Addition of tris(dipivalomethanate)europium(III) resulted in chemical shifts which revealed the characteristic coupling pattern for the γ-pyrone protons: α-H, d, J = 5.8 Hz; β-H, d, J = 2.4 Hz; and β-H, dd, J = 5.8 and 2.4 Hz.

Anal. Calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95; O, 31.34; mol wt, 204.0422. Found: C, 64.69; H, 3.98; O, 31.44; mol wt, 204.0411 (mass spectrum).

Formation of LL-Z1220 from 3 by Valence Isomerization. Rearrangement product 3 (100 mg) was dissolved in 5 ml of ethyl acetate and heated at reflux for 60 min. The reformed antibiotic 1 (11 mg) crystallized from the solution on cooling. These crystals had nmr, ir, and uv spectra identical with those of the original antibiotic but were optically inactive. The material that remained in solution was shown to be 3 by tlc. Layers developed with ethyl acetate gave the antibiotic, R_f 0.08, and the rearrangement product, R_f 0.27.

Periodate Oxidation Reaction of LL-Z1220. LL-Z1220 (75 mg) was added to 25 ml of H_2O containing 0.75 ml of 18 N H_2SO_4. The mixture was stirred for ~20 min to effect solution and 50 ml of 0.02 M sodium metaperiodate was added. The resulting solution started turning yellow almost immediately. Aliquots (5 ml) were removed from the reaction at intervals, mixed with 40 ml of 1% potassium iodide, and immediately titrated with 0.100 N sodium thiosulfate. A rapid uptake of 0.82 mol of periodate/mol of LL-Z1220 was observed. Tlc studies showed that the major product from the periodate reaction remained the same from several minutes to 3⅓ hr reaction time.

The remaining reaction mixture (45 ml), after 3⅓ hr of reaction time, was passed through a 1.2 × 24 cm column of Amberlite XAD-2. The column was washed with 50 ml of water and eluted with 20 ml of methanol. The eluate was evaporated to 15 mg of semicrystalline residue 4, which was sublimed at 90–120° (0.05 mm) to obtain 2.5 mg of colorless sublimate: mp 133–137°; uv max 210 nm (ε 16,200), 277 (12,300); mass spectrum (70 eV) m/e (rel intensity) 162 (100), 134 (33), 105 (9), 95 (29), 92 (60); ir (KBr) 1658 cm^{-1} (C=O). The nmr spectrum (CD_3OD) showed protons characteristic of the pyrone ring at δ 8.11 (1 H, d, J = 5.8 Hz), 6.67 (1 H, d, J = 2.5 Hz), 6.42 (1 H, dd, J = 5.8, 2.5 Hz), and three 1-H multiplets for the furan at 8.23, 7.69, and 6.91.

Anal. Calcd for $C_9H_6O_3$: mol wt, 162.0316. Found: mol wt, 162.0309 (mass spectrum).

Reaction of LL-Z1220 with Methanolic HCl. An anhydrous methanolic HCl solution was prepared by adding 1.5 ml of acetyl chloride to 25 ml of methanol cooled in a Dry Ice bath. The solution was allowed to warm to room temperature, 100 mg of LL-Z1220 was added, and the resulting solution was heated at reflux for 5 min. The reaction mixture was evaporated to a residue, which was purified by preparative tlc on Analtech silica gel CG, 2 mm, layers. After the layers were developed with acetone, the major zone was detected at R_f 0.5 by uv quenching. Sections of the layers containing the zones were removed and eluted with acetone. The extracted product was then rechromatographed on the same type of layer developed with 95% ethanol. From the major zone (R_f 0.7) was obtained 42 mg of clear, slightly yellow oil 5: uv max 264 nm (ε 16,000); mass spectrum (70 eV) m/e (rel intensity) 272 (6), 254 (6), 242 (5), 237 (8), 225 (8), 213 (37), 207 (41), 177 (100), 163 (28); ir (KBr) 1658 cm^{-1} (C=O). The nmr spectrum (acetone-d_6) had peaks for a γ-pyrone at δ 8.07 (1 H, d, J = 5.8 Hz), 6.66 (1 H, d, J = 2.5 Hz), and 6.29 (1 H, dd, J = 2.5, 5.8 Hz), an olefinic proton at δ 6.43 (d, J = 2.3 Hz), protons on sp^3 carbons bearing O or Cl at δ 4.80 (1 H, dd, J = 8.0 and 3.1 Hz) and 4.5–3.9 (3H, m), and an OMe singlet at δ 3.55.

