concentrated NH_4OH, and filtered to give 11.4 g of base product. This product was converted to its HCl salt in Et_2O–EtOH to give 12.0 g of (+)-**4**, mp 261–263°, $[\alpha]^{25}D$ +83.0° (*c* 2.5, MeOH). Anal. ($C_{16}H_{22}NOCl$) C, H, N.

In a similar manner, (−)-**3** was converted to the corresponding phenol, (−)-**4**, which gave an HCl salt with mp 260–262°, $[\alpha]^{25}D$ −82.8° (*c* 2.5, MeOH). Anal. ($C_{16}H_{22}NOCl$) C, H, N.

Hydrogenation of (+)-3. A solution of 350 mg of (+)-3 ($[\alpha]^{25}D$ +69.3) in 75 ml of EtOH containing 0.5 ml of concentrated HCl was hydrogenated over 100 mg of PtO_2 in a Parr shaker at 23 psi. After 20 min, H_2 uptake was completed. The catalyst was filtered and the filtrate was concentrated to dryness. The residue was crystallized from H_2O to give 150 mg of product with mp 115–119° and $[\alpha]^{25}D$ −43.2° (*c* 2, MeOH). This product had an ir spectrum identical with that of (−)-**1**·HCl.

Preparation of the Ester Derivative (−)-13β-Amino-5,6,7,8,9,10,11,12-octahydro-5α-methyl-5,11-methanobenzocyclodecen-3-ol Cyclopropanecarboxylate (7). A mixture of 5.0 g of the HBr salt of (−)-**6**, 2.8 g of benzyl chloroformate, 200 ml of saturated $NaHCO_3$, and 200 ml of CH_2Cl_2 was stirred for 2 h. The CH_2Cl_2 layer was separated, dried ($MgSO_4$), and concentrated to give an oil. The oil was washed several times with hexane to remove the last traces of benzyl chloroformate. The resultant viscous material was dissolved in 200 ml of C_6H_6 containing 1.7 g of Et_3N. To this stirred solution was added slowly 1.7 g of cyclopropylcarboxoyl chloride in 15 ml of C_6H_6. The reaction mixture was stirred an additional 0.5 h, washed with H_2O followed by dilute $NaHCO_3$, dried ($MgSO_4$), and concentrated to give an essentially pure ester derivative which still had the *N*-benzyloxycarbonyl-blocking group. This material was dissolved in 250 ml of THF containing 3.0 g of dry HCl and hydrogenated over 1.6 g of 10% Pd/C at 45 psi of H_2 for 3 h. The catalyst was filtered and the filtrate concentrated. The residue was crystallized from THF–Et_2O to give 2.3 g of the HCl salt of **7**, mp 278°, $[\alpha]^{25}D$ −39.5° (*c* 2, MeOH). Anal. ($C_{20}H_{28}NO_2Cl$) C, H, N.

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(2) M. E. Freed, J. R. Potoski, E. H. Freed, G. L. Conklin, and S. C. Bell, *J. Med. Chem.*, paper in this issue.
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(5) The complete animal pharmacology of this compound, designated in our laboratory as WY-16225, has been disclosed by J. L. Malis, M. E. Rosenthale, and M. I. Gluckman, *J. Pharmacol. Exp. Ther.*, **194**, 488 (1975).

3-Cyanocephems, and Carbon-13 Heterocyclic-Substituted Cephems via 1,3-Dipolar Cycloadditions[1]

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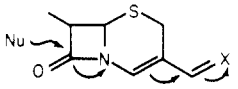
The transformation is described of 3-formylcephem **1** into its oxime, substituted oximes, and substituted hydrazones and, thence, into the 3-cyano, 3-diazomethyl, and 3-oxonitrilomethyl derivatives. These reactive 1,3-dipoles undergo 1,3-dipolar cycloadditions with various dipolarophiles to give C-3 heterocyclic-substituted cephems.

