the by-product *N*-methylolcarbamate (**14a**), yielding the same intermediate product as that obtained through rupture of the N–C bond.
(23) A. W. Frank, in preparation.
(24) Nor any **17a** after oxidation with hydrogen peroxide.
(25) A. Einhorn, *Ann.*, **361**, 113 (1908).
(26) H. Schüssler and W. Mühl, German Patent 518 926 to I. G. Farbenindustrie A.-G., 1931; *Chem. Abstr.*, **25**, 3359 (1931).
(27) The identity of the by-products was not established. The reagents could react with **16** giving products of the type $N(CH_2NHCO_2R)_3$ or $RO_2CNHCH_2SO_3Na$, or they could abstract formaldehyde from **14** giving products such as hexamethylenetetramine or the bisulfite adduct of formaldehyde.
(28) J. D. Reid, R. M. Reinhardt, and J. S. Bruno, *Am. Dyest. Rep.*, **54**, 485 (1965).
(29) In the absence of a strong base, reaction would probably occur, if at all, at phosphorus, since phosphorus is a stronger nucleophile than uncharged nitrogen. The P substituted product, a quaternary phosphonium hydroxide, should revert to **13a** and **16a** (or **14a**) on heating.
(30) Likewise, formaldehyde must be displaced from methylene glycol before it can react with urea: G. A. Crowe, Jr., and C. C. Lynch, *J. Am. Chem. Soc.*, **71**, 3731 (1949).
(31) J. Sand, *Ber.*, **34**, 2906 (1901).
(32) A. Hoffman, *J. Am. Chem. Soc.*, **43**, 1684 (1921).
(33) A. Hoffman, *J. Am. Chem. Soc.*, **52**, 2995 (1930).
(34) M. Grayson, *J. Am. Chem. Soc.*, **85**, 79 (1963).
(35) S. E. Ellzey, Jr., W. J. Connick, Jr., G. J. Boudreaux, and H. Klapper, *J. Org. Chem.*, **37**, 3453 (1972).
(36) N. Filipescu, L. M. Kindley, H. E. Podall, and F. A. Serafin, *Can. J. Chem.*, **41**, 821 (1963).
(37) W. A. Reeves, F. F. Flynn, and J. D. Guthrie, *J. Am. Chem. Soc.*, **77**, 3923 (1955).
(38) M. Reuter and L. Orthner, U.S. Patent 3 030 421 to Farbwerke Hoechst A. G. (1962).
(39) L. Maier, *Helv. Chim. Acta*, **7**, 1723 (1967).
(40) Melting points are corrected. Elemental analyses were performed by Enviro Analytical Laboratory, Knoxville, Tenn. IR spectra were taken on a Perkin-Elmer Model 137B instrument with NaCl optics. NMR spectra were taken on a Varian A-60 using Me_4Si as an internal standard and, for phosphorus, a Varian HA-60-IL at 24.3 MHz using 85% H_3PO_4 as an external standard.
(41) Naming of firms or their products in this paper does not imply their endorsement by the U.S. Department of Agriculture.
(42) H. Hellmann, J. Bader, H. Birkner, and O. Schumacher, *Ann. Chem.*, **659**, 49 (1962).
(43) D. W. Allen, I. T. Millar, and J. C. Tebby, *Tetrahedron Lett.*, 745 (1968).
(44) Hooker Chemicals and Plastics Corp., Niagara Falls, N.Y.
(45) A. N. Booth, M. R. Gumbmann, W. E. Gagne, and J. D. Reid, "A Study of Possible Toxic Effects of Carbamate Finishing Agents", ARS 72-58, U.S. Department of Agriculture, New Orleans, La., 1967.
(46) "Dowex Ion Exchange", Dow Chemical Co., Midland, Mich., 1964, p 65.
(47) T. L. Davis and S. C. Lane, Org. Synth., Collect. Vol. I, 1941, 140.
(48) D. K. George, U.S. Patent 3 065 232 to FMC Corp., 1962; *Chem. Abstr.*, **58**, 4587a (1963).
(49) O. G. Seidbekova, Sh. A. Iseeva, G. G. Almamedov, and B. A. Dadashev, *Azerb. Khim. Zh.*, 89 (1964); *Chem. Abstr.*, **64**, 6490g (1966).
(50) I. M. Kolthoff and R. Belcher, "Volumetric Analysis", Vol. 3, Interscience, New York, N.Y., 1957, p 252.

Derivatives of 6β-Methylpenicillanic Acid

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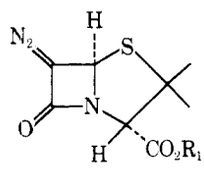
Diazo compounds **1** have been converted to intermediates **2** by two methods: reaction with aqueous *N*-bromosuccinimide, and treatment with triphenylphosphine and nitrous acid. Reaction of **2** with Wittig reagents gives a series of C_6 carbon analogues **6** and, after Curtius rearrangement, C_6 penicillin homologues **8**.

The C_6 carbon analogue of penicillin V has been synthesized and found to have interesting antibiotic activities.[1] The synthetic method for such analogues has therefore been improved and extended to make a series of carbon analogues available for further study.

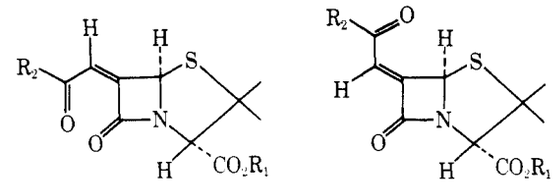
The starting intermediates for these syntheses are the 6-diazopenicillanates **1** (R_1 = CH_2CCl_3, CH_2Ph) which were synthesized according to a known method.[2] Compounds **1**



1

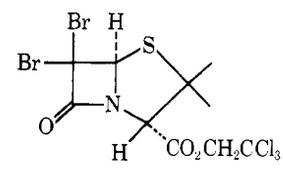
react with *N*-bromosuccinimide in aqueous solvents or Ph_3P followed by nitrous acid[3] to give keto compounds **2**.[4] Compounds **2** are relatively unstable and are not usually isolated, but used directly for further reactions.