Anal. Calcd for $C_{12}H_{13}O_5Cl$: mol wt, 272.04515. Found: mol wt, 272.04487 (mass spectrum).

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Registry No. 1, 36431-52-4; 2, 36162-59-1; 3, 49664-64-4; 4, 36162-60-4; 5, 36153-69-2.

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Total Synthesis of β-Lactam Antibiotics. IV. Epimerization of 6(7)-Aminopenicillins and -cephalosporins from α to β[1]

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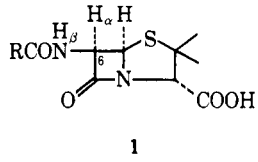
6α-Aminopenicillins and 7α-aminocephalosporins can be epimerized largely to their β epimers by treatment of their *p*-nitrobenzaldehyde Schiff bases with phenyllithium followed by protonation under kinetically controlled conditions. This reaction enables the completion of new total syntheses of both penicillins and cephalosporins.

The most direct total syntheses of penicillins 1 and cephalosporins 2 utilize the cycloaddition of a masked glycine moiety to a thiazoline[2] or thiazine[1] for the construction of the azetidinone ring. A major drawback, however, is that the newly created stereochemistry of the lactam hydrogen atoms is trans instead of cis, as it is in the natural substances. The trans epimers are biologically inactive.[3-5] Since the thermodynamically more stable forms are trans, probably because 6(7) substituents are more crowded in the β configuration than in the α, they cannot be epimerized from trans to cis by simple equilibration, *e.g.*, through the enolate anion, beyond the equilibrium amount, which ranges from 0 to 47% cis for various derivatives.[6]



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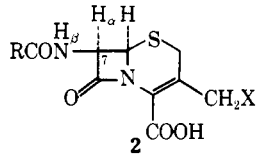

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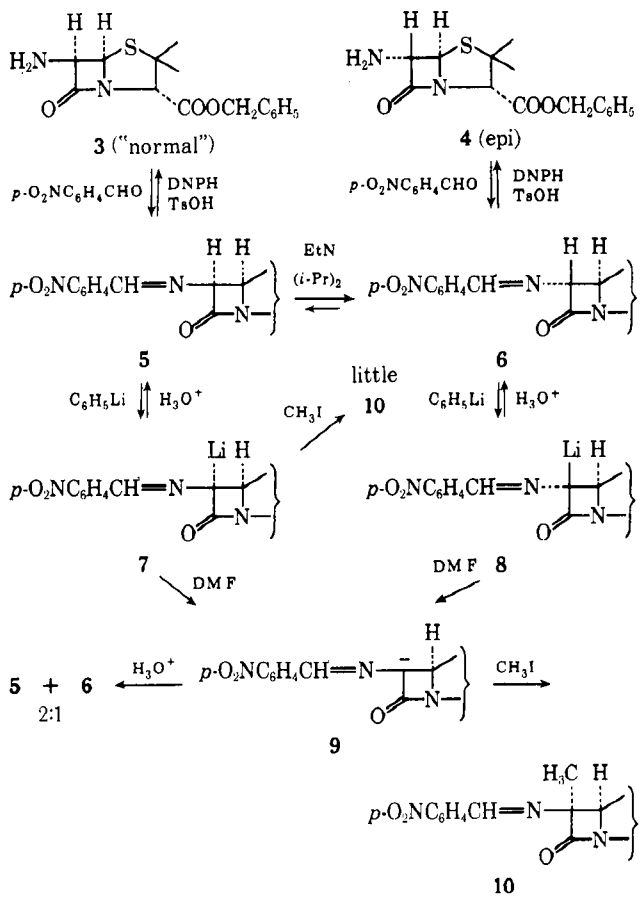
Although equilibration of isomers by means of a reversible reaction goes inevitably to the thermodynamically more stable isomer, it is possible to proceed in the opposite direction through kinetic control. The method used in the present problem was to create an anion at the 6(7) position and then protonate in a subsequent irreversible step. Since the least hindered side of the molecule is α, the proton tends to be added from this side, affording an amount of β-oriented substituent in excess of the thermodynamic proportion. Steric approach control is already well established for the irreversible addition of bulkier groups to intermediates with planar C-6(7),[5,7-9] and even the relatively small steric requirement for proton transfer gives rise to a definite contrathermodynamic effect.