In the course of a program designed to produce cephems modified in the 3 position, analogues in which the dihydrothiazine ring contains proximate unsaturation seemed particularly attractive, because extension of the unsaturated system might increase the reactivity of the β-lactam; thus



The introduction of substituents at higher oxidation levels seemed especially interesting because they might provide enhanced reactivity. Extension of our interest in these compounds has led to the preparation of reactive 1,3-dipoles at the 3 position which have been utilized in the preparation of C-3 heterocyclic-substituted cephems by 1,3-dipolar cycloaddition. At the inception of this work, no examples of 1,3-dipoles directly attached to C-3 were known,[2-4] but recently the preparation and cycloaddition reactions of a 3-nitrone have been reported.[5]

Reaction of hydroxylamine with β-lactam antibiotics results in rapid cleavage of the β-lactam ring and has been used as a chemical assay method.[6] However, a suspension of the 3-formylcephem **1**[7] reacted with 2 equiv of hydroxylamine hydrochloride in refluxing isopropyl alcohol within 10 min to give the 3-aldoxime **2**. The ester could be cleaved with TFA–anisole in the usual way to the free acid **3**.

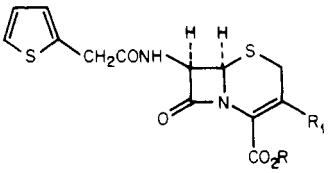
The oxidation level of the 3-substituent could now be raised by simply dehydrating the oxime with thionyl chloride, producing the nitrile **11**, which was deblocked to the acid **12** with TFA–anisole. Both **3** and **12** underwent facile hydrolytic cleavage of the β-lactam upon raising the pH above 7.8.

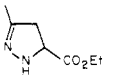
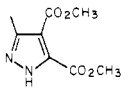
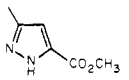
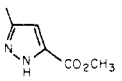
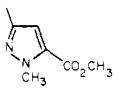
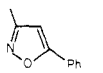
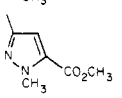
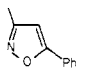
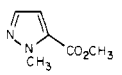
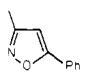
An essentially similar condensation of **1** with aminooxyacetic acid hemihydrochloride produced the 3-[[[(carboxymethylene)oxy]imino]methyl]cephem **5**. Diazomethane treatment gave the corresponding 3-[[[(methoxycarbonylmethyl)oxy]imino]methyl] **6** in quantitative yield. Cleavage of the ester as before gave the free acid **7**. Analogously, formation of oximes **9** and **10** was achieved in ca. 50% yield by condensation of **1** with methoxyamine or benzyloxyamine in $CHCl_3$–MeOH at 25°.

Substituted hydrazines were also found to condense with **1** under conditions in which they were nucleophilic enough to react with the 3-formyl substituent and yet not basic enough to rupture the β-lactam ring. Thus, an equimolar solution of **1** and *p*-toluenesulfonylhydrazine in $CHCl_3$ gave the tosylhydrazone **13** quantitatively in 15 min at 25°. Subsequent reaction with diazomethane provided the *N*-methyl tosylhydrazone **14**. The condensation was found to be generally applicable, and cephems **17–20** were prepared using the appropriate hydrazines.

The preparation of diazoalkanes by pyrolysis of salts of *p*-tosylhydrazones has been reported.[8] A solution of the tosylhydrazone **13** in THF at −78° reacted with 1 equiv of

Table I. 3-Substituted Cephems



No.	R_1	R	No.	R_1	R
1	CHO	$CHPh_2$	11	CN	$CHPh_2$
2	CH=NOH	$CHPh_2$	12	CN	H
3	CH=NOH	H	13	CH=NNHTos	$CHPh_2$
4	CH=NOH	CH_3	14	CH=NN(CH_3)Tos	$CHPh_2$
5	CH=NOCH$_2$CO$_2$H	$CHPh_2$	15	CH=NN(CH_3)Tos	H
6	CH=NOCH$_2$CO$_2$CH$_3$	$CHPh_2$	16	CH=NN(CH_3)Tos	CH_3
7	CH=NOCH$_2$CO$_2$CH$_3$	H	17	CH=NNHC$_6$H$_4$-*p*-NO$_2$	$CHPh_2$
8	CH=NOCH$_2$CO$_2$CH$_3$	CH_3	18	CH=NNHCOPh	$CHPh_2$
9	CH=NOCH$_3$	$CHPh_2$	19	CH=NNHOAc	$CHPh_2$
10	CH=NOCH$_2$Ph	$CHPh_2$	20	CH=NNHCO$_2$Et	$CHPh_2$
21	CH=NN(Li)SO$_2$C$_6$H$_4$-*p*-CH$_3$	$CHPh_2$	28		$CHPh_2$
22	CH=$\overset{+}{N}$=$\overset{-}{N}$	$CHPh_2$	29		$CHPh_2$
23		$CHPh_2$	30		$CHPh_2$
24		H	31	C=$\overset{+}{N}$—$\overset{-}{O}$	$CHPh_2$
25		CH_3	32		$CHPh_2$
26		$CHPh_2$	33		H
27		H	34		CH_3

