OCHO). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 67.98; H, 9.80; N, 6.80.

7-Oxoheptyl Tetrahydropyranyl Ether (4). Ethyl acetate (4.5 g, 0.05 mol) was added dropwise to a stirred suspension of $LiAlH_4$ (1.95 g, 0.05 mol) in ethyl ether at 0°. Then **3** (10.55 g, 0.05 mol) was added dropwise over a 10-min period and the reaction mixture was stirred for an additional 50 min at ice-bath temperature. Water (2 ml), 15% NaOH (2 ml), and water (6 ml) were added dropwise in that order, the mixture was filtered, and the filtrate was concentrated. The crude imine was stirred for 1 hr at room temperature in a mixture of 40 ml of water, 40 ml of ethyl alcohol, and 20 ml of glacial acetic acid;[11] then the mixture was diluted with water and extracted with petroleum ether. The organic layer was washed with brine, saturated sodium bicarbonate, and brine and dried. After removal of the solvent, **4** (5.0 g, 45%) was purified by short-path distillation: bp 95–100° (0.05 mm); ir 1729 cm^{-1}; NMR δ 2.35 (m, 2, $-CH_2CHO$), 3.2–4.0 (m, 4, $-CH_2O-$), 4.48 (broad s, 1, OCHO), 9.67 (t, 1, -CHO). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.24, H, 10.22.

(*Z*)- and (*E*)-8-Methyl-7-hexacosenyl Tetrahydropyranyl Ethers (5). Ethylidenetriphenylphosphorane was prepared from ethyltriphenylphosphonium bromide in THF using 2.0 *M* *n*-butyllithium in hexane in the usual manner. One equivalent of 1-bromooctadecane was added to the ylide solution (ca. 10°) and 10 min later HMPA, 1 ml/ml THF, was added. The deep red solution remained homogeneous. After 2 days the solution, lighter in color but still red, was diluted with 1,2-dichloroethane and washed with H_2O several times. The organic phase was dried ($MgSO_4$) and concentrated. The oily salt, (1-methylnonadecyl)triphenylphosphonium bromide, was freed of traces of 1,2-dichloroethane by washing with anhydrous Et_2O several times and then concentrating the residue on a flash evaporator. A solution of the salt was prepared in dry THF and used as soon as possible.

The secondary alkylphosphonium salt (0.045 mol) was converted to its ylide at 5° in 100 ml of THF with *n*-butyllithium (23 ml of 2.0 *M* in hexane) and the aldehyde **4** (8.2 g, 0.038 mol) was added dropwise. The ice bath was removed and after 1 hr the reaction mixture was worked up in the usual manner with petroleum ether to extract the olefin **5**. The crude product was deposited on a column of silica gel (100 g) and then eluted with 200 ml of petroleum ether and 200 ml of 15% Et_2O in petroleum ether. The combined eluates were then rechromatographed (silica gel, 100 g) and eluted with 200 ml of petroleum ether and 400 ml of 15% Et_2O in petroleum ether. Compound **5** was obtained in the last 200 ml and weighed 18.3 g (56%); $n^{25}D$ 1.4625; NMR δ 0.88 (t, ca. 3, CH_3), 3.2–4.0 (m, 4, CH_2), 4.48 (s, 1, OCHO), 5.03 (t, 1, -CH). Anal. Calcd for $C_{32}H_{62}O_2$: C, 80.26; H, 13.05. Found: C, 80.50; H, 13.30.

8-Methylhexacosanyl Tetrahydropyranyl Ether (6). Olefin **5** (10.0 g, 0.021 mol) was hydrogenated at atmospheric pressure in hexane (150 ml) with 10% Pd/C (1 g). Filtration and concentration provided **6** quantitatively: $n^{25}D$ 1.4577; NMR δ 0.87 (t, ca. 3, CH_3), 3.2–4.0 (m, 4, CH_2O), 4.45 (s, 1, OCHO). Anal. Calcd for $C_{32}H_{64}O_2$: C, 79.93; H, 13.42. Found: C, 79.74; H, 13.22.

1-Bromo-8-methylhexacosane (7). A solution of triphenylphosphine dibromide was prepared by adding bromine (7.0 g, 0.0436 mol) dropwise to a chilled, stirred solution of triphenylphosphine (11.4 g, 0.0436 mol) in 120 ml of CH_2Cl_2 maintained at 0–10°. The THP ether **6** (9.5 g, 0.0198 mol) in 10 ml of CCH_2Cl_2 was then added at once. The mixture was allowed to stir for 16 hr under nitrogen at room temperature. The black solution was washed with H_2O (2 × 100 ml), dried ($MgSO_4$), and deposited on 45 g of alumina (Fisher, neutral). The resulting mixture was placed onto a column of silica gel (125 g) and eluted with petroleum ether (500 ml). Concentration of the eluate provided the bromide as a colorless liquid, 8.1 g (91%): $n^{25}D$ 1.4641; NMR δ 0.88 (t, ca. 3, CH_3), 3.30 (t, 2, CH_2Br). Anal. Calcd for $C_{27}H_{55}Br$: C, 70.55; H, 12.06; Br, 17.39. Found: C, 70.75; H, 12.08; Br, 17.16.

(2-Oxobutylidene)triphenylphosphorane. To a cooled solution (−78°) of 10.5 g (0.033 mol) of (2-oxopropylidene)triphenylphosphorane[12] in 250 ml of dry THF was added under nitrogen 20 ml (0.033 mol) of 1.6 *N* *n*-butyllithium in hexane. The deep red solution of the ylide anion was stirred at −78° for 15 min, then 6.0 g (0.042 mol) of methyl iodide was added slowly. The color of the anion was discharged at the end of the addition. The reaction mixture was allowed to warm to room temperature and a clear solution resulted. Excess solvents were removed with a flash evaporator and the remaining solid was filtered to yield 10 g of crude (2-oxobutylidene)triphenylphosphorane. Recrystallization from chloroform–ethyl acetate gave 8 g (75%) of product, mp 218–219° (lit.[7] mp 221–222°).