For example, compound **2** (R_1 = CH_2CCl_3), as a crude oil derived from the treatment of **1** with aqueous NBS, reacted with $Ph_3P{=}CHCO_2CH_2Ph$ to give the syn and anti isomers **3** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph). These isomers were isolated in 32 and 3% yield [based on diazo compound **1** (R_1 = CH_2CCl_3)]. The major product was assigned the sterically less hindered anti structure. A major by-product of this series of reactions is the dibromide **4**, isolated in yields ranging from 13 to 32%. The triphenylphosphine–nitrous acid method of



3

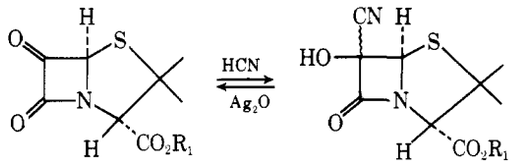
synthesizing compound **2** followed by reaction with the same Wittig reagent gave compounds **3** (R_1 = CH_2CCl_3; R_2 =



4

OCH_2Ph) in 60% yield. Similarly, ketone **2** (R_1 = CH_2CCl_3) reacted with $Ph_3P{=}CHCOCH(Ph)NH$-*tert*-Boc to give **3** (R_1 = CH_2CCl_3; R_2 = $CH(Ph)NH$-*tert*-Boc), mostly in the anti form. The yields, based on **1**, were 9% for the NBS method and 26% for the triphenylphosphine–nitrous acid method.

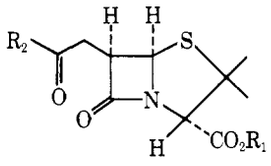
Addition of HCN to compound **2** (R_1 = CH_2Ph) gives a crystalline cyanohydrin **5** which can be used to regenerate the pure keto compound or react with other reagents.[5] For instance, cyanohydrin **5** (R_1 = CH_2Ph) reacts directly with an ylide such as $Ph_3P{=}CHCO_2$-*tert*-Bu or $Ph_3P{=}CHCOCH(Ph)NH$-*tert*-Boc to give compounds **3** (R_1 = CH_2Ph; R_2 = *O*-*tert*-Bu or $CH(Ph)NH$-*tert*-Boc) in 97 and



2 5

80% yields, respectively. Both isomers are also observed spectroscopically but were not isolated separately. The condensation of a Wittig reagent with a cyanohydrin can only proceed if enough of the ketone form is available. This seems to be the case with compound **4** (R_1 = CH_2Ph).

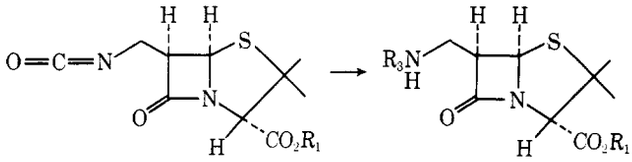
Hydrogenation of **3** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph or CH(Ph)NH-*tert*-Boc, or R_1 = CH_2Ph; R_2 = *O-tert*-Bu) in the presence of rhodium on alumina gave only one isomer **6**. The carboxyl-protecting group of R_2 was removed by hydrogenolysis over Pd on charcoal (R_2 = OCH_2Ph) or trifluoroacetic acid treatment (R_2 = *O-tert*-Bu) to give the half-esters. Compound **6** (R_1 = CH_2Ph; R_2 = OH) was isolated as a solid material.



6

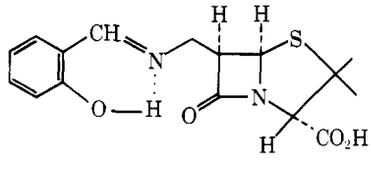
Half-esters **6** (R_1 = CH_2CCl_3 or CH_2Ph; R_2 = OH) were esterified and treated with amines to give a series of esters and amides. All reactions were done with diisopropylcarbodiimide with the exception of benzylamine which was coupled with carbonyldiimidazole. Removal of protecting groups gave penicillin C_6 carbon analogues with the following R_2 groups: $PhCH(CH_2NHCHO)O$, $PhCH_2O$, PhNH, $PhCH_2NH$, $PhCH(CO_2H)NH$, $HCl{\cdot}H_2NCH_2CH_2S$ and $H_3{}^+NCH(Ph)$, $C_4H_3SCH_2O$, naphthyl-O.

Compound **6** (R_1 = CH_2Ph; R_2 = OH) was treated with sodium azide and rearranged to give **7**. Treatment of **7** (R_1 = CH_2Ph) with *tert*-butyl alcohol gave the penicillin homologue **8** (R_1 = CH_2Ph; R_3 = COO-*tert*-Bu). Compound **8** (R_1 = CH_2Ph; R_3 = COO-*tert*-Bu) is easily deblocked at the C_6 side chain to give the free amine, isolated as the trifluoroacetate salt.



7 8

Acylation of **8** (R_1 = CH_2Ph; R_3 = H) and removal of the benzyl group gave the following penicillin C_6 homologues: R_1 = H; R_3 = $PhCH_2CO$, EtOCO, $PhCH(NH_2)CO$, PhNHCO, CH_3PhSO_2, $PhCH_2SO_2$. Reaction of **8** (R_1 = R_3 = H) with salicylaldehyde gave the Schiff base **9**.



9

We have consistently observed a low β-lactam infrared frequency (1740–1750 cm^{-1}) for the penicillin homologues **8** (R_1 = CH_2Ph). However, the NMR spectra were consistent with a β-lactam structure. On deblocking the C_3 carboxyl, the infrared frequency appeared again at 1775 cm^{-1}. We have no explanation for this anomaly, although hydrogen bonding or solvation are the most likely explanations. Some of our compounds have coupling constants, $J_{5,6}$, of 6 Hz. Such a high $J_{5,6}$ value is not usually observed for penicillin compounds, although it is not unusual for β-lactam structures[6] in general.

