyl ester (13.3 g, 0.04 mol) was dissolved in 50 ml of benzene; 4.2 g (0.04 mol) of benzaldehyde and 10 g of $MgSO_4$ were added. This mixture was stirred at room temperature for 16 hr before the $MgSO_4$ was removed by filtration. The organic solution was evaporated to dryness *in vacuo* to give 13.7 g (82% yield) of a yellow oil: nmr ($CDCl_3$) 517 (d, J = 2.0 Hz, 1, CH=N), 439 (m, 9, aromatic), 338 (d, J = 4 Hz, 1, C_5H), 321 (d of d, J = 2 and 4 Hz, 1, C_6H), 309 (s, 2, CH_2Ph), 264 (s, 1, C_3H), 225 (s, 3,

(16) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgins, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, **93**, 2308 (1971).

OCH_3), 96 (s, 3, C_2CH_3), 84 Hz (s, 3, C_2CH_3); ir ($CHCl_3$) 1782 (β-lactam), 1738 (ester), 1638 cm^{-1} (imine).

N-Benzylidene-6-amino-6α-methylpenicillanic Acid p-Methoxybenzyl Ester.—Compound **1** (170 mg, 0.4 mequiv) was dissolved in anhydrous glyme (12 ml, distilled from $LiAlH_4$) and cooled to −40°. Methyl iodide (2 ml) was added, followed by the addition of 43.2 mg (0.4 mequiv) of sublimed potassium *tert*-butoxide. The reaction was allowed to proceed under nitrogen atmosphere at −40° for 3 hr. The mixture was then diluted to 100 ml with $CHCl_3$ and washed several times with 50-ml portions of distilled water. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to give 166 mg (95% yield) of a clear oil: nmr ($CDCl_3$) 520 (s, 1, CH=N), 439 (m, 9, aromatic), 321 (s, 1, C_5H), 308 (s, 2, CH_2Ph), 260 (s, 1, C_3H), 227 (s, 3, OCH_3), 106 (s, 3, C_6CH_3), 89 (s, 3, C_2CH_3), 81 Hz (s, 3, C_2CH_3).

6-Amino-6α-methylpenicillanic Acid p-Methoxybenzyl Ester (2).—*N*-Benzylidene-6-amino-6α-methylpenicillanic acid *p*-methoxybenzyl ester (2.58 g, 5.9 mequiv) was dissolved in 75 ml of EtOAc at room temperature. *p*-Toluenesulfonic acid monohydrate, 1.61 g, (8.5 mequiv), and 1.61 ml (0.09 equiv) of distilled water were added. Precipitation of a white solid started almost immediately. The reaction was allowed to proceed for 3 hr before the white solid was filtered off and dried *in vacuo* to give 2.47 g of the salt (80% yield), mp 171–174°. The latter was treated with dilute aqueous $NaHCO_3$ to liberate the crystalline free amine **2**, which was recrystallized from EtOAc–hexane to give 1.33 g (65% yield) of **2**: mp 84–87°; nmr ($CDCl_3$) 426 (q, 4, aromatic), 314 (s, 1, C_6H), 308 (s, 2, CH_2Ph), 265 (s, 1, C_3H), 223 (s, 3, OCH_3), 118 (s, 6, C_6CH_3, C_2CH_3), 83 Hz (s, 3, C_2CH_3); ir ($CHCl_3$) 3380 cm^{-1} ($-NH_2$). *Anal.* Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.27; H, 6.33; N, 8.00. Found: C, 58.53; H, 6.50; N, 7.80.

6α-Methyl-6-phenoxyacetamidopenicillanic Acid p-Methoxybenzyl Ester (3).—Compound **2** (1.33 g, 3.8 mequiv) was dissolved in 50 ml of dry $CHCl_3$ and treated with 652 mg (3.8 mequiv) of phenoxyacetyl chloride and 384 mg (3.8 mequiv) of triethylamine for 4 hr at ice-bath temperature. $CHCl_3$ (150 ml) was then added and this organic solution was washed twice with 50-ml portions of 0.1 *N* HCl and twice with 50-ml portions of distilled water before being dried ($MgSO_4$) and evaporated to dryness *in vacuo*. **3** (1.89 g) was isolated as a colorless oil: nmr ($CDCl_3$) 425 (m, 9, aromatic), 324 (s, 1, C_5H), 305 (s, 2, CH_2Ph), 267 (s, 2, OCH_2CO), 263 (s, 1, C_3H), 226 (s, 3, OCH_3), 108 (s, 3, C_6CH_3), 85 (s, 3, C_2CH_3), 80 Hz (s, 3, C_2CH_3).