butyllithium to give the lithium salt **21**. On warming slowly to 40°, the 3-diazomethylcephem **22** was formed; it was obtained as a pale yellow oil in 66% yield after chromatography. It was stable for days at room temperature in CH_2Cl_2.

A $CHCl_3$ solution of **22** and 1 equiv of methyl propiolate underwent 1,3-dipolar cycloaddition at 50–55° for 24 h, affording the pyrazole **23** as the only isolable cycloaddition product. Assignment of the methoxycarbonyl substituent to the 5 position on the pyrazole ring is based upon analogous orientation in other diazoalkane 1,3-dipolar cycloadditions.[9] Diazomethane reacted with **23** in ether over 3 h to give the 3-(*N*-methyl-5-methoxycarbonylpyrazol-3-yl)cephem **26**. Conversion to the free acids **24** and **27** was again effected with TFA–anisole.

Other heterocycles were formed under essentially similar conditions. Ethyl acrylate and **22** gave a 3-(5-ethoxycarbonylpyrazolin-3-yl)cephem **28**. Dimethyl acetylenedicarboxylate and **22** gave the 3-(4,5-dimethoxycarbonylpyrazol-3-yl)cephem **29**. Reaction of **22** with trifluoroacetonitrile in acetonitrile solution required an excess of trifluoroacetonitrile under anhydrous conditions for 5 days, giving a trifluoromethyltriazole derivative **30**.

The lead tetraacetate oxidation of *syn*-aldoximes gives nitrile oxides.[10] In CH_2Cl_2 solution at −78°, the oxime **2** reacted with 2 equiv of lead tetraacetate to give, after rapid work-up and chromatography, the 3-(oxonitrilomethyl)-cephem **31**. The nitrile oxide function is stable for several hours in solution and, presumably, dimerization to a furoxan is hindered by the bulky benzhydryl ester. However, it reacts rapidly with dipolarophiles. A solution of **31** in phenylacetylene at room temperature for 30 min reacted to give the 3-(5-phenylisoxazol-3-yl)cephem **32**. The direction of orientation is assumed on the basis of analogous nitrile oxide cycloadditions.[11] Treatment with TFA–anisole once again provided the bioactive free acid **33**.

All of the benzhydrylcephalosporins were deblocked to the corresponding free acids. While the in vitro gram-positive activity of these compounds was quite similar to that of cephalothin, activity against gram-negative organisms was markedly diminished. Compounds **3**, **7**, **12**, **15**, **24**, **27**, and **33** had MIC's of <0.39, 12.5, 0.78, <0.39, 3.12, 0.78, and <0.39 μg/ml against *Staphylococcus aureus* MB-2865. The MIC's of all compounds against *Streptococcus pyogenes* MB-3124 were <0.39 μg/ml.

Experimental Section

Benzhydryl 3-(Hydroxyiminomethyl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (2). A suspension of benzhydryl 3-formyl-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (**1**) (414 mg, 8.0×10^{-4} mol), powdered hydroxylamine hydrochloride (116 mg, 16×10^{-4} mol), and 25 ml of 2-propanol was stirred under N_2 at 60–65 °C until solution occurred. The orange solution was cooled, evaporated to an oil, dissolved in CH_2Cl_2 (50 ml), washed with brine (4 × 50 ml), dried with $MgSO_4$, filtered, and chromatographed by PLC on silica gel with $CHCl_3$–EtOAc (5:1). The product, 124 mg (29%), had R_f 0.4 and

mp 190–191°: ir (film) 3300, 1780, 1735, 1670 cm^{-1}; NMR ($CDCl_3$) δ 3.40 (d, 1 H, J = 18 Hz), 3.80 (s, 2 H), 4.03 (d, 1 H, J = 18 Hz), 4.96 (d, 1 H, J = 5 Hz), 5.90 (dd, 1 H, J = 5, 8 Hz), 6.73 (d, 1 H, J = 8 Hz), 7.2–7.6 (m, 15 H), 8.40 (s, 1 H); MS 366 ($M^+ - CHPh_2$).