The epimerization of a penicillin in both directions is illustrated in Scheme I.

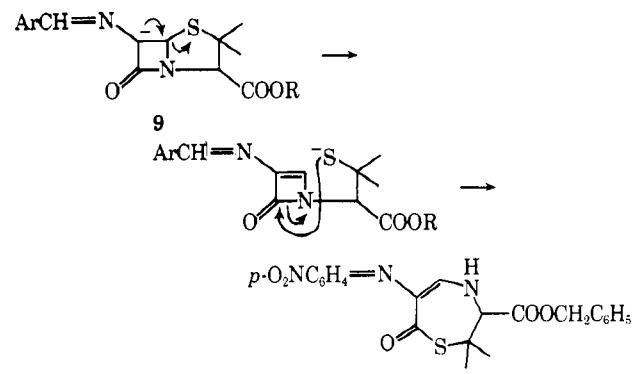
Scheme I



The C-6 proton of 6-APA benzyl ester 3 is rendered more acidic by formation of the *p*-nitrobenzaldehyde Schiff base 5. Weak bases such as diisopropylethylamine produce a moderate blue color, presumably the anion in low concentration, which rapidly changes to a pale blue-green as epimerization to the more stable 6 proceeds. Since this reaction is reversible it can be used to convert "normal" 5 into "epi" 6 but not 6 into 5. For the latter transformation a kinetically controlled procedure was found.

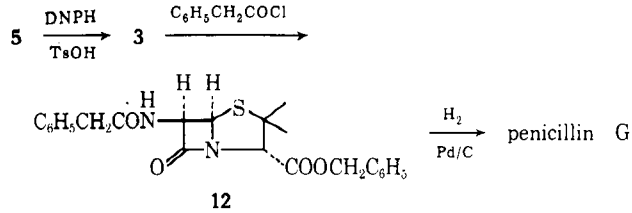
Pure 5 with phenyllithium at −78° gives the intensely blue 7, and pure 6 (*vide infra*) similarly affords 8. The lithium atoms in 7 and 8 must be either covalently bound or else present in a tight ion pair which maintains configuration, because 5 and 6, respectively, are regenerated upon acidification; also, 7 is very sluggish toward methyl iodide. However, when DMF is added at −78° to either 7 or 8, the free anion 9 is formed, in which configurational memory has now been lost, because it gives the same products whether it was made from 5 or 6. Methyl iodide reacts readily[5] at about −20°, approaching from the less hindered α direction to give the 6α-methyl derivative 10, and even the solvated proton approaches principally from the α direction, producing a mixture of 5 and 6 in approximately 2:1 ratio. This is far richer in the thermodynamically less stable 5 than the equilibrium amount (<15%), but, since the protonation of 9 is conducted under irreversible conditions, by adding THF-H_2O-excess AcOH, the kinetically determined raio prevails. By this method, 6-epipenicillins and 7-epicephalosporins can be largely inverted to the normal configuration.

An important side reaction of 9 is rearrangement to the thiazepine 11, a previously known reaction.[10] That 9 is



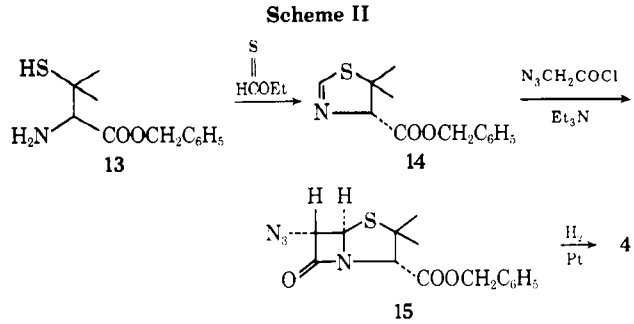
really the intermediate in this rearrangement[11] is shown by the fact that 10, which can form no anion at C-6, is stable to thiazepine formation. Because of this reaction, pure 6 had to be prepared in an indirect way. Epimerization of 5 with diisopropylethylamine for *ca.* 2 half-lives produced mostly 6 with a little 11. The mixture of principally 5 and 6 was converted to 3 and 4, from which pure 4 was obtained by crystallization. Treatment with *p*-nitrobenzaldehyde then provided pure epi Schiff base 6.