All compounds were tested for biological activity. C_6 carbon analogues derived from **6** showed some gram-positive activity. Homologues **8** and **9** were inactive against gram-positive or gram-negative organisms.

Experimental Section

General. 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 tetramethylsilane.

Synthesis of β,β,β-Trichloroethyl 6-Oxopenicillanate 2 (R_1 = CH_2CCl_3) and β,β,β-Trichloroethyl 6,6-Dibromopenicillanate (4). Method 1. *N*-Bromosuccinimide (0.54 g, 2.8 mmol) was added all at once to an ice-cold solution of the diazo ester **1** (R_1 = CH_2CCl_3; 1.0 g, 2.8 mmol) and 1 mL of pyridine in 25 mL of acetone and 5 mL of H_2O. After the addition, there was an immediate evolution of nitrogen. The solution was stirred at 0 °C for 1 h, diluted with CH_2Cl_2, washed with H_2O and ice-cold dilute HCl, and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was chromatographed on silicic acid initially using CH_2Cl_2 as an eluent. Isolation of the faster moving fraction gave 438 mg (32%) of β,β,β-trichloroethyl 6,6-dibromopenicillinate (**4**) as an oil. Further purification by chromatography gave an analytically pure sample: IR (neat) 1790 and 1755 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 4.70 (s, 1 H), 4.84 (s, 2 H), 5.84 (s, 1 H).

Anal. Calcd for $C_{10}H_{10}Br_2Cl_3NO_3S$: C, 24.49; H, 2.06; N, 2.86; Br, 32.59; Cl, 21.69; S, 6.54. Found: C, 24.68; H, 2.11; N, 2.94; Br, 32.57; Cl, 21.82; S, 6.62.

The polarity of the eluting system was increased with ether. Isolation of the slower moving fraction gave β,β,β-trichloroethyl 6-oxopenicillanate (**2**) (R_1 = CH_2CCl_3) as an impure oil, 0.48 g: IR ($CHCl_3$) 2960, 1830, 1775, 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (s, 3 H), 1.70 (s, 3 H), 4.84 (s, 2 H), 4.94 (s, 1 H), 5.80 (s, 1 H).

Synthesis of β,β,β-Trichloroethyl 6-Oxopenicillanate 2 (R_1 = CH_2CCl_3). Method 2. Diazo ester **1** (R_1 = CH_2CCl_3; 7.16 g, 0.02 mol) and triphenylphosphine (5.24 g, 0.02 mol) were dissolved in 550 mL of CH_2Cl_2 at 0 °C. A solution of $NaNO_2$ (6.80 g, 0.10 mol) and F_3AcOH (8.90 g, 0.12 mol) in 250 mL of Me_2SO at 0 °C was added to the above mixture and stirred at 0 °C for 1.75 h. The solution was washed extensively with water, 5% sodium bicarbonate, and saturated salt solution. The organic layer was dried ($MgSO_4$) and evaporated to give 12.1 g of an oil containing the keto compound **2** (R_1 = CH_2CCl_3) and triphenylphosphine oxide. Spectra were identical with those obtained from the NBS method except for the presence of Ph_3PO. The keto compound was used directly without further purification.

Synthesis of 3 (R_1 = CH_2CCl_3; R_2 = CH_2Ph). In the same manner as described above, treatment of the diazo ester **1** (R_1 = CH_2CCl_3) with NBS in aqueous acetone containing pyridine gave a mixture of dibromo and keto esters. The mixture was dissolved in benzene. Benzyloxycarbonylmethylenetriphenylphosphorane (2–3 equiv) was added and the mixture refluxed for 30 h. After removal of the solvent under reduced pressure, the dark-brown residue was chromatographed on silicic acid using methylene chloride as an eluent. Isolation of the fastest moving fraction gave β,β,β-trichloroethyl 6,6-dibromopenicillinate (**4**) (13.7%) as an oil. Isolation of a slower moving fraction gave the anti unsaturated ester **3** (R_1 = CH_2CCl_3, R_2 = OCH_2Ph) in 32% yield based on starting diazo ester. Further purification by chromatography gave an analytically pure sample: IR ($CHCl_3$) 1780 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 3 H), 1.63 (s, 3 H), 4.67 (s, 1 H), 4.77 (s, 2 H), 5.20 (s, 2 H), 5.97 (d, 1 H, J = 1.0 Hz), 6.30 (d, 1 H, J = 1.0 Hz), 7.35 (s, 5 H).

Anal. Calcd for $C_{19}H_{18}NO_5Cl_3S$: C, 47.66; H, 3.79; N, 2.93; Cl, 22.22; S, 6.70. Found: C, 47.40; H, 3.77; N, 2.77; Cl, 22.40; S, 6.72.

Isolation of the slowest moving fraction gave 3% yield of the syn unsaturated ester **3** (R_1 = CH_2CCl_3, R_2 = CH_2Ph) as an oil which crystallized on standing. Recrystallization from ether gave an analytically pure sample: mp 108–109 °C; IR ($CHCl_3$) 1780 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.72 (s, 3 H), 4.75 (s, 1 H), 4.80 (s,

2 H), 5.26 (s, 2 H), 5.76 (d, 1 H, J = 0.5 Hz), 6.04 (d, 1 H, J = 0.5 Hz), 7.38 (s, 5 H).

Anal. Calcd for $C_{19}H_{18}NO_5Cl_3S$: C, 47.66; H, 3.79; N, 2.93; Cl, 22.22; S, 6.70. Found: C, 47.76; H, 3.43; N, 2.93; Cl, 22.41; S, 6.71.