3-(Hydroxyiminomethyl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylic Acid (3). This procedure will serve as the prototype for hydrolysis of all the benzhydryl esters. A solution of 58 mg of **2** and 1.0 ml of anisole at 0° was treated with 5.0 ml of TFA. After 2 min the TFA was removed under vacuum and then the anisole at ca. 30°. More anisole was then added and removed in vacuo. The residue was taken up in 50 ml of aqueous $NaHCO_3$ and washed thrice with $CHCl_3$. The aqueous layer was brought to pH 2 with 5% H_3PO_4 and extracted thrice with EtOAc (which had been prewashed with aqueous K_2HPO_4 to remove AcOH). The organic layers were dried with $MgSO_4$, filtered, and evaporated to afford 19 mg of **3**, 45%. The NMR resembled that of **2**, lacking the benzhydryl group. The methyl ester **4**, made with CH_2N_2, had m/e 381 (M^+), 364, 336, 200, 181.

Benzhydryl 3-[[[(Carboxymethylene)oxy]imino]-methyl]-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (5). A mixture of **1** (103 mg, 2.0 × 10^{-4} mol), aminooxyacetic acid hemihydrochloride (43.8 mg, 4.0 × 10^{-4} mol), and 10 ml of 2-propanol was stirred 30 min at 50–60° and evaporated, and the resulting oil was partitioned between 30 ml of EtOAc and 30 ml of water. The organic extract was dried with $MgSO_4$, filtered, and evaporated to give 102 mg of **5**: 87%; ir (film) 3300, 1780, 1725, 1665 cm^{-1}; NMR ($CDCl_3$) δ 3.35 (d, 1 H, J = 18 Hz), 3.80 (s, 2 H), 3.98 (d, 1 H, J = 18 Hz), 4.67 (s, 2 H), 4.95 (d, 1 H, J = 5 Hz), 5.90 (dd, 1 H, J = 5, 8 Hz), 6.8–7.8 (m, 16 H), 8.50 (s, 1 H). Cleavage of the ester as for **2** gave the free acid which was converted to the dimethyl ester **8** with CH_2N_2: m/e 453 (M^+), 364, 273.

Benzhydryl 3-[[[(Methoxycarbonylmethylene)oxy]imino]methyl]-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (6). A solution of 119 mg of **5** in 5 ml of CH_2Cl_2 was treated with excess ethereal CH_2N_2. Removal of solvent gave a white crystalline product: 120 mg (100%); mp 181–183°; ir (film) 3300, 1780, 1755, 1675 cm^{-1}; NMR ($CDCl_3$) δ 3.37 (d, 1 H, J = 18 Hz), 3.73 (s, 3 H), 3.80 (s, 2 H), 4.00 (d, 1 H, J = 18 Hz), 4.95 (d, 1 H, J = 5 Hz), 5.90 (dd, 1 H, J = 5, 8 Hz), 6.7–7.6 (m, 15 H), 8.45 (s, 1 H); m/e 605 (M^+), 438, 425, 394, 181. Cleavage of the ester with TFA–anisole gave the free acid **7**, mp 163–165°, which gave the dimethyl ester **8** with CH_2N_2.

Benzhydryl 3-(N-Methoxyiminomethyl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (9). A mixture of compound **1** (311 mg, 6.0 × 10^{-4} mol), methoxyamine hydrochloride (50 mg, 6.0 × 10^{-4} mol), 15 ml of MeOH, 10 ml of $CHCl_3$, and NaOAc (49 mg, 6.0 × 10^{-4} mol) was stirred at room temperature 20 min, diluted with $CHCl_3$, washed with aqueous pH 8 phosphate, dried with $MgSO_4$, filtered, and evaporated to give 141 mg (43%) of **9**: ir (film) 3300, 1790, 1720, 1660 cm^{-1}; NMR ($CDCl_3$) δ 3.40 (d, 1 H, J = 18 Hz), 3.80 (s, 2 H), 3.95 (s, 3 H), 4.02 (d, 1 H, J = 18 Hz), 4.96 (d, 1 H, J = 5 Hz), 5.90 (dd, 1 H, J = 5, 9 Hz), 6.70 (d, 1 H, J = 9 Hz), 6.9–7.6 (m, 14 H), 8.35 (s, 1 H).