Deblocking and functionalization of normal Schiff base 5 *via* the sequence 5 → 3 → 12 → penicillin G were done by established procedures.[5] Thus, completion of a new



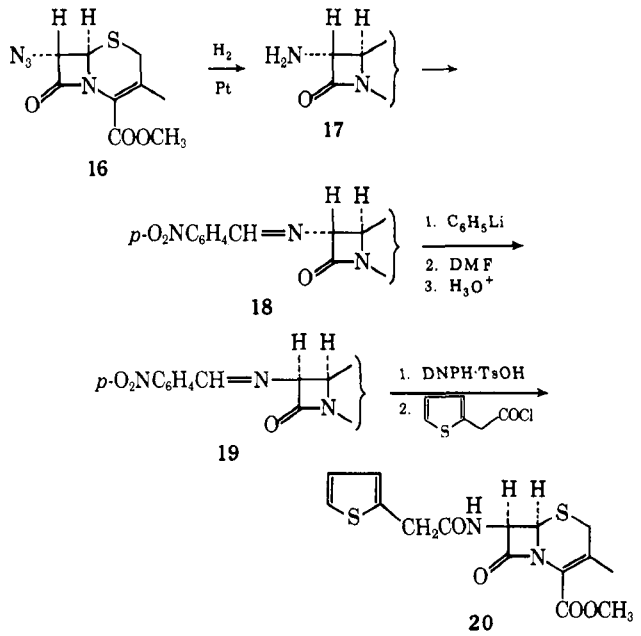
total synthesis of penicillins required only a link between 4 and the total synthesis of epipenicillins of Bose and coworkers.[2] This was done according to Scheme II.

Scheme II



D-Penicillamine[12a] benzyl ester 13 was converted to the thiazoline 14 with ethyl thionoformate in 72% yield, an improvement over the original sequence[2] of N-formylation and BF_3-catalyzed cyclization. Cycloaddition of azidoacetyl chloride and reduction of the azide 15 produced 4,[12b] providing the link which completes the total synthesis.

Scheme III



The new Ratcliffe–Christensen total synthesis[1] opens up an efficient route to cephalosporins bearing a 7α-amino group, which can be converted to the natural configuration by means of the present epimerization procedure. An example is depicted in Scheme III.

Reduction of 7α-azido-3-methyl-4-carbomethoxy-3-cephem (**16**)[1] produced the 7α-amino compound **17**, which was converted to the *p*-nitrobenzaldehyde Schiff base **18**. Successive treatment in THF at −78° with phenyllithium, DMF, and THF–H_2O–AcOH provided the 7β epimer **19** plus **18**, in 2:1 ratio. Deblocking, thienylacetylation, and chromatographic separation afforded pure, totally synthetic 7β-[2-(2-thienyl)acetamido]-3-methyl-4-carbomethoxy-3-cephem (**20**). The total syntheses of cephalothin, 7α-methoxycephalothin, and cefoxitin are described elsewhere.[1]

A final point of interest is the attempted deuteration of Schiff base **5**. When the lithium derivatives **7** or **9** were treated with THF–D_2O–CD_3CO_2D, little or no deuterium was introduced into the product **5**.[13] Tightening all experimental controls was without effect, as was substitution of deuterated THF for protiated. The work-up procedure was shown to be not responsible. There appears to be an unusually high isotope effect, but judgment must be reserved for the time being, and the phenomenon is presently under investigation.