6α-Methyl-6-phenoxyacetamidopenicillanic Acid (4).—Compound **3** (570 mg) was dissolved in a 10 ml dioxane–2 ml water mixture; 1.2 g of 10% palladium on calcium carbonate catalyst was added. This mixture was hydrogenolyzed at room temperature and atmospheric pressure until the uptake of hydrogen had ceased. This occurred after 4 hr, and 14 ml of hydrogen had been taken up (53% of theoretical). The catalyst was removed by filtration through Celite. The filtrate was diluted with 75 ml of $CHCl_3$ and washed twice with 15 ml of saturated aqueous $NaHCO_3$. The organic extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness to give 345 mg of colorless oil, mainly starting material (**3**). The aqueous $NaHCO_3$ (30 ml) was acidified to pH 1 with 5 *N* aqueous HCl. This solution was extracted with five 50-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo* to yield 168 mg of amorphous material: mass spectrum M^+ *m/e* 364; nmr ($CDCl_3$) 473 (s, 1, COOH), 427 (m, 5, aromatic), 326 (s, 1, C_5H), 372 (s, 2, OCH_2CO), 119 (s, 3, C_6CH_3), 91 and 89 Hz (s, 6, C_2CH_3); ir ($CHCl_3$) 3330 and 2616 (COOH), 1780 cm^{-1} (β-lactam).

***N*-Benzylidene-7-aminodeacetoxycephalosporanic Acid *tert*-Butyl Ester (6) (R = H).**—Concentrated sulfuric acid (30 ml) was added to 600 ml of dioxane in a 1-l. pressure bottle and chilled in an ice bath until the solution began to freeze. Liquid isobutylene (200 ml) and 30.0 g of 7-aminodeacetoxycephalosporanic acid were then added. The pressure bottle was stoppered, clamped in frame, and shaken overnight at room temperature. The reaction mixture was rechilled in ice prior to opening of the pressure bottle. The solution was poured into a stirred, ice-cold solution of 150 g of $NaHCO_3$ in 2.5 l. of water and extracted with three 800-ml portions of $CHCl_3$. The organic extracts were washed with water and saturated NaCl, dried ($MgSO_4$), and stripped to dryness *in vacuo*, yielding 25 g (66% yield) of 7-aminodeacetoxycephalosporanic acid *tert*-butyl ester as a yellow, crystalline solid. These 25 g (92.5 mequiv) were immediately dissolved in 450 ml of benzene. Benzaldehyde (9.8 g, 92.5 mequiv) and 50 g of anhydrous $MgSO_4$ were then added. This mixture was stirred for 2 hr at room temperature before it was filtered and evaporated to dryness *in vacuo*. The yellow, crystalline product was recrystallized from benzene to yield a total of 30.8 g of **6** (R″ = H) (93% yield), mp 118–119°. *Anal.* Calcd for $C_{19}H_{22}N_2O_3S$: C, 63.67; H, 6.19; N, 7.82. Found: C, 63.37; H, 6.40; N, 7.65.

***N*-Benzylidene-7-amino-7α-methyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (7) (R = CH_3; R″ = H).**—Compound **6** (500 mg, 1.4 mequiv) was dissolved in 25 ml of anhydrous glyme and cooled to −30° before 156 mg (1.4 mequiv) of potassium *tert*-butoxide was added. The anion was allowed to form under nitrogen for a few minutes, and then 2 ml of methyl iodide was added. The reaction was allowed to proceed at −30° and under nitrogen for 20 min. The mixture was diluted with 100 ml of $CHCl_3$ and washed with 50 ml of distilled water. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to give 512 mg of slightly yellow crystals (97% crude yield) (recrystallized from CH_2Cl_2–hexane): mp 138–140°; nmr ($CDCl_3$) 526 (s, CH=N–), 451 (s, 5, aromatic), 388 (s, 1, C_6H), 216 (d, J = 19 Hz, 1, C_2H), 184 (d, J = 18 Hz, 1, C_2H), 124 (s, 3, $\geq CH_3$), 110 (s, 3, C_7CH_3), 96 Hz (s, 9, *t*-Bu). *Anal.* Calcd for $C_{20}H_{24}N_2O_3S$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.38; H, 6.33; N, 7.41.

7-Amino-7α-methyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (8) (R = CH_3; R″ = H).—Compound **7** (R = CH_3; R″ = H) (5.72 g, 15.4 mequiv) was dissolved in 140 ml of EtOAc at room temperature, and then 2.93 g (15.4 mequiv) of *p*-toluenesulfonic acid and 28 ml of water were added. In 2 min, a white precipitate began to form. The reaction was continued for another 2 hr before the white solid was removed by filtration. The latter was redissolved in 100 ml of $CHCl_3$ and shaken well with 100 ml of 5% $NaHCO_3$. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness *in vacuo* to give 1.63 g of white, crystalline **8** (R = CH_3; R″ = H) (36.3% yield), recrystallized from benzene: mp 132–133°; nmr ($CDCl_3$) 278 (s, 1, C_6H), 212 (d, J = 18 Hz, 1, C_2H), 195 (d, J = 18 Hz, 1, C_2H), 122 (s, 5, NH_2 and $\geq CH_3$), 112 (s, 3, C_7CH_3), 92 Hz (s, 9, *t*-Bu); ir (Nujol) 3390 (NH_2), 1780 (β-lactam), 1750 cm^{-1} (*t*-Bu ester). *Anal.* Calcd for $C_{13}H_{20}N_2O_3S$: C, 54.92; H, 7.09; N, 9.85. Found: C, 54.67; H, 6.89; N, 9.71.