Benzhydryl 3-(N-Benzyloxyiminomethyl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (10). A mixture of **1** (52 mg, 10^{-4} mol), MeOH (0.5 ml), $CHCl_3$ (0.5 ml), NaOAc (8.2 mg, 10^{-4} mol), and *O*-benzylhydroxylamine hydrochloride (16 mg, 10^{-4} mol) was stirred at room temperature 2.5 h, diluted with $CHCl_3$, washed with aqueous pH 8 phosphate, dried with $MgSO_4$, filtered, and evaporated to give 15 mg (24%) of **10**: ir (film) 3300, 1790, 1725, 1660 cm^{-1}; NMR ($CDCl_3$) δ 3.4–3.8 (m, 2 H), 3.80 (s, 2 H), 4.95 (d, 1 H, J = 5 Hz), 5.05 (s, 2 H), 5.6–6.0 (m, 1 H), 6.8–7.6 (m, 20 H), 8.42 (s, 1 H).

Benzhydryl 3-Cyano-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (11). A mixture of compound **2** (58 mg, 1.1 × 10^{-4} mol), 10 ml of $CHCl_3$, and 1.0 ml of $SOCl_2$ was refluxed 10 min, cooled, evaporated, and chromatographed by PLC on silica gel with $CHCl_3$–EtOAc (5:1). The product **11**, 19 mg (30%), had R_f 0.65: ir (film) 3250, 2200, 1790, 1675 cm^{-1}; NMR ($CDCl_3$) δ 3.21 (s, 2 H), 3.77 (s, 2 H), 4.80 (d, 1 H, J = 5 Hz), 5.96 (dd, 1 H, J = 5, 8 Hz), 6.9–7.7 (m, 15 H); m/e 348 ($M^+ - CHPh_2$). Cleavage of the ester as for **2** gave the free acid **12** in 70% yield: ir (film) 2200, 1790, 1720, 1660 cm^{-1}.

Benzhydryl 3-(Tosylhydrazonoformyl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (13). A mixture of compound **1** (1.06 g, 2.05 × 10^{-3} mol), *p*-tosylhydrazine (0.38 g, 2.05 × 10^{-3} mol), and $CHCl_3$ (35 ml) was stirred at room temperature for 30 min with 3 g of $MgSO_4$. The mixture was filtered and evaporated, affording 1.44 g of **13** (100%): mp 103–105°; ir (film) 3550, 3300, 1780, 1740, 1665 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3 H), 3.30 (d, 1 H, J = 18 Hz), 3.80 (s, 2 H), 4.00 (d, 1 H, J = 18 Hz), 4.90 (d, 1 H J = 5 Hz), 5.87 (dd, 1 H, J = 5, 9 Hz), 6.70 (d, 1 H, J = 9 Hz), 6.8–8.0 (m, 19 H), 8.40 (s, 1 H). Treatment with CH_2N_2 provided the *N*-methyl tosylhydrazone **14**: ir like **13**; NMR ($CDCl_3$) δ 2.92 (s, 3 H), others like **13**. Conversion to the free acid **15** as for **2**, followed by CH_2N_2 esterification, provided material **16** with mass spectral fragmentation identical with that obtained from cleavage–esterification of **13**: m/e 548 (M^+), 393, 368, 181.

Benzhydryl 3-(p-Nitrophenylhydrazonoformyl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (17). A mixture of **1** (104 mg, 10^{-4} mol), *p*-nitrophenylhydrazine (31 mg, 2 × 10^{-4} mol), $CHCl_3$ (40 ml), and 1 g of $MgSO_4$ was stirred 1 h at 50°, filtered, evaporated, and chromatographed by PLC with $CHCl_3$–EtOAc (10:1) to give 45 mg (34%) of **17** at R_f 0.55: ir (film) 3330, 1780, 1720, 1650, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 3.30 (d, 1 H, J = 18 Hz), 3.40 (s, 2 H), 3.80 (d, 1 H, J = 18 Hz), 4.75 (d, 1 H, J = 5 Hz), 5.50 (dd, 1 H, J = 5, 9 Hz), 6.6–8.2 (m, 20 H), 8.75 (d, 1 H, J = 9 Hz). Treatment with TFA–anisole followed by CH_2N_2 afforded the methyl ester: m/e 501 (M^+).