Experimental Section

Benzyl 6β-(*p*-Nitrobenzylideneamino)penicillanate (5). A mixture of 2.957 g (0.00963 mol) of 6-APA benzyl ester **3**, 1.453 g (0.00963 mol) of *p*-nitrobenzaldehyde, and 100 ml of benzene was refluxed for 2 hr under a water separator. After evaporation of the benzene the crude Schiff base crystallized, and was recrystallized from benzene–cyclohexane, mp 90–92°. *Anal.* Calcd for $C_{22}H_{21}N_3SO_5$: C, 60.13; H, 4.79; N, 9.57; S, 7.29. Found: C, 59.96; H, 4.70; N, 9.46; S, 7.46. Ir ($CHCl_3$) 5.62 (β-lactam), 5.72 (ester), 6.09 μ (C=N); nmr ($CDCl_3$) δ 4.44 (s, 3-H), 5.24 (q, *J* = 4, 2 Hz, 6-H), 5.69 (d, *J* = 4 Hz, 5-H), 8.75 (d, *J* = 2 Hz, CH=N).

Conversion of 5 back to 3. Schiff base **5**, 110 mg (0.00025 mol), in 0.5 ml of $CHCl_3$ was added to a mixture of 49.6 mg (0.00025 mol) of pulverized 2,4-dinitrophenylhydrazine (DNPH) and 49.0 mg (0.00025 mol) of *p*-toluenesulfonic acid monohydrate in 4 ml of ethanol, which had been previously stirred for 45 min. After another 45 min of stirring, the mixture was filtered and the precipitate was washed with ethanol. The filtrate was evaporated and washed with ether. The resulting pale yellow crystalline substance was dissolved in water containing K_2HPO_4 (pH 8) and extracted three times with ether. The ether was dried with $MgSO_4$, filtered, and evaporated, leaving 69 mg of **3** (90% yield).

Epimerization of 5 to 6. To 50 ml of dry DMF and 2.0 ml of diisopropylethylamine at −18° was added 1.100 g (0.00250 mol) **5**, and the solution was stirred for 18 min at −18°. The color, initially deep blue, changed to pale blue-green at the end. Benzene (250 ml) was added, and the solution was washed six times with water. Wash 2 had pH 2 phosphate added, and 5 had pH 8 phosphate. The benzene layer was dried with $MgSO_4$, filtered, and evaporated, leaving 1.145 g of **6** plus **5**, in 3:1 ratio by nmr.

Pure Benzyl 6α-Aminopenicillanate (4). The mixture of **5** and **6** was treated with DNPH–TsOH as above, affording 720 mg of mixed **3** and **4**, from which **4** crystallized. After four recrystallizations from benzene–cyclohexane, 110 mg of pure **4** was obtained, mp 120–122°. *Anal.* Calcd for $C_{15}H_{18}N_2SO_3$: C, 58.82; H, 5.88; N, 9.15; S, 10.45. Found: C, 58.53; H, 5.79; N, 8.92; S, 10.47. Nmr ($CDCl_3$) δ 1.39 (s), 1.55 (s) (*gem*-dimethyl), 2.09 (NH_2), 4.23 (d, *J* = 1.5 Hz, 6-H), 5.11 (d, *J* = 1.5 Hz, 5-H), 4.50 (s, 3-H), 5.22 (s, OCH_2), 7.40 (s, C_6H_5).

Benzyl 6α-(*p*-Nitrobenzylideneamino)penicillanate (6). This was prepared from **4** in the same manner as **5** from **3**: nmr ($CDCl_3$) δ 4.52 (s, 3-H), 4.90 (t, *J* = 1.5, 1.5 Hz, 6-H), 5.46 (d, *J* = 1.5, 5-H), 8.51 (d, *J* = 1.5 Hz, CH=N).

Lithiation of 5 and Reacidification. Schiff base **5** (110 mg, 0.00025 mol) in 2.5 ml of THF at −78° under N_2 was treated with 0.108 ml (0.00025 mol) of 2.3 *M* phenyllithium, forming an intense blue solution. Addition of 2 ml of THF containing 1.1 equiv of AcOH (16.5 λ) and 5 equiv of H_2O (22.5 λ) caused fading of the color to pale red. The mixture was evaporated, taken up in benzene, and washed with aqueous pH 2 phosphate, water, and aqueous K_2HPO_4. After drying with $MgSO_4$, filtration, and evaporation, 125 mg of oil was obtained, which by nmr was **5** containing traces of epi Schiff base **6** and thiazepine **11**.