7α-Methyl-7-phenylacetamidodeacetoxycephalosporanic Acid *tert*-Butyl Ester (9) (R = CH_3; R″ = H).—Compound **8** (R = CH_3; R″ = H) (310 mg, 1.08 mequiv) was dissolved in 25 ml of anhydrous $CHCl_3$. Phenylacetyl chloride (170 mg, 1.09 mequiv) and 110 mg (1.09 mequiv) of triethylamine were added. The reaction was allowed to proceed for 4 hr at room temperature under nitrogen before being diluted with 100 ml of $CHCl_3$. The organic layer was washed first with 50 ml of 0.1 *N* HCl and then with 50 ml of water, dried ($MgSO_4$), and evaporated to dryness to give 413 mg of oil (94% yield): nmr ($CDCl_3$) 436 (s, 5, aromatic), 410 (s, 1, NH), 284 (s, 1, C_6H), 213 (s, 2, $PhCH_2CO$), 200 (d, J = 19 Hz, 1, C_2H), 179 (d, J = 19 Hz, C_5H), 123 (s, 3, $\geq CH_3$), 107 (s, 3, C_7CH_3), 89 Hz (s, 9, *t*-Bu).

7α-Methyl-7-phenylacetamidodeacetoxycephalosporanic Acid (11).—Compound **9** (R = CH_3; R′ = C_6H_5; R″ = H) (783 mg) was treated with 3 ml of trifluoroacetic acid (TFA) at room temperature for 5 min. Excess TFA was removed by evaporation before the residue was dissolved in 50 ml of $CHCl_3$. This solution was extracted with two 10-ml portions of saturated $NaHCO_3$. The combined $NaHCO_3$ layers were acidified with 5 *N* HCl to pH 1 and extracted with three 50-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined, dried ($MgSO_4$), and evaporated to dryness to give 437 mg of white crystals **11** (48% yield), recrystallized from EtOAc: mp 99–105°; mass spectrum M^+ *m/e* 346; nmr ($CDCl_3$) 436 (s, 5, aromatic), 389 (s, 1 NH), 284 (s, 1, C_6H), 215 (s, 2, $PhCH_2CO$), 192 (s, 2, SCH_2), 128 (s, 3, $\geq CH_3$), 120 Hz (s, 3, C_7CH_3); ir (Nujol) 3290, 2590 (COOH), 1770 (β-lactam), 1715 (COOH), 1700 (amide I), 1550 cm^{-1} (amide II). Analysis of this compound was not possible, since the molecule seemed to retain about one molecule of solvent. Any prolonged heating *in vacuo*, even at 60°, decomposed the material.

7α-Methyl-7-phenylglycylaminodeacetoxycephalosporanic Acid (13).—*N*-*tert*-Butoxycarbonylphenylglycine (705 mg, 2.7 mequiv) was dissolved in 20 ml of anhydrous tetrahydrofuran (THF) and stirred at −5°. Triethylamine (272 mg, 2.7 mequiv) and 370 mg (2.7 mequiv) of isobutyl chloroformate were added and the stirring was continued for 30 min. Compound **8** (R =

CH_3; R'' = H) (819 mg, 2.7 mequiv) in 15 ml of anhydrous TFA was added. The temperature of the reaction was allowed to rise to 23°, and stirring was continued for another 2 hr. The mixture was poured into 50 ml of ice-cold water and 50 ml of $CHCl_3$. The pH was raised to 7.5 and, after shaking, the layers were separated. The aqueous layer was extracted once more with 50 ml of $CHCl_3$. The organic layers were combined, dried ($MgSO_4$), and evaporated to dryness *in vacuo* to give 1.48 g (99% yield) of the deprotected acid **13**: nmr ($CDCl_3$) 441 (s, 5, aromatic), 390 (s, 1, CONH), 348 (d, J = 6 Hz, 1, PhNCHCO), 311 [d, J = 6 Hz, 1, $NHCOOC(CH_3)_3$], 284 (s, 1, C_6 H), 192 (d, J = 4 Hz, 2, SCH_2), 123 (s, 3, $\geqslant CH_3$), 109 (s, 3, C_7 CH_3), 91 and 83 Hz each (s, 9, *t*-Bu); ir ($CHCl_3$) 3410 (NH), 1775 (β-lactam), 1720 and 1710 (esters), 1690 (amide I), 1480 cm^{-1} (amide II). The latter was treated with 5 ml of TFA at 0° for 5 min. The solution was evaporated to dryness *in vacuo*, and the residue was triturated several times with ether to leave 540 mg of an off-white, amorphous powder (TFA salt of **13**, 70% yield): nmr (CD_3OD) 452 (m, 5, aromatic), 185 (s, 2, SCH_2), 123 (s, 3, $\geqslant CH_3$), 99 Hz (s, 3, C_7 CH_3); ir (Nujol) 3400, 2600 (COOH), 1760 (β-lactam), 1680 (amide I and carboxylate, 1540 cm^{-1} (amide II). Compound **13** was liberated by dissolving its TFA salt in 20 ml of water and passing this solution through 50 g of IR 4B ion-exchange resin. The aqueous extracts were lyophilized to give 259 mg of **12**: mp 150–154° dec; nmr (DMSO-d_6) 441 (m, 5, aromatic), 200 (s, 2, SCH_2), 124 (s, 3, $\geqslant CH_3$), 95 Hz (s, 3, C_7CH_3).