Benzhydryl 3-(Benzoylhydrazonoformyl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (18). A solution of **1** (52 mg, 10^{-4} mol) and benzoylhydrazine (13.6 mg, 10^{-4} mol) in 0.5 ml of MeOH was stirred overnight, diluted with benzene, washed with aqueous pH 8 phosphate, dried with $MgSO_4$, filtered, and evaporated to give 19 mg (30%) of **18**: ir (film) 3300, 1790, 1725, 1660 cm^{-1}; NMR ($CDCl_3$) δ 3.42 (d, 1 H, J = 18 Hz), 3.80 (s, 2 H), 3.90 (d, 1 H, J = 18 Hz), 4.95 (d, 1 H, J = 5 Hz), 6.0 (m, 1 H), 6.9–7.6 (m, 21 H), 8.0 (s, 1 H).

Benzhydryl 3-(Acetylhydrazonoformyl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (19). A solution of **1** (52 mg, 10^{-4} mol) and acetylhydrazine (7.4 mg, 10^{-4} mol) in 0.5 ml of $CHCl_3$ and 0.5 ml of MeOH was stirred overnight. Work-up as for **18** gave 19 mg of **19**: 41%; ir (film) 3300, 1785, 1720, 1660 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (s, 3 H), 3.40 (d, 1 H, J = 18 Hz), 3.82 (s, 2 H), 4.0 (d, 1 H, J = 18 Hz), 5.02 (d, 1 H, J = 5 Hz), 5.94 (dd, 1 H, J = 5, 8 Hz), 6.70 (d, 1 H, J = 8 Hz), 6.8–7.6 (m, 15 H), 8.00 (s, 1 H).

Benzhydryl 3-(Carbethoxyhydrazonoformyl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (20). A solution of 1 (52 mg, 10^{-4} mol) and ethyl carbazate (10.4 mg, 10^{-4} mol) in 0.5 ml of MeOH and 0.5 ml of $CHCl_3$ was stirred 2 h and chromatographed by PLC on silica gel with $CHCl_3$–EtOAc (4:1) to give 21 mg of **20**: 35%; ir (film) 3300, 1790, 1735, 1665 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3 H, J = 6 Hz), 3.40 (d, 1 H, J = 18 Hz), 3.82 (s, 2 H), 3.86 (d, 1 H, J = 18 Hz), 4.20 (q, 2 H, J = 6 Hz), 4.95 (d, 1 H, J = 5 Hz), 5.93 (dd, 1 H, J = 5, 8 Hz), 6.66 (d, 1 H, J = 8 Hz), 6.9–7.6 (m, 14 H), 8.22 (s, 1 H).

Benzhydryl 3-Diazomethyl-7β-(2-thienylacetyl)-3-cephem-4-carboxylate (22). A solution of compound **13**, 0.352 g (5.0 × 10^{-4} mol), in 8 ml of THF under N_2 at −78° reacted with 1 equiv of *n*-butyllithium (0.23 ml, 2.2 M in hexane) to give the Li salt **21**. The solution was slowly brought to room temperature, warmed briefly to 40° to complete thermolysis, filtered, and chromatographed by PLC on silica gel with $CHCl_3$–EtOAc (1:1) to give the 3-diazocephem **22** as a pale yellow oil: 186 mg (66%); ir (film) 3300, 2100, 1760, 1670 cm^{-1}; NMR ($CDCl_3$) δ 3.10 (d, 1 H, J = 18 Hz), 3.37 (d, 1 H, J = 18 Hz), 3.92 (s, 2 H), 4.98 (d, 1 H, J = 5 Hz), 5.42 (dd, 1 H, J = 5, 8 Hz), 6.50 (s, 1 H), 6.9–7.6 (m, 17 H), 7.80 (d, 1 H, J = 8 Hz).