Lithiation of 6 and Reacidification. A sample of 3:1 **6**:**5**, prepared by direct epimerization of **5**, was treated with phenyllithium and then quenched, exactly as in the previous example. The product, 129 mg, was 3:1 **6**:**5** by nmr. The same result was obtained when the quench was done at 0° instead of −78°.

Methylation of Epi Schiff Base 6 to 10. Pure **6**, 301 mg (0.00069 mol), in 11 ml of THF at −78° under N_2 was treated with 0.302 ml (0.00069 mol) of 2.3 *M* phenyllithium, forming an intense blue solution, to which a mixture of 13.7 ml of DMF and 0.55 ml of CH_3I was added dropwise. After 10 min of stirring at −78°, the reaction mixture was allowed to come to room temperature and stirred for 15 min. The final color was pale blue-green. Then a mixture of 2.8 ml of THF, 0.3 ml of AcOH, and 0.3 ml of H_2O was added, followed by *ca.* 50 ml of benzene. The solution was washed six times with water, with pH 2 phosphate added to wash 2, and pH 8 phosphate in 5, dried with $MgSO_4$, filtered, and evaporated, leaving 420 mg of oil whose nmr showed it to be the 6α-methyl derivative **10**, identical with known material.[5] As further proof that the methyl group was α, **10** was deblocked to the free amine and phenylacetylated as described before, affording intermediates that were identical with those previously obtained[5] in nmr, ir, and (where crystalline) melting point and mixture melting point.

Epimerization of 6 to 5. A sample of 3:1 **6**:**5** (110 mg) was lithiated as before in 4 ml of THF. DMF (5 ml) was added and the quench was then performed as before at either −78 or −10°. The mixture was diluted with benzene, washed six times in the manner described above, dried, filtered, and evaporated, affording 130 mg of oil which was 2:1 **5**:**6** by nmr. The same product mixture was obtained when the starting material was pure **5**.

Rearrangement of 5 to Thiazepine 11. Schiff base **5** (110 mg) was treated overnight with 1 equiv of triethylamine in 3 ml of THF under N_2. The color became deep orange. The solvent was evaporated and the product was purified by plc on silica gel with 25:1 $CHCl_3$–EtOAc, affording 44 mg of oil whose ir spectrum was the same as that of the crude product (film): 3.0 (NH), 5.73 (C=O), 6.13 μ (C=N); nmr ($CDCl_3$) δ 9.40 (CH=N). Spectral properties corresponded to those of previously reported examples. In 0.6 ml of acetonitrile, rearrangement of 20 mg of **5**, using 10 mg of diisopropylethylamine as catalyst, was substantially over within 10 min by tlc. Under the same (latter) conditions, 6α-methyl Schiff base **10** was recovered unchanged after 24 hr.

Phenylacetylation of 3 to 12. Compound **3**, 100 mg (0.00033 mol), in 2 ml of CH_2Cl_2 with 0.1 ml of pyridine, was treated with 0.0505 g (0.00033 mol) of phenylacetyl chloride in 1 ml of CH_2Cl_2. After 2 min, benzene was added and the solution was washed with aqueous pH 2 phosphate, water, and aqueous K_2HPO_4. After drying with $MgSO_4$, filtration, and evaporation, 150 mg of

oil was obtained (108% weight yield) which was **12**[14] by ir and nmr.

Hydrogenation of 12 to Penicillin G. Compound **12** (96 mg) was hydrogenated at 40 psi for 1 hr in 4 ml of MeOH containing 1 ml of water, 19 mg of $NaHCO_3$, and 100 mg of 10% Pd/C (Bolhofer). The mixture was filtered and lyophilized, leaving 75 mg (93%) of sodium penicillin G by nmr.