***N*-Benzylidene-7α-acetyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (7) (R = $COCH_3$; R'' = H).**—The procedure for the preparation of **7** (R = CH_3; R'' = H) was followed, except that the equivalents of acetyl chloride, rather than of methyl iodide, were used to quench the anion. Compound **7** (R = $COCH_3$; R'' = H) was prepared in this manner as white crystals (95% yield), recrystallized from EtOAc–hexane: mp 138–139°; nmr ($CDCl_3$) 533 (s, 1, CH=N), 460 (m, s, aromatic), 327 (s, 1, C_7H), 213 (d, J = 18 Hz, 1, C_2H), 180 (d, J = 18 Hz, 1, C_2H), 142 (s, 3, $COCH_3$), 124 (s, 3, $\geqslant CH_3$), 93 (s, 9, *t*-Bu).

Anal. Calcd for $C_{21}H_{24}N_2O_4S$: C, 62.99; H, 6.04; N, 7.00. Found: C, 62.91; H, 6.29; N, 6.93.

7-Acetamido-7α-acetyldeacetoxycephalosporanic Acid (14).—The procedure for the preparation of **9** (R = CH_3; R'' = H) was followed, except that acetyl chloride was used as the acylating agent and **7** (R = $COCH_3$; R'' = H) was the starting Schiff base. The *tert*-butyl ester of **14** was isolated in 66% yield as white crystals recrystallized from EtOAc: mp 168–169°; nmr ($CDCl_3$) 470 (s, 1, NH), 331 (s, 1, C_6 H), 210 (d, J = 16 Hz, 1, C_2H), 188 (d, J = 18 Hz, 1, C_2H), 139 (s, 3, $COCH_3$), 129 and 127 (2, s, 6, $\geqslant CH_3$ and CH_3CONH), 90 Hz (s, 9, *t*-Bu); ir (Nujol) 3250 (NH), 1778 (β-lactam), 1720 (ester), 1611 cm^{-1} (amide).

Anal. Calcd for $C_{16}H_{22}N_2O_5S$: C, 54.33; H, 6.26; N, 7.91. Found: C, 54.16; H, 6.11; N, 7.82.

By following the procedure for synthesis of free acid **11**, **14** was prepared in 67% yield, recrystallized from EtOAc: mp 181–183°; nmr (CD_3OD) 333 (s, 1, C_6H), 2.5 (d, J = 18 Hz, 1, C_2H), 192 (d, J = 16 Hz, 1, C_2H), 135 (s, 3, $COCH_3$), 126 Hz [s, 3, CH, CONH (?)] [s, 3, $\geqslant CH_3$ (?)].

Anal. Calcd for $C_{12}H_{14}N_2O_5S$: C, 48.32; H, 4.73; N, 9.39. Found: C, 48.10; H, 5.00; N, 9.17.

7α-Acetyl-7-phenylacetamidodeacetoxycephalosporanic Acid (15).—The procedure for the preparation of **14** was followed, except that phenylacetyl chloride was used as the acylating agent. The *tert*-butyl ester of **15** was isolated as white crystals recrystallized from EtOAc: mp 155–156°; nmr ($CDCl_3$) 457 (s, 1, NH), 430 (s, 5, aromatic), 328 (s, 1, C_6 H), 218 (s, 2, CH_2CO), 205 (d, J = 18 Hz, 1, C_2H), 195 (d, J = 18 Hz, 1, C_2H), 131 (s, 3, $COCH_3$), 125 (s, 3, $\geqslant CH_3$), 89 Hz (s, 9, *t*-Bu).

Anal. Calcd for $C_{22}H_{26}N_2O_5S$: C, 61.38; H, 6.09; N, 6.51. Found: C, 61.18; H, 6.21; N, 6.48.