Synthesis of 3 [R_1 = CH_2CCl_3; R_2 = CH(Ph)NH-*tert*-Boc]. Two grams of Ph_3P=CHCOCH(Ph)NH-*tert*-Boc (3.9 mmol) and 3.4 g of crude **2** (derived from 4.0 g, 5.5 mmol 1 by the NBS method) (R_1 = CH_2CCl_3) were dissolved in 80 mL of dry benzene. The mixture was stirred under N_2 at room temperature for 22 h. The mixture was evaporated and rapidly chromatographed on silica gel with methylene chloride–ether (8:1). The oil obtained was crystallized from ether to give white crystals, 9%: mp 175–178 °C (dec); IR (CH_2Cl_2) 2975, 1770, 1705, 1670, 1485 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.57 (s, 3 H), 1.62 (s, 3 H), 4.65 (s, 1 H), 4.78 (s, 2 H), 5.50 (d, 1 H, J = 6 Hz), 5.85 (d, 1 H, J = 6 Hz), 6.03 (s, 1 H), 6.72 (s, 1 H), 7.40 (s, 5 H); R_f (methylene chloride–ether, 6:1) 0.7.

The same reaction was carried out with ketone **2** derived from the triphenylphosphine–nitrous acid method to give 0.83 g (26%) of light-yellow crystals. Spectra and physical constants were the same as described above.

***tert*-Butoxycarbonyl-α-amino-α-phenylacetylmethylenetriphenylphosphorane.** The ylide was synthesized according to published methods[7,8] to give 7.91 g (71% based on D-*tert*-butoxycarbonylphenylglycine) of yellow crystals. Recrystallization from ether gave an analytical sample: mp 112.4–114 °C; IR (CH_2Cl_2) 3375, 3050, 2980, 1700, 1550–1560 cm^{-1}; NMR ($CDCl_3$) δ 1.19 (s, 9 H), 5.12 (d, 1 H, J = 3.5 Hz), 6.19 (d, 1 H, J = 3.5 Hz), 7.2–7.7 (m, 21 H).

Anal. Calcd for $C_{32}H_{32}NO_3P$ (509.56): C, 75.42; H, 6.34; N, 2.75; P, 6.08. Found: C, 75.26; H. 6.50; N, 2.72; P, 5.85.

Synthesis of 3 (R_1 = CH_2Ph; R_2 = *O-tert*-Bu). Cyanohydrin **5**[5] (R_1 = CH_2Ph) (8.0 g, 0.024 mol) was dissolved in 240 mL of benzene. *tert*-Butoxycarbonylmethylenetriphenylphosphine (10.8 g, 0.029 mol) in 300 mL of benzene was added and the solution stirred at 20 °C. for 24 h. The solution was evaporated and the residue chromatographed on silica gel with methylene chloride–ethyl ether (50:1) to give 8.8 g (97%) of **3** (R_1 = CH_2Ph; R_2 = *O-tert*-Bu) as an oil: IR (film) 2970, 1775, 1725, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.40 and 1.45 (s, 15 H), 4.58 (s, 1 H), 5.15 (s, 2 H), 5.95 (s, 1 H), 6.10 (s, 1 H), 7.33 (s, 5 H).

Compound **3** [R_1 = CH_2Ph; R_2 = CH(Ph)NH-*tert*-Boc] was synthesized in the same manner from 2 mmol of cyanohydrin **5** and 2 mmol of Ph_3P=CHCOCH(Ph)NH-*tert*-Boc to give 0.85 g (80%) of **3** as an oil: IR ($CDCl_3$) 2975, 1770, 1730–1760, 1670, 1485 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (s, 12 H), 1.55 (s, 3 H), 4.56 (d, 1 H, J = 2 Hz), 5.19 (s, 2 H), 5.42 (m, 1 H), 5.79 (m, 1 H), 5.99 (s, 1 H), 6.49 (s, 1 H), 7.38 (s, 10 H).

Hydrogenation of 3. Compound **3** (R_1 = CH_2Ph; R_2 = *O-tert*-Bu; 8.5 g, 0.020 mol) was dissolved in 400 mL of ethyl acetate. Rhodium on alumina (5%, 17.2 g) was added and the mixture was hydrogenated at atmospheric pressure for 10 h at 20 °C. The solution was filtered, evaporated, and chromatographed on silica gel with methylene chloride–ethyl ether (50:1) to give **6** (R_1 = CH_2Ph, R_2 = *O-tert*-Bu) as a yellow oil, 6.0 g (70%); NMR ($CDCl_3$) δ 1.50 and 1.65 (s, 15 H), 2.70–2.90 (m, 2 H), 3.75–4.10 (m, 1 H), 4.40 (s, 1 H), 5.10 (s, 2 H), 5.57 (d, 1 H, J = 4 Hz), 7.35 (s, 5 H); IR (film) 2980, 1775, 1740, 1725 cm^{-1}.

Compound **3** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph) was hydrogenated in the same way. Chromatography gave **6** (R_1 = CH_2CCl_3, R_2 = OCH_2Ph) as an oil (42%) which could be crystallized from ether–petroleum ether: mp 42–50 °C; IR ($CHCl_3$) 1775, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.74 (s, 3 H), 2.8–3.1 (m, 2 H), 3.8–4.3 (m, 1 H), 4.50 (s, 1 H), 4.74 (s, 2 H), 5.10 (s, 2 H), 5.53 (d, 1 H, J = 4.0 Hz), 7.26 (s, 5 H).

Compound **3** (R_1 = CH_2CCl_3; R_2 = CH(Ph)NH-*tert*-Boc) was hydrogenated in the same manner to give 50% **6** (R_1 = CH_2CCl_3, R_2 = CH(Ph)NH-*tert*-Boc) as an oil: IR ($CDCl_3$) 2975, 2925, 1770, 1740, 1700, 1475 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.40 (s, 9 H), 1.55 (s, 3 H), 2.80–3.02 (m, 2 H), 3.75–4.10 (m, 1 H), 4.35 (s, 1 H), 5.20 (s, 2 H), 5.35 (d, 1 H, J = 4 Hz), 5.50 (d, 1 H, J = 5 Hz), 5.82 (d, 1 H, J = 5 Hz), 7.4 (s, 5 H).