D-Penicillamine Benzyl Ester Hydrochloride (13 HCl).[15] A solution of 25.9 g of D-penicillamine, 65 g of polyphosphoric acid, and 325 ml of benzyl alcohol was heated in a 110° oil bath for 6 hr, cooled, and added to 2.5 l. of 0.6 *N* HCl. The solution was extracted twice with 1250 ml of ether and the ether was reextracted twice with 500 ml of 1 *N* HCl. The combined aqueous layers were brought to pH 9.6 with Na_2CO_3 and extracted with 5 × 750 ml of ether. The ether solution was dried with $MgSO_4$, filtered, and evaporated to give 40.8 g of oil (crude **13**), which was taken back into 500 ml of ether and saturated with HCl gas at 0°. The white precipitate of 13 HCl was filtered, washed with ether, and dried; yield 20.6 g (43%); ir (Nujol) 5.72 μ; nmr ($CDCl_3$) δ 1.53 (s), 1.66 (s, *gem*-dimethyl), 2.98 (SH), 4.30 (s, CH), 5.31 (s, OCH_2), 7.41 (s, C_6H_5), 9.0 (NH_3^+). *Anal.* Calcd for $C_{12}H_{18}ClNO_2S$: C, 52.26; H, 6.58; N, 5.08; S, 11.62. Found: C, 52.29; H, 6.36; N, 4.97; S, 12.39.

4-Carbobenzyloxy-5,5-dimethyl-2-thiazoline (14). To a solution of 13.8 g of 13 HCl in CH_2Cl_2 was added 7.0 ml of triethylamine at 0°, and then, over 45 min at 25°, 5.5 ml of ethyl thionoformate[16] in 50 ml of CH_2Cl_2. The mixture was stirred for 30 min more at 25°, washed with 3 × 100 ml of water, dried with $MgSO_4$, evaporated to 13.7 g of oil, and chromatographed on 450 ml of silica gel (E. Merck) with $CHCl_3$, providing 8.9 g of **14**: ir (film) 5.70, 5.8 μ (sh); nmr ($CDCl_3$) δ 1.27 (s), 1.67 (s, *gem*-dimethyl), 4.62 (d, J = 2.5 Hz, CHCOOR), 5.23 (s, OCH_2), 7.39 (s, C_6H_5), 8.10 (d, J = 2.5 Hz, CH=N); mass spectrum m/e 249. *Anal.* Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62; S, 12.86. Found: C, 62.69; H, 5.95; N, 5.24; S, 12.88. **14** had mp (from cyclohexane) 62–63°.

7α-Azido-3α-carbobenzyloxypenam 15. To thiazoline **14** (2.493 g, 10 mmol) and Et_3N (1.113 g, 11 mmol) in 100 ml of CH_2Cl_2 was added, over 3.5 hr, 1.313 g (11 mmol) of azidoacetyl chloride. The solution was washed with 4 × 100 ml of water, dried with $MgSO_4$, filtered, and evaporated to 3.15 of oil, which was chromatographed on 60 g of silica gel (E. Merck) with CH_2Cl_2, affording 0.406 g (12.7%) of **15**: ir (CCl_4) 4.73, 5.59, 5.71 μ; nmr ($CDCl_3$) δ 1.37 (s), 1.53 (s, *gem*-dimethyl), 4.53 (s, 3-H), 4.59 (d, J = 1.5 Hz, 6-H), 5.18 (s, OCH_2), 5.21 (d, J = 1.5 Hz, 5-H), 7.39 (s, C_6H_5); mass spectrum m/e 304 ($M^+ - N_2$).

Hydrogenation of 15 to 4. Compound **15** (57 mg) was hydrogenated at 40 psi for 1 hr in 30 ml of benzene with 30 mg of PtO_2. The catalyst was filtered and washed with benzene and ethyl acetate, affording 36 mg of crude **4** which was purified by plc on silica gel with 3:1 benzene–EtOAc. The purified product, 20 mg, was identical with authentic **4** by ir, nmr, and mass spectrum.

Hydrogenation of 16 to 17, Methyl 7α-Amino-3-methyl-3-cephem-4-carboxylate. Azidocephem **16**[1] (49 mg) was hydrogenated for 50 min at 25 psi in 2 ml of benzene with 50 mg of PtO_2, filtered, and evaporated, affording 31 mg of an oil: single spot on tlc, silica gel, 4:1 ether–acetone; ir (film) 5.67, 5.79 μ; nmr ($CDCl_3$) δ 1.90 (s, NH_2), 2.08 (s, 3-CH_3), 2.91, 3.22, 3.36, 3.65 (SCH_2), 3.88 (s, OCH_3), 4.10 (t, J = 1.5 Hz, 6-H), 4.44 (d, J = 1.5 Hz, 7-H; mass spectrum m/e 228.