Free acid **15** was isolated and recrystallized from EtOAc–hexane: mp 129–130°; nmr ($CDCl_3$) 530 (s, 1, COOH), 451 (s, 1, NH), 438 (s, 5, aromatic), 327 (s, 1, C_6 H), 219 (s, 2, CH_2CO), 195 (s, 2, CH_2S), 131 Hz (s, 6, CH_3CO and $\geqslant CH_3$).

Anal. Calcd for $C_{18}H_{18}N_2O_5S$: C, 57.75; H, 4.85; N, 7.48. Found: C, 57.94; H, 5.10; N, 7.20.

7α-Acetyl-7-phenoxyacetamidodeacetoxycephalosporanic Acid (16).—Compound **7** (R = $COCH_3$; R'' = H) (1 g, 2.5 mequiv) was dissolved in 5 ml of $CHCl_3$ and cooled in an ice bath. Phenoxyacetyl chloride (426 mg, 2.5 mequiv) and 1 drop of water were added. The reaction was allowed to proceed at 3° for 16 hr before being diluted with 100 ml of $CHCl_3$. This organic solution was washed with 50 ml of dilute aqueous $NaHCO_3$ and 50 ml of dilute aqueous HCl with two 50-ml portions of water. The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo* to give 1.0 g of the crystalline *tert*-butyl ester of **16** (97% crude yield) recrystallized from isopropyl alcohol–hexane: mp 165–166°; nmr ($CDCl_3$) 459 (s, 1, NH), 429 (m, 5, aromatic), 328 (s, 1, C_6H), 276 (s, 2, OCH_2), 200 (s, 1, SCH_2), 141 (s, 3, $COCH_3$), 131 (s, 3, $\geqslant CH_3$), 91 Hz (s, 9, *t*-Bu).

Anal. Calcd for $C_{22}H_{26}N_2O_6S$: C, 59.18; H, 5.87; N, 6.28. Found: C, 58.90; H, 5.92; N, 6.23.

The free acid **16** was liberated from its *tert*-butyl ester as described previously for compound **11**. Compound **16** was obtained as an amorphous material (72% yield): nmr ($CDCl_3$) 545 (s, 1, COOH), 469 (s, 1, NH), 430 (m, 5, aromatic), 338 (s, 1, C_6 H), 279 (s, 2, CH_2O), 200 (broad singlet, 2, CH_2S), 143 (s, 3, $COCH_3$), 137 Hz (s, 3, $\geqslant CH_3$); ir ($CHCl_3$) 3250, 2580 (COOH), 1775 (β-lactam), 1720 (COOH), 1690 (amide I), 1600 (aromatic), 1550 cm^{-1} (amide II).

***N*-Benzylidene-7-aminocephalosporanic Acid *tert*-Butyl Ester (6) (R'' = OAc).**—The procedure for the preparation of **6** (R'' = H) was followed using 7-aminocephalosporanic acid to give a 38.5% yield of **6**: nmr ($CDCl_3$) 518 (d, J = 3 Hz, 1, CH=N), 456 (m, 5, aromatic), 326 (d of d, J = 3 and 6 Hz, 1, C_7 H), 309 (d, J = 6 Hz, 1, C_6 H), 305 (d, J = 14 Hz, 1, CHOAc), 284 (d, J = 14 Hz, CHOAc), 218 (d, 18 Hz, 1, C_2 H), 196 (d, J = 18 Hz, 1, C_2H), 123 (s, 3, $OCOCH_3$), 93 Hz (s, 9, *t*-Bu); ir ($CHCl_3$) 1778 (β-lactam), 1735 (ester), 1720 (acetate), 1640 cm^{-1} (imine).

7α-Acetyl-7-phenylacetamidocephalosporanic Acid (17).—The procedure for the preparation of **15** was followed, substituting **6** (R'' = OAc) for **6** (R'' = H). The *tert*-butyl ester of **17** was isolated in 36% crude yield from **6** (R'' = OAc) crystallized from EtOAc–hexane: mp 135–136°; nmr ($CDCl_3$) 440 (s, 5, aromatic), 330 (s, 1, C_6 H), 306 (d, J = 12.0 Hz, 1, CHOAc), 288 (d, J = 12.0 Hz, 1, CHOAc), 219 (s, 2, CH_2Ph), 216 (d, J = 18.0 Hz, 1, C_2 H), 192 (d, J = 18.0 Hz, 1, C_2H), 131 (s, 3, C_7 $COCH_3$), 124 (s, 3, $OCOCH_3$), 88 Hz (s, 9, *t*-Bu).

Anal. Calcd for $C_{24}H_{28}N_2O_7S$: C, 59.01; H, 5.78; N, 5.74. Found: C, 59.21; H, 6.02; N, 5.57.