Synthesis of 6 (R_1 = CH_2CCl_3; R_2 = OH). The ester **6** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph; 303 mg, 0.63 mmol) was dissolved in EtOAc and hydrogenated in the presence of a 10% Pd-C catalyst for 2.5 h at room temperature and 1 atm of pressure. After removal of the catalyst by filtration through celite and washing of the surface with ether, the solvent was removed under reduced pressure using no heat. The residual oil was dissolved in methylene chloride and extracted with aqueous $NaHCO_3$. After separation of the organic layer and acidification of the aqueous layer with ice-cold dilute HCl, the acid was isolated as an oil (246 mg, 62%) by extraction with methylene chloride, drying ($MgSO_4$), and removal of the solvent under reduced pressure using no heat: NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 2.8–3.2 (m, 2 H), 3.8–4.3 (m, 1 H), 4.53 (s, 1 H), 4.79 (s, 2 H), 5.56 (d, 1 H, J = 4.0 Hz), 8.40 (s, 1 H).

Synthesis of 6 (R_1 = CH_2Ph; R_2 = OH). The ester **6** (R_1 = CH_2Ph; R_2 = *O-tert*-Bu) (1.9 g, 4.7 mmol) was dissolved in 60 mL of trifluoroacetic acid at 0 °C and stirred for 0.5 h. F_3AcOH was evaporated at 0 °C and the resultant oil freeze dried from benzene to give a quantitative yield of an oil: IR (film) 3000, 1775, 1725, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.42 and 1.57 (s, 6 H), 2.8–3.4 (m, 3 H), 4.65 (s, 1 H), 5.20 (s, 2 H), 5.72 (d, 1 H, J = 6 Hz), 7.40 (s, 5 H). Crystallization of the oil from ether gave a white solid which is probably a hydrate according to spectra: IR (KBr) 3000, 1725, 1670 cm^{-1}; NMR ($CDCl_3$) same as above plus δ 7.57 (s, 2 H).

Synthesis of 6 (R_1 = CH_2Ph; R_2 = $NHCH_2Ph$). Acid **6** (R_1 = CH_2Ph; R_2 = OH) (350 mg, 1.0 mmol) was dissolved in 5 mL of methylene chloride at 0 °C. 1,1′-Carbonyldiimidazole (178 mg, 1.1 mmol) was added and the solution stirred for 5 min. Benzylamine (107 mg, 1.0 mm) in 5 mL of methylene chloride was added and the solution was allowed to stand at 5 °C for 12 h. The solution was washed with cold HCl (0.05 N), saturated sodium bicarbonate solution, and water. After drying and evaporation, the oil obtained was chromatographed on silica gel with methylene chloride–ethyl ether (10:1) to give 88 mg (19%) of a yellow oil: IR (film) 3350, 2900, 1775, 1730, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.35, 1.50 (s, 6 H), 2.6–3.2 (m, 3 H), 4.40 (d, 2 H, J = 5 Hz), 4.55 (s, 1 H) 5.15 (s, 2 H), 5.63 (d, 1 H, J = 6 Hz), 6.75 (m, 1 H), 7.25, 7.32 (s, 10 H).

Synthesis of 6 [R_1 = CH_2Ph; R_2 = $NHCH(CO_2CHPh_2)Ph$]. Acid **6** (R_1 = CH_2Ph; R_2 = OH) (350 mg, 1 mmol) was dissolved in 20 mL of CH_2Cl_2 at 0 °C. Benzyhydryl phenylglycinate as the tosylate salt (982 mg, 2 mmol) was suspended in 20 mL of CH_2Cl_2 and pyridine (0.25 mL, 3 mmol) at 0 °C. The solutions were mixed and diisopropylcarbodiimide (0.31 mL, 2 mmol) was added. The mixture was stirred at 0 °C. for 1 h and at 20 °C for 24 h. The solution was washed with 0.05 N HCl, saturated bicarbonate solution, and water. After drying and evaporation, the residue was chromatographed on silica gel with methylene chloride–ethyl ether (10:1) to give 367 mg (55%) of oil: IR (film) 3300, 3000, 1745, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.30, 1.45 (s, 6 H), 2.55–3.25 (m, 3 H), 4.45 (s, 1 H), 5.02 (s, 2 H), 5.45 (d, 1 H, J = 6 Hz), 5.65 (s, 1 H), 6.70 (s, 1 H). 7.15 (s, 20 H).

Synthesis of 6 (R_1 = CH_2CCl_3; R_2 = $OCH_2C_4H_3S$). Compound **6** (R_1 = CH_2CCl_3; R_2 = OH) (105 mg, 0.36 mmol) was esterified with 2-thiophenemethanol (57 mg, 0.50 mmol) in the presence of pyridine (35 μL, 0.43 mmol) and *N,N′*-diisopropylcarbodiimide (70 μL, 0.45 mmol). The product was isolated as an oil (45 mg, 32%) after chromatography on silica gel using 2% MeOH–$CHCl_3$ as an eluent: IR ($CHCl_3$) 2985, 1770, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 2.8–3.1 (m, 2 H), 3.9–4.3 (m, 1 H), 4.53 (s, 1 H), 4.77 (s, 2 H), 5.27 (s, 2 H), 5.55 (d, 1 H, J = 4.0 Hz), 6.7–7.5 (m, 3 H).

Synthesis of 6 (R_1 = CH_2CCl_3; R_2 = CH_2CCl_3; R_2 = O-Naphthyl). In the same manner as described above, the 2-naphthol ester was isolated as a crystalline material (72%) after chromatography on silicic acid using methylene chloride as an eluent. The product was recrystallized from CH_2Cl_2–petroleum ether: mp 119–120 °C; IR ($CHCl_3$) 1780 (sh) and 1760 cm^{-1}; NMR ($CDCl_3$) δ 1.66 (s, 3 H), 1.80 (s, 3 H), 3.1–3.4 (m, 2 H), 4.0–4.5 (m, 1 H), 4.64 (s, 1 H), 4.80 (s, 2 H), 5.70 (d, 1 H, J = 4.0 Hz), 7.0–8.0 (m, 7 H).