Methyl 7α-(*p*-Nitrobenzylideneamino)-3-methyl-3-cephem-4-carboxylate (18). Compound **17** (342 mg) was treated with 215 mg of *p*-nitrobenzaldehyde and 2 g of $MgSO_4$ in 15 ml of CH_2Cl_2 for 2 hr. The solution was filtered and evaporated to give 562 mg of **18**: nmr ($CDCl_3$) δ 4.89 (t, J = 1.5, 1.5 Hz, 6-H), 4.99 (d, J = 1.5 Hz, 7-H), 8.62 (d, J = 1.5 Hz, CH=N).

Epimerization of 18 to 19, the 7β Schiff Base. Compound **18** (47.5 mg) was treated in 2 ml of THF at −78° under N_2 with 57.2 λ of 2.3 *M* phenyllithium, producing an inky blue solution. DMF (2.5 ml) was added, and the reaction was then quenched at −19° with 2 ml of THF containing 18 λ of AcOH and 23 λ of water. Benzene was added and the work-up was done as before, affording 49 mg of **19** plus **18** in 2:1 ratio by nmr. Nmr of **19** ($CDCl_3$) δ 5.16 (d, J = 5 Hz, 6-H), 5.40 (q, J = 5, 1.5 Hz, 7-H), 8.73 (d, J = 1.5 Hz, CH=N). When the reaction was quenched at −78° instead of −19° the result was the same.

Methyl 7β-[2(2-Thienyl)acetamido]-3-methyl-3-cephem-4-carboxylate (20). A sample of 600 mg of **19** + **18** from an epimerization of **18** as described above was converted with DNPH–TsOH to the mixed methyl 7-amino-3-cephem-4-carboxylates (400 mg). To this in 25 ml of CH_2Cl_2 was added 0.4 ml of pyridine and then 253 mg of 2-thienylacetyl chloride in 10 ml of CH_2Cl_2. The mixture was stirred for 5 min, evaporated, taken up in 25 ml of benzene, washed with aqueous pH 2 phosphate, water and aqueous K_2HPO_4, dried with $MgSO_4$, filtered, and evaporated, affording 636 mg of oil. This was chromatographed on 18 g of silica gel, eluting with 10:1 $CHCl_3$–EtOAc. Compound **20** (63 mg) was the fourth band (R_f *ca.* 0.4 on tlc), followed by its 7 epimer (23 mg): ir of **20** (film) 3.02, 5.61, 5.78, 5.95 μ; nmr of **20** ($CDCl_3$) δ 4.92 (d, J = 5 Hz, 6-H), 5.72 (q, J = 9, 5 Hz, 7-H), 6.68 (d, J = 9 Hz, NH), 2.10 (s, 3-CH_3), 2.91, 3.23, 3.36, 3.68 (SCH_2), 3.71 (s, OCH_3, CH_2C=O), 6.91, 6.98, 7.17, 7.22, 7.28 (thienyl); mass spectrum m/e 352, 321, 171.

Registry No.—**3**, 3956-31-8; **4**, 49626-54-2; **5**, 36273-76-4; **6**, 49626-56-4; **11**, 49626-57-5; **12**, 1254-56-4; **13**, 49626-59-7; 13 HCl, 49626-60-0; 13 free acid, 52-67-5; **14**, 49626-61-1; **15**, 49626-62-2; **16**, 49626-63-3; **17**, 49626-64-4; **18**, 49626-65-5; **19**, 49626-66-6; **20**, 37049-57-3.

References and Notes

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(12) (a) H. M. Crooks, Jr., in "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp 455–472. (b) Synthetic benzyl 6α-aminopenicillanate (**4**) had $[\alpha]_D$ +172° ($CHCl_3$). The **4** obtained by epimerization of **3** had $[\alpha]_D$ +180° ($CHCl_3$). These observations indicate that synthetic **4** was produced in a highly stereospecific manner *via* cycloaddition to the β face of **14** with at least 98% retention of asymmetry at C-3. Had significant cycloaddition occurred from the α face, followed by epimerization at C-3 to the more stable epimer, **4** of lower optical purity would have been obtained.
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