Free acid **17** was prepared in 85% crude yield recrystallized from MeOH–$CHCl_3$: mp 169–170°; nmr (CD_3OD) 436 (s, 5, aromatic), 333 (s, 1, C_6 H), 308 (d, J = 14 Hz, 1, CHOAc), 289 (d, J = 14 Hz, 1, CHOAc), 222 (d, J = 18 Hz, 1, C_2 H), 198 (d, J = 18 Hz, 1, C_2 H), 127 (s, 3, C_7 $COCH_3$), 123 Hz (s, 3, $OCOCH_3$).

Anal. Calcd for $C_{20}H_{20}N_2O_7S$: C, 55.55; H, 4.66; N, 6.48. Found: C, 55.43; H, 4.80; N, 6.18.

7α-Methyl-7-phenoxyacetamidocephalosporanic Acid (18).—The procedure for the preparation of **17** was followed, using methyl iodide as the alkylating agent and phenoxyacetyl chloride as the acylating agent. The *tert*-butyl ester of **18** was isolated and purified by preparative thin layer chromatography on silica gel (4% acetone in $CHCl_3$) (19% yield from **6**, R'' = OAc): mass spectrum m/e 476; nmr ($CDCl_3$) 426 (m, 5, aromatic), 306 (d, J = 13 Hz, 1, CHOAc), 294 (d, J = 13 Hz, 1, CHOAc), 290 (s, 1, C_6 H), 269 (s, 2, OCH_2), 214 (d, J = 18 Hz, 1, C_2H), 192 (d, J = 18 Hz, 1, C_2 H), 124 (s, 3, $OCOCH_3$), 114 (s, 3, C_7 CH_3), 94 Hz (s, 9, *t*-Bu).

Free acid **18** was obtained in 43% yield from its *tert*-butyl ester: nmr ($CDCl_3$) 425 (m, 5, aromatic), 312 (d, J = 15 Hz, 1, CHOAc), 292 (d, J = 15 Hz, 1, CHOAc), 293 (s, 1, C_6H), 273 (s, 2, CH_2O), 203 (broad singlet, 2, CH_2S), 125 (s, 3, $OCOCH_3$), 115 Hz (s, 3, C_7 CH_3).

6α-Methyl-6-phenoxyacetamidopenicillanic Acid Methyl Ester (20).—*N*-Benzylidene-6-amino-6α-methylpenicillanic acid methyl ester[1] (2.9 g, 8.5 mequiv) was dissolved in 50 ml of $CHCl_3$ and stirred with 1.45 g (8.5 mequiv) of phenoxyacetyl chloride and 2 drops of water for 2 hr at room temperature. The reaction mixture was then diluted with 150 ml of $CHCl_3$ and washed with 50 ml of 0.1 *N* HCl, 50 ml of dilute $NaHCO_3$, and two 50-ml portions of water. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to leave an oil. This oil was purified on preparative silica gel thin layer chromatography using chloroform as the eluent. Compound **20** (707 mg) was isolated as an oil (23% yield): nmr ($CDCl_3$) 430 (m, 6, aromatic and NH), 328 (s, 1, C_5 H), 272 (s, 2, OCH_2CO), 266 (s, 1, C_3H), 226 (s, 3, OCH_3), 110 (s, 3, C_6CH_3), 91 Hz [s, 6, $C_2(CH_3)_2$]; ir ($CHCl_3$) 3320 (amide), 1780 (β-lactam), 1740 (ester), 1685 (amide I), 1600 (aromatic), 1520 cm^{-1} (amide II).

6α-Acetyl-6-phenoxyacetamidopenicillanic Acid Methyl Ester (21).—*N*-Benzylidene-6-aminopenicillanic acid methyl ester (3.39 g, 10.3 mequiv) was dissolved in 100 ml of glyme and cooled to −40° under nitrogen, 1.16 g (10.3 mequiv) of potassium *tert*-butoxide was added, and the anion was allowed to form for 3 min. Acetyl chloride (810 mg, 10.3 mequiv) was added and the reaction was allowed to proceed at −40° for 5 min. The reaction mixture was diluted with 150 ml of $CHCl_3$ and washed with three 100-ml portions of water. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to give 3.6 g of *N*-benzylidene-6α-acetylpenicillanic acid methyl ester as an oil which did not crystallize (93% crude yield): nmr ($CDCl_3$) 527 (s, 1, CH=N), 457 (m, 5, aromatic), 353 (s, 1, C_5 H), 263 (s, 1, C_3 H), 225 (s, 3, OCH_3), 139 (s, 3, $COCH_3$), 91 and 87 Hz [2, s, 6, $C_2(CH_3)_2$]. This oil (3.37 g, 9.35 mequiv) was dissolved in 100 ml of $CHCl_3$ and cooled to 0°, and then 1.6 g (9.35 mequiv) of phenoxyacetyl chloride and 0.5 ml of water were added. After the reaction was completed (45 min), 150 ml of $CHCl_3$ was added to the reaction mixture and this solution was washed with 100 ml each of 0.1 *N* HCl, dilute $NaHCO_3$, and water. The organic extract was dried ($MgSO_4$) and evaporated to dryness to leave 3.45 g of yellow oil, which was purified by preparative silica gel thin layer chromatography using 10% hexane in $CHCl_3$ as the eluent. Compound **21** was isolated as an oil (523 mg) that could not be crystallized: nmr ($CDCl_3$) 475 (s, 1, NH), 421 (m, 5, aromatic), 360 (s, 1, C_5 H), 277 (s, 2, OCH_2CO), 269 (s, 1, C_3 H), 226 (s, 3, OCH_3), 139 (s, 3, $COCH_3$), 87 Hz [s, 6, $C_2(CH_3)_2$]; ir ($CHCl_3$) 3330 (amide), 1785 (β-lactam), 1745 (ester), 1685 (amide I), 1600 (aromatic), 1500 cm^{-1} (amide II).