Anal. Calcd for $C_{22}H_{20}NO_5SCl_3$: C, 51.13; H, 3.90; N, 2.71; Cl, 20.58; S, 6.20. Found: C, 51.40; H, 4.00; N, 2.58; Cl, 20.79; S, 5.99.

Synthesis of 6 [R_1 = CH_2CCl_3; R_2 = $PhCH(CH_2NHCHO)O$]. Prepared in the same manner as described above, the mixture of diastereomeric esters was separated by chromatography on silicic acid using 5:1 methylene chloride–ether (v/v) as an eluent.

Less polar isomer: NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.73 (s, 3 H), 2.85 (d, 2 H, J = 8.0 Hz), 3.3–4.4 (m, 3 H), 4.57 (s, 1 H), 4.81 (d, 2 H, J = 1 Hz, CH_2CCl_3),[9] 5.61 (d, 1 H, J = 4.0 Hz), 5.7–6.3 (m, 1 H), 6.3–6.6 (m, 1 H), 7.35 (s, 5 H), 8.16 (s, 1 H).

More polar isomer: NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.70 (s, 3 H), 2.87 (d, 2 H, J = 8.0 Hz), 3.2–4.4 (m, 3 H), 4.50 (s, 1 H), 4.79 (d, 2 H, J = 1 Hz, CH_2CCl_3),[9] 5.48 (d, 1 H, J = 4.0 Hz), 5.6–6.0 (m, 1 H), 6.3–6.8 (m, 1 H), 7.23 (s, 5 H), 8.00 (s, 1 H).

Synthesis of 6 (R_1 = CH_2CCl_3; R_2 = PhNH). In the same manner as described above, the amide was isolated as an oil (56%) after chromatography on silicic acid using 20:1 CH_2Cl_2–ether (v/v) as an eluent: IR ($CHCl_3$) 3405, 3305, 1775 (sh), 1755, 1685, and 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.75 (s, 3 H), 2.90 (d, 2 H, J = 8.0 Hz), 3.8–4.4 (m, 1 H), 4.54 (s, 1 H), 4.70 (d, 1 H, J = 12.0 Hz), 4.90 (d, 1 H, J = 12.0 Hz), 5.60 (d, 1 H, J = 4.0 Hz), 6.9–7.7 (m, 5 H), 8.32 (s, 1 H).

Deblocking of Benzyl Esters. An ester **6** (R_1 = CH_2Ph) (0.20 mmol) was dissolved in 10 mL of ethyl acetate. Palladium on carbon

(10%), 0.5 g, was added and the mixture hydrogenated at 20 °C for 1 h. After filtration, the solution was evaporated to 2 mL, and a solution of potassium 2-ethylhexanoate (0.10 g in 2 mL of ethyl acetate) was added if the free acid did not precipitate. Cooling usually gave a white solid in 40–50% yield. If an oil was obtained, the solution was concentrated and petroleum ether was added. In the case of **6** [R_1 = CH_2Ph; R_2 = CH(Ph)NH-*tert*-Boc] the solution was evaporated after filtration and the oil obtained dissolved in trifluoroacetic acid. The solution was freeze-dried, glacial acetic acid was added, and the solution freeze-dried again. The free acids and salts all had infrared frequencies at 1770–1780 cm^{-1} (β-lactam) and NMR spectra identical to the blocked ester minus a benzyl group.

Deblocking of Trichloroethyl Esters. The ester (100–200 mg) was dissolved in 10 mL of 90% HOAc (1–2 mL of DMF was added if the ester did not dissolve) and the solution cooled to 0 °C before 1–1.5 g of zinc dust was added. The mixture was stirred at 0 °C for 3–5 h. Removal of the zinc by filtration through Celite into a flask containing 100 mL of ice water and washing of the zinc with methylene chloride yielded a two-phase system. Separation of the organic layer, extraction of the cold aqueous layer with several methylene chloride–zinc washings, drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat) afforded the free acid.

Benzyl 6-*tert*-Butoxycarbonylaminomethylpenicillanate (8) (R_1 = CH_2Ph; R_3 = CO_2-*tert*-Bu). Acid **6** (R_1 = CH_2Ph; R_2 = OH) (1.80 g, 5.16 mmol in 120 mL of THF was cooled to −30 °C. Triethylamine (0.73 mL, 1 equiv) was added followed by ethyl chloroformate (0.49 mL, 1 equiv). The mixture was stirred at −30 °C for 90 min. Sodium azide (335 mg, 5.16 mmol) in 50 mL of water was added and the solution stirred at 0 °C for 30 min. The solution was diluted with methylene chloride, washed with water and saturated salt solution, dried, and evaporated to give an oil. The oil was dissolved in 50 mL of benzene and refluxed for 90 min. *tert*-Butyl alcohol (50 mL) was added and refluxing continued for 2 h. The solvents were evaporated and the residue was chromatographed on silica gel with methylene chloride–ethyl ether (10:1). Elution with ether gave a yellow oil, 0.87 g (40%): IR (film) 3400, 3000, 1750, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.37, 1.42, 1.52 (s, 15 H), 2.5–2.9 (m, 2 H), 4.1–4.5 (m, 1 H), 4.63 (s, 1 H), 5.18 (s, 2 H), 5.30 (d, J = 5 Hz, 1 H), 7.35 (s, 5 H).

Anal. Calcd for $C_{21}H_{28}O_5N_2S$: C, 59.97; H, 6.71; N, 6.66; S, 7.62. Found: C, 59.37; H, 6.71; N, 6.43; S, 7.35.