3,11-Dimethylnonacosan-2-one (1). A solution of (2-oxobutylidene)triphenylphosphorane (0.33 g, 0.001 mol) in THF (10 ml) was cooled to −78° under nitrogen and treated with 1.2 ml (0.002 mol) of 1.6 *M* *n*-butyllithium in hexane. The resulting deep red solution was stirred for 15 min, and then a solution of 1-bromo-8-methylhexacosane (**7**, 0.40 g, 0.00087 mol) in THF (15 ml) was added (**7** separated from solution at the low temperature). The cooling bath was removed, stirring was continued for 20 hr at room temperature, then water (ca. 5 ml) was added (color discharged) and the mixture was refluxed for 24 hr. The solvent was evaporated and the residue was partitioned between ether and water. Alumina (ca. 6 g) was added to the dried ether solution, the ether was evaporated, and the residue was added to a column of silica gel (20 g). After eluting with petroleum ether, the ketone **1** (0.11 g, 28%) was obtained by elution with 10% ether in petroleum ether.

The reaction was repeated with a twofold excess of the phosphorane with no increase in the yield of **1**.

The products of the two reactions (0.21 g) were combined and rechromatographed on silica gel to give an analytical sample: ir 1716 cm^{-1}; NMR δ 2.0 (s, CH_3CO), 0.83 (*t*-CH_3).

Anal. Calcd for $C_{31}H_{62}O$: C, 82.59; H, 13.86. Found: C, 82.82; H, 13.77.

Registry No.—**1**, 53623-10-2; **2**, 2009-84-9; **3**, 33803-59-7; **4**, 34335-17-6; (*E*)-**5**, 55590-31-3; (*Z*)-**5**, 55590-32-4; **6**, 55590-33-5; **7**, 55590-34-6; **8**, 55590-35-7.

References and Notes

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(7) K. Fujiwara, H. Takahashi, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **35**, 2042 (1962).
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(9) Professor S. Ishii informs us that in his behavioral bioassay our synthetic material was as active as the isolated natural material. Positive responses with synthetic material as well as with crude cuticular extracts of female cockroaches were also obtained by V. E. Adler of this institute, using the electroantennogram technique.
(10) Mention of a trade name or proprietary product does not constitute a USDA endorsement.
(11) The tetrahydropyranyl ether linkage was unaffected under these conditions.
(12) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).

Cephem-*N*-methylnitrones

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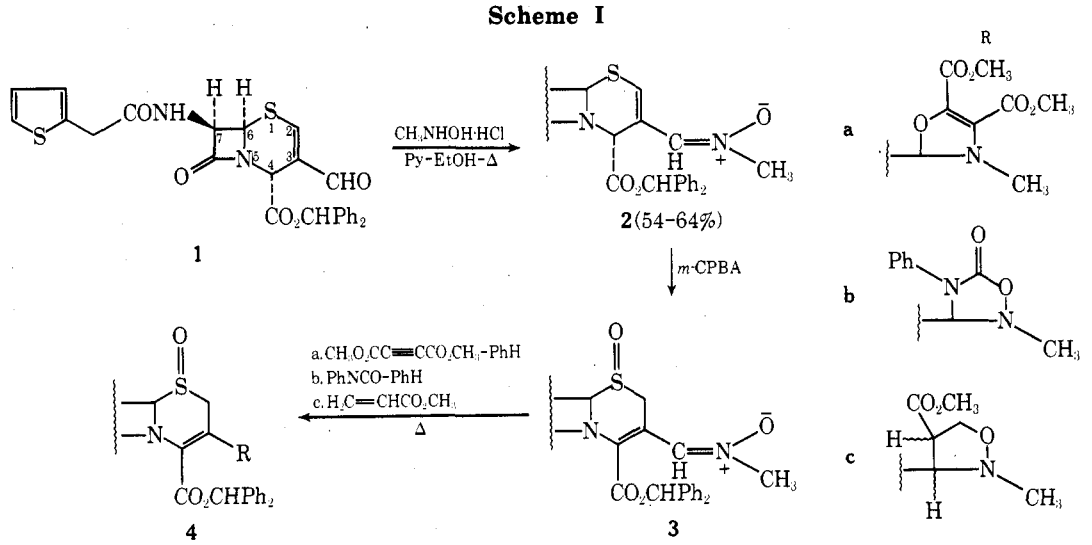
Our interest in the synthesis of 2-C–3-C-tricyclic cephalosporins,[1] of cephem-3-*C*-carboxamides,[2] and in the synthesis of cephalosporins with ring substituents attached directly at 3-C vs. 3-C′ [3a,3b] led us to explore some of the chemistry of the *C*-3-*C*-cephem-*N*-methylnitrones. Thus aldonitrones are known to undergo rearrangement with a variety of reagents (acetic anhydride, acetyl chloride, sulfur dioxide, etc.) to give amides and to undergo inter- and intramolecular cycloaddition reactions to give heterocyclic ring systems.[4]

Treatment of the Δ^2-3-*C*-formyl derivative (**1**) with *N*-methylhydroxylamine followed by chromatography on silica gel gave the *N*-methylnitrone (**2**) in moderate yield (Scheme I). Sulfur oxidation with *m*-chloroperbenzoic acid

Scheme I