7α-Acetyl-7-*tert*-butoxycarbonylphenylglycylaminodeacetoxycephalosporanic Acid *tert*-Butyl Ester (28).—The procedure for the preparation of **13** was followed, except that **8** (R = $COCH_3$; R″ = H) was used as the starting free amine. The crude yield of **28** was 95%. The product, however, failed to crystallize and was, therefore, purified by preparative thin layer chromatography on silica gel using $CHCl_3$ as the eluent. After this purification, **28** was isolated as an oil in 51% yield: nmr ($CDCl_3$) 440 (m, 5, aromatic), 341 (d, J = 7 Hz, 1, PhCNHCO), 324 (s, 1, C_6 H), 317 (d, J = 7 Hz, 1, NHCOO-*t*-Bu), 198 (d, J = 18 Hz, 1, C_2 H), 177 (d, J = 18 Hz, 1, C_2 H), 137 (s, 3, $COCH_3$), 124 (s, 3, $\geq CH_3$), 90 (s, 9, *t*-Bu), 85 Hz (s, 9, *t*-Bu).

Compound 27.—Compound **28** (50 mg, 0.9 mequiv) was dissolved in 2 ml of TFA and allowed to stand at room temperature for 2 min. Excess TFA was removed *in vacuo* to leave 25 mg of a brown glass: mass spectrum M^+ *m/e* 515, 286, 303; nmr (D_2O–CF_3COOH) 451 (s, 5, aromatic), 318 (s, 1, C_6 H), 199 (d, J = 18 Hz, 1, C_2 H), 174 (d, J = 18 Hz, 1, C_2 H), 141 (s, 3, $COCH_3$), 124 Hz (s, 3, $\geq CH_3$); electrophoresis, Eh value[17] −53.

Dimer 31.—Compound **7** (R = $COCH_3$; R″ = OAc) (100 mg, 0.25 mequiv) was dissolved in 2 ml of acetone and stirred with 1 ml of 0.1 *N* HCl for 10 min at room temperature. The reaction mixture was poured into ice water and extracted twice with 50 ml of $CHCl_3$. The combined $CHCl_3$ extracts were washed with distilled water, dried ($MgSO_4$), and evaporated to dryness *in vacuo*, to give 76 mg of a clear glass: nmr ($CDCl_3$) 309 (s, 2, CH_2OAc), 294 (s, 1, C_6 H), 219 (d, J = 18 Hz, 1, C_2 H), 198 (d, J = 18 Hz, 1, C_2 H), 148 (s, 3, $\geq CH_3$), 124 (s, 3, $OCOCH_3$), 92 Hz (s, 9, *t*-Bu); electrophoresis, Eh value[17] 0.