Benzyl 6-Aminomethylpenicillanate 8 (R_1 = CH_2Ph; R_3 = $H_2{}^+CF_3CO_2{}^-$). Compound **8** (R_1 = CH_2Ph; R_3 = CO_2-*tert*-Bu) (200 mg, 0.48 mmol) was dissolved in 10 mL of trifluoracetic acid and stirred for 30 min at 0 °C. The solution was freeze-dried from benzene to give a quantitative yield of salt: IR (film) 3000, 1775–1700 (br) cm^{-1}; NMR (Me_2SO-d_6) δ 1.15, 1.55 (s, 6 H), 2.75–3.0 (m, 2 H), 3.8–4.05 (m, 1 H), 4.3 (s, 1 H), 5.10 (s, 2 H), 5.20 (d, J = 5 Hz, 1 H), 7.25 (s, 5 H).

Benzyl 6β-(*N*-Phenylacetyl)aminomethylpenicillanate 8 (R_1 = CH_2Ph; R_3 = $COCH_2Ph$). Triethylamine (138 mg, 2 equiv) in 5 mL of CH_2Cl_2 was dropped into phenylacetyl chloride (159 mg, 1.5 equiv) in 5 mL of CH_2Cl_2 at 0 °C. Compound **8** (R_1 = CH_2Ph; R_2 = $H_2{}^+CF_3CO_2{}^-$) (300 mg, 0.69 mmol) in 5 mL of CH_2Cl_2 was dropped into the cold mixture and stirring was continued for 3 h at 0 °C. The solution was washed with saturated bicarbonate and water, dried, and evaporated. The oil obtained was chromatographed on silica gel with methylene chloride–ether (1:1) to give an oil which can be crystallized from ethyl acetate–ether–petroleum ether: 60 mg (20%); mp 128–130 °C; IR (film) 3280, 1745, 1710, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.50 (s, 3 H), 2.68 (dd, J_1 = 6 Hz, J_2 = 10 Hz), 3.50 (s, 2 H), 4.40 (m, 1 H), 4.52 (s, 1 H), 5.10 (s, 2 H), 5.20 (d, 1 H, J = 5 Hz). 6.61 (d, J = 6 H), 7.20 and 7.26 (s, 10 H).

Anal. Calcd for $C_{24}H_{26}O_4N_2S$ (438.53): C, 65.74; H, 5.98; N, 6.39; S, 7.31. Found: C, 65.25; H, 5.98; N, 6.36; S, 7.30.

Benzyl 6-Ethoxycarbonylaminomethylpenicillante 8 (R_1 = CH_2Ph; R_3 = $COCH_2CH_3$). Compound **8** (R_1 = CH_2Ph; R_3 = $H_2{}^+CF_3CO_2{}^-$) (0.77 g, 1.77 mmol) was coupled with PhCH(NH-*tert*-Boc)COOH using the mixed anhydride method. Chromatography on silica gel with CH_2Cl_2/ether (5:1) gave 0,41 g (35%) of compound **8** (R_1 = CH_2Ph; R_3 = $CO_2CH_2CH_3$) instead of the expected product; IR (film) 3300, 2960, 1750–1680 cm^{-1}; NMR ($CDCl_3$) 1.25 (t, 3 H), 1.35, 1.50 (s, 6 H), 2.5–2.9 (m, 2 H), 4.10 (q, 2 H), 4.35–4.60 (s on m, 2 H), 5.15 (s, 2 H), 5.35 (d, J = H Hz, 1 H), 6.15 (J = 8 Hz, 1 H), 7.30 (s, 5 H).

Compound 8 [R_1 = CH_2Ph; R_3 = $COCH(NHCO_2CH_2Ph)Ph$]. Compound **8** (R_1 = CH_2Ph; R_3 = $H_2{}^+CF_3CO_2{}^-$) (0.38 g, 0.87 mmol) in 10 mL of THF, *p*-nitrophenyl *N*-carbobenzoxyphenylglycinate (0.32 g, 1 equiv) and triethylamine (0.25 mL, 2 equiv) were stirred at 25 °C for 2.5 h. The solvent was evaporated and the oil obtained was chromatographed on silica gel with methylene chloride–ether (2:1). A foam was obtained which was rechromatographed with methylene chloride–ether (5:1) to give a white foam, 43%: IR (film) 3280, 1740–1675 (br) cm^{-1}; NMR ($CDCl_3$) 1.25, 1.40 (s, 6 H), 2.3–2.7 (dd, 2 H, J_1 = 8 Hz, J_2 = 6 Hz), 4.0–4.4 (m, 1 H), 4.45 (s, 1 H), 4.9 (s, 2 H), 4.95 (s, 2 H), 5.10–5.20 (s on d, J = 6 Hz, 2 H), 6.10 (d, J = 8 Hz, 2 H), 7.1 (s, 15 H).

Benzyl 6-Tosylamidomethylpenicillanate 8 (R_1 = CH_2Ph; R_2 = SO_2PhCH_3). To compound **8** (R_1 = CH_2Ph; R = $H_2{}^+CF_3CO_2{}^-$) (0.22 g, 0.51 mmol) in 5 mL of CH_2Cl_2 was added tosyl chloride (0.10 g, 0.51 mmol) in 5 mL of CH_2Cl_2 and triethylamine (0.14 mL, 2 equiv). The solution was stirred at 25 °C for 16 h, washed with saturated bicarbonate and water, and evaporated. The residue was chromatographed on silica gel with methylene chloride–ether (5:1). Elution with ether gave a white foam, 65 mg (27%): IR (film) 3250, 2975, 1750, 1700, 1600 cm^{-1}; NMR ($CDCl_3$) 1.38, 1.50 (s, 6 H), 2.45–2.73 (s on m, 5 H), 3.7–4.2 (m, 1 H), 4.56 (s, 1 H), 5 15 (s, 2 H), 5.38 (d, J = 6 Hz, 1 H), 6.25 (d, J = 8 Hz, 1 H), 7.2–7.8 (m, 9 H).