Benzhydryl 3-(5-Methoxycarbonylpyrazol-3-yl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (23). A solution of compound **22** (186 mg, 3.33 × 10^{-4} mol) and methyl propiolate (28 μl, 3.33 × 10^{-4} mol) in 7 ml of $CHCl_3$ was stirred at 50–55° overnight. The solvent was removed and the resulting oil chromatographed by PLC on silica gel with $CHCl_3$–EtOAc (1:1) to give the product at R_f 0.47: 123 mg (60%); mp 188–189°; ir (film) 3300, 1780, 1735, 1705, 1665 cm^{-1}; NMR ($CDCl_3$) δ 3.47 (d, 1 H, J = 18 Hz), 3.87 (d, 1 H, J = 18 Hz), 3.87 (s, 5 H), 5.03 (d, 1 H, J = 5 Hz), 5.90 (dd, 1 H, J = 5, 8 Hz), 6.53 (s, 1 H), 6.7–7.5 (m, 16 H). The free acid **24** was obtained in quantitative yield with TFA–anisole. Conversion to the methyl ester with CH_2N_2

effected methylation of the pyrazole nitrogen also (**25**): *m/e* 476 (M^+), 296, 181.

Benzhydryl 3-(*N*-Methyl-5-methoxycarbonylpyrazol-3-yl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (26). Compound **23** (53 mg, 10^{-4} mol) in 3 ml of CH_2Cl_2 was treated with excess CH_2N_2 in ether. After 3 h the solvent was removed to give a quantitative yield of product: mp 206–208°; ir (film) 3320, 1790, 1755, 1675 cm^{-1}; NMR ($CDCl_3$) δ 3.53 (d, 1 H, *J* = 18 Hz), 3.90 (d, 1 H, *J* = 18 Hz), 3.80 (s, 2 H), 3.87 (s, 6 H), 5.03 (d, 1 H, *J* = 5 Hz), 5.90 (dd, 1 H, *J* = 5, 8 Hz), 6.47 (d, 1 H, *J* = 8 Hz), 6.54 (s, 1 H), 7.0–7.5 (m, 14 H); *m/e* 628 (M^+), 448, 417. Conversion with TFA–anisole to the free acid **27** followed by treatment with CH_2N_2 gave **25** with the mass spectrum identical with that of the previous sample.

Benzhydryl 3-(5-Ethoxycarbonylpyrazolin-3-yl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (28). A solution of compound **22** (106 mg, 2.0×10^{-4} mol) and ethyl acrylate (20 μl, 2×10^{-4} mol) in CH_2Cl_2 was refluxed 12 h, evaporated, and chromatographed by PLC on silica gel with EtOAc–$CHCl_3$ (1:1) to give 46 mg of product (36%) at R_f 0.65: ir (film) 3300, 1780, 1730, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.1–1.6 (m, 5 H), 3.42 (br s, 2 H), 3.81 (s, 2 H), 4.0–4.6 (m, 4 H), 4.98 (d, 1 H, *J* = 4 Hz), 5.85 (dd, 1 H, *J* = 4, 9 Hz), 6.70 (d, 1 H, *J* = 9 Hz), 6.9–7.6 (m, 14 H). The free acid was obtained with TFA–anisole.

Benzhydryl 3-(4,5-Diethoxycarbonylpyrazol-3-yl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (29). A solution of **22** (42 mg, 8.0×10^{-5} mol) and diethyl acetylenedicarboxylate (12.4 μg, 8.0×10^{-5} mol) in CH_2Cl_2 was stirred at room temperature for 2 h, evaporated, and chromatographed by PLC on silica gel with $CHCl_3$–EtOAc (1:1) to give 20 mg of product (36%): *m/e* 700 (M^+).

Benzhydryl 3-(5-Trifluoromethyl-1,2,3-triazol-4-yl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (30). Trifluoroacetonitrile was slowly bubbled into a solution of **22** (106 mg, 2.0×10^{-4} mol) in 50 ml of acetonitrile for 3 h. The mixture was stoppered for 5 days. The solvent was then removed and the resulting oil chromatographed by PLC on silica gel with EtOAc–$CHCl_3$ (1:1) to give 62 mg of product (50%): *m/e* 625 (M^+).