7α-Dimethylaminomethyl-7-phenylacetamidodeacetoxycephalosporanic Acid *tert*-Butyl Ester (25) and the 7β Isomer (26).—Compound **6** (R″ = H) (4 g, 11.2 mequiv) was dissolved in 200 ml of anhydrous glyme and cooled to −30°, and then 1.25 g (11.2 mequiv) of potassium *tert*-butoxide was added under nitrogen. The anion was allowed to develop for about 10 min before 1.54 g (11.2 mequiv) of dimethylbromomethylamine was added. The reaction mixture was allowed to come to room temperature over a 2-hr period before being poured into 100 ml of distilled water. This mixture was then extracted three times with 75-ml portions of $CHCl_3$. The organic extracts were combined, washed with water, dried ($MgSO_4$), and evaporated to dryness *in vacuo* to give 4.4 g of oil. This oil was taken up in 50 ml of acetone and shaken with 100 ml of 0.1 *N* HCl for 25 min. Distilled water (250 ml) was added, and this acidic solution was washed with 200 ml of $CHCl_3$. The acidic aqueous layer was brought to pH 7.5 with dilute $NaHCO_3$ and then extracted four times with 100-ml portions of $CHCl_3$. The organic extracts were combined, washed with 150 ml of water, dried ($MgSO_4$), and evaporated to dryness to give 2.15 g of oil **8** [R = α- and β-$CH_2N(CH_3)_2$, R″ = H, yield 46%]. The oil (6.85 mequiv) was dissolved in 50 ml of dry $CHCl_3$ and treated with 1.01 g (6.55 mequiv) of phenylacetyl chloride and 6.65 mg (6.55 mequiv) of triethylamine at room temperature, under nitrogen, for 35 min. The reaction mixture was diluted with 100 ml of $CHCl_3$, then washed with 100 ml of 0.1 *N* HCl followed by 100 ml of water. The organic layer was dried ($MgSO_4$) and evaporated to dryness *in vacuo* to give 2.64 g of yellow oil. Thin layer chromatography on silica gel (Eastman chromagram plates, 6060 silica gel) showed that the oil consisted of two major and at least three minor components. It was, therefore, purified by preparative thin layer chromatography on silica gel, using $CHCl_3$ as the eluent. By this method of purification, 410 mg of **25** [14% yield, mass spectrum *m/e* 446; nmr ($CDCl_3$) 438 (s, 5, aromatic), 283 (s, 1, C_6 H), 209 (s, 3, CH_2CON), 190 (d, J = 6 Hz, 4, C_2 CH_2 and CH_2N), 143 (s, 6, $N(CH_3)_2$), 126 (s, 3, $\geq CH_3$), 91 Hz (s, 6, *t*-Bu)], and 421 mg of **26** [14.4% yield; mass spectrum M^+ *m/e* 446; nmr ($CDCl_3$) 440 (s, 5, aromatic), 316 (s, 1, C_6H), 217 (s, 2, CH_2CON), 202 (s, J = 10 Hz, 1, C_2 H), 183 (d, J = 10 Hz, 1, C_2 H), 173 (d, J = 14 Hz, 1, $CHN(Me)_2$), 153 (d, J = 14 Hz, 1, $CHN(Me)_2$), 128 (s, 6, $N(CH_3)_2$), 120 (s, 3, $\geq CH_3$), 96 Hz (s, 9, *t*-Bu)] were isolated as oils.

Stability Studies.—Two sets of solutions of **19**, **20**, and **21**, *ca.* 3 mg/ml, were prepared: (a) 1:1 glyme/citrate buffer, pH 8.0; (b) 1:1 glyme/citrate buffer, pH 3.0. The citrate buffers were prepared from 0.1 *M* citric acid solution adjusted to the proper pH values with NaOH pellets. The penicillin solutions were kept in stoppered flasks at 50°.

Samples were assayed at various times by iodometric titration. A 1-ml aliquot was hydrolyzed for 30 min with 1 ml of 1 *N* NaOH, then acidified with 1 ml of 1 *N* HCl. Phthalate buffer (5 ml, pH 4.5) and 10.0 ml of 0.01 *N* iodine solution were added, and the solution was allowed to stand for 30 min. Excess iodine was titrated with 0.01 *N* sodium thiosulfate. Phthalate buffer (5 ml) and 10.0 ml of iodine solution were added to a second 1-ml aliquot, which was then allowed to stand for 30 min. Excess iodine was titrated with the thiosulfate solution. The percentage assay was calculated from these titer values.

Registry No.—**1**, 36954-77-5; **2**, 36954-78-6; **3**, 36954-79-7; **4**, 36954-80-0; **6** (R″ = H), 36954-81-1; **6** (R″ = OAc), 36954-82-2; **7** (R = CH_3; R″ = H), 33627-23-5; **7** (R = $COCH_3$; R″ = H), 36954-84-4; **8** (R = CH_3; R″ = H), 36954-85-5; **9** (R = CH_3; R″ = H), 36954-86-6; **11**, 36994-24-8; **12**, 32956-88-0; **13**, 37156-99-3; **14**, 36954-88-8; **14** (*t*-Bu ester), 36954-89-9; **15**, 36954-90-2; **15** (*t*-Bu ester), 36954-91-3; **16**, 36954-92-4; **16** (*t*-Bu ester), 36954-93-5; **17**, 36954-94-6; **17** (*t*-Bu ester), 36954-95-7; **18**, 36954-96-8; **18**, (*t*-Bu ester), 36954-97-9; **20**, 36954-98-0; **21**, 36954-99-1; **25**, 36955-00-7; **26**, 36955-01-8; **27**, 36955-02-9; **28**, 36955-03-0; **31**, 36955-04-1; *N*-benzylidene-6-amino-6α-methylpenicillanic acid *p*-methoxybenzyl ester, 36955-05-2; *N*-benzylidene-6α-acetylpenicillanic acid methyl ester, 36955-06-3.

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(17) Eh value is the ratio of the migration of the compound in centimeters to the distance between caffeine and picric acid multiplied by 100.