Synthesis of 9. Compound **8** (R_1 = H; R_3 = $H_2{}^+CF_3CO_2{}^-$) (0.141 g, 0.40 mmol) was dissolved in 10 mL of ethanol. Triethylamine was added to pH ~8.5, followed by *o*-hydroxybenzaldehyde (0.49 g, 10 equiv). The solution was stirred at 25 °C for 45 h, acidified with dilute HCl to pH ~6.5, and evaporated. After addition of ether, the mixture was filtered and evaporated. The yellow oil was dissolved in CH_2Cl_2 and 1.6 equiv of potassium 2-ethylhexanoate was added. Addition of petroleum ether gave a yellow solid, 110 mg, 72%: IR (nujol) 3350, 1775, 1700 (br), 1765 cm^{-1}; NMR (acetone-d_6) δ 1.40 (s, 6 H), 2.7–3.0 (m, 2 H), 3.8–4.2 (s on m, 2 H), 5.55 (d, J = 6 Hz, 1 H), 6.8–7.4 (m, 4 H), 8.5 (s, 1 H).

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Registry No.—**1** (R_1 = CH_2CCl_3), 51056-24-7; **2** (R_1 = CH_2CCl_3), 63784-21-4; *anti*-**3** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph), 63784-22-5; *syn*-**3** (C_1 = CH_2CCl_3; R_2 = OCH_2Ph), 63784-23-6; *anti*-**3** (R_1 = CH_2CCl_3; R_2 = CH(Ph)NH-*tert*-Boc), 63784-24-7; *syn*-**3** (R_1 = CH_2Ph; (R_2 = O-*tert*-Bu), 63784-25-8; *anti*-**3** (R_1 = CH_2Ph; R_2 = O-*tert*-Bu), 63784-26-9; *syn*-**3** (R_1 = CH_2 Ph; R_2 = CH(Ph)NH-*tert*-Boc, 63784-27-0; *anti*-**3** (R_1 = CH_2Ph; R_2 = CH(Ph)NH-*tert*-Boc, 63784-28-1; **4**, 63797-55-7; **5** (R_1 = CH_2Ph), 39486-17-4; **6** (R_1 = CH_2Ph; R_2 = O-*tert*-Bu), 63784-29-2; **6** (R_1 = CH_2CCl_3; R_2 = OCH_2Ph), 63200-60-2; **6** (R_1 = CH_2CCl_3; R_2 = CH(Ph)NH-*tert*-Boc, 63784-30-5; **6** (R_1 = CH_2CCl; R_2 = OH), 63784-31-6; **6** (R = CH_2Ph; R_2 = OH), 63784-32-7; **6** (R_1 = CH_2Ph; R_2 = $NHCH_2Ph$), 63784-33-8; **6** (R = $CH_2Ph_1R_2$ = $NHCH(CO_2CHPh_2)Ph$), 63784-34-9; **6** (R_1 = CH_2CCl_3; R_2 = $OCH_2C_4H_3$), 63784-35-0; **6** (R_1 = CH_2CCl_3; R_2 = *O*-naphthyl, 63784-36-1; **6** (R_1 = CH_2CCl_3; R_2 = PhCH(CH_2NHCHO)O) isomer 1, 63784-37-2; **6** (R_1 = CH_2CCl_3; R_2 = PhCH(CH_2NHCHO)O) isomer 2, 63784-38-3; **6** (R_1 = CH_2CCl_3; R_2 = PhNH), 63784-39-4; **8** (R_1 = CH_2Ph; R_3 = CO_2-*tert*-Bu), 63784-40-7; **8** (R_1 = CH_2Ph; R_3 = $H_2{}^+CF_3CO_2{}^-$), 63784-42-9; **8** (R_1 = CH_2Ph; R_3 = $COCH_2Ph$), 63784-43-0; **8** (R_1 = CH_2Ph; R_3 = $CO_2CH_2CH_3$), 63784-44-1; **8** [R_1 = CH_2Ph; R_3 = $COCH(NHCO_2CH_2Ph)Ph$], 63797-57-9; **8** (R_1 = CH_2Ph; R_3 = SO_2PhCH_3), 63784-45-2; **9**, 63784-46-3; Ph_3P=$CHCO_2CH_2Ph$, 15097-38-8; Ph_3P=CHCOCH(Ph)NH-*tert*-Boc, 63784-47-4; Ph_3P=CHCO2Bu^t, 35000-38-5; PhCH(CH_2NHCHO)-OH, 58644-57-8; PhCH(NH-*tert*-Boc)COOH, 3601,66-9; benzylamine, 100-46-9; benzhydrylphenylglycinate tosylate salt, 63784-48-5; 2-thiophenemethanol, 636-72-6; 2-naphthol, 135-19-3; phenylamine, 62-53-3; *tert*-butyl alcohol, 75-65-0; phenylacetyl chloride, 103-80-0; *p*-nitrophenyl-*N*-carbobenzoxyphenyglycinate, 63784-49-6; tosyl chloride, 98-59-9; *o*-hydroxybenzaldehyde, 90-02-8.

References and Notes

(1) J. C. Sheehan and Y. S. Lo, *J. Org. Chem.*, **38**, 3227 (1973), and references cited therein.
(2) J. C. Sheehan, Y. S. Lo, J. Löliger, and C. C. Podewell, *J. Org. Chem.*, **39**, 1444 (1974), and references cited therein.
(3) H. J. Bestmann, H. Buckschewski, and H. Leube, *Chem. Ber.*, **92**, 1345 (1959).
(4) Compound **2** (R_1 = CH_2Ph) has been synthesized by an alternative method; see: Y. S. Lo and J. C. Sheehan, *J. Am. Chem. Soc.*, **94**, 8253 (1972).
(5) J. C. Sheehan and Y. S. Lo, *J. Org. Chem.*, **40**, 191 (1975).
(6) K. D. Barrow and T. M. Spotswood, *Tetrahedron Lett.*, 3329 (1965).
(7) H. J. Bestmann and B. Arnason, *Ber.*, **95**, 1513 (1962).
(8) M. Miyano and M. A. Stealey, *J. Org. Chem.*, **40**, 2840 (1975).
(9) These lines are probably the inner lines of a CH_2CCl_3 AB system. However, the outer lines were not observed in the spectrum because they are very weak and are masked by neighboring absorptions.