Benzhydryl 3-(Oxonitrilomethyl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (31). To a stirred suspension of compound **2** (106.9 mg, 2.0×10^{-4} mol) in CH_2Cl_2 at −78° was added 60 μl of triethylamine (9×10^{-4} mol). After 5 min a solution of 96 mg of lead tetraacetate (2.0×10^{-4} mol) in 5 ml of CH_2Cl_2 was added dropwise. The reaction mixture was allowed to warm to 0°, poured into 100 ml of ice water, and extracted with 5 × 15 ml of ether. The ether solution was dried with $MgSO_4$, filtered, evaporated, and chromatographed by PLC on silica gel with benzene–THF (5:1), developing for only 15 min, to give 35 mg of product: 33%; ir (film) 3220, 2285, 1790, 1730, 1675 cm^{-1}; NMR ($CDCl_3$) δ 3.38 (d, 1 H, *J* = 7 Hz), 3.78 (s, 2 H), 4.02 (d, 1 H, *J* = 7 Hz), 4.92 (d, 1 H, *J* = 5 Hz), 6.00 (dd, 1 H, *J* = 5, 8 Hz), 6.9–7.6 (m, 15 H).

Benzhydryl 3-(5-Phenylisoxazol-3-yl)-7β-(2-thienylacetamido)-3-cephem-4-carboxylate (32). A solution of **31** (106 mg, 2.0×10^{-4} mol) in 1 ml of phenylacetylene was kept 30 min at room temperature and then chromatographed by PLC on silica gel with benzene–THF (5:1), affording 36 mg of product, 28%, at R_f 0.70: ir (film) 3300, 1790, 1740, 1675 cm^{-1}; NMR ($CDCl_3$) δ 3.18 (d, 1 H, *J* = 18 Hz), 3.80 (s, 2 H), 3.97 (d, 1 H, *J* = 18 Hz), 4.97 (d, 1 H, *J* = 5 Hz), 5.95 (dd, 1 H, *J* = 5, 8 Hz), 6.54 (d, 1 H, *J* = 8 Hz), 6.9–7.5 (m, 20 H). Cleavage to the acid **33** followed by CH_2N_2 gave methyl ester **34**: *m/e* 481 (M^+), 422, 301, 181.

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References and Notes

(1) A preliminary account of this work was presented at the Symposium on the Chemistry of Penicillins and Cephalosporins, American Chemical Society Meeting-in-Miniature, Stevens Institute of Technology, Hoboken, N.J., May 14, 1975. H. H. Peter, B. Müller, and H. Bickel communicated the syntheses of the oximes **2**, **5**, **9**, and the 3-cyanocephem **12** at the Fifth International Congress of Heterocyclic Chemistry, University of Ljubljana, Yugoslavia, July 13–18, 1975.
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Book Reviews

Advances in Chromatography. Volume 12. Edited by J. C. Giddings, E. Grushka, R. A. Keller, and J. Cazes. Marcel Dekker, New York, N.Y. 1975. xiv + 278 pp. 15 × 23.5 cm. $22.50.

This book, the twelfth volume in the series, consists of seven chapters covering a wide range of chromatography topics. Anyone, except the most serious chromatographer, will find only a few chapters of this book (and previous volumes) to be of interest. In this particular book, readers of Journal of Medicinal Chemistry will probably find Chapter 1, "The Use of High Pressure Liquid Chromatography in Pharmacology and Toxicology", and Chapter 3, "Practical Methods of High Speed Liquid Chromatography", to be most useful. These are the first two chapters which truly describe modern high-pressure liquid chromatography to appear in the Advances in Chromatography Series.

Dr. P. R. Brown in Chapter 1 "whets the appetite" by showing many examples of how liquid chromatography already has analyzed mixtures of physiological fluids, cell extracts, drugs, and many other biologically active compounds. Since the writing of this chapter the technology of high-pressure liquid chromatography has advanced so that in 1975 even faster analyses can be obtained or more complex samples can be resolved. Two types of analyses described by Dr. Brown are carbohydrates in urine and nucleotides in whole blood.

Chapter 3, "Practical Methods of High Speed Liquid Chromatography", by G. J. Fallick is a good follow up to Chapter 1. If Chapter 1 gets your attention that high-pressure liquid chromatography could be used in your research, then Chapter 3 will give you a basic introduction to the jargon of the technique and how to select conditions (column packing material, solvents, etc.). The chapter also describes the technique of scaling analytical liquid chromatographic analyses up to preparing pure compounds in the few hundred milligram range.

The other five chapters are all very well written but will have only limited interest to readers of this Journal. Chapter 2 reviews chromatographic separations of cellulose and its derivatives; Chapter 4 discusses measuring diffusion coefficients by gas chromatography; Chapter 5 gives examples of GC analyses of polychlorinated biphenyls; Chapter 6 presents high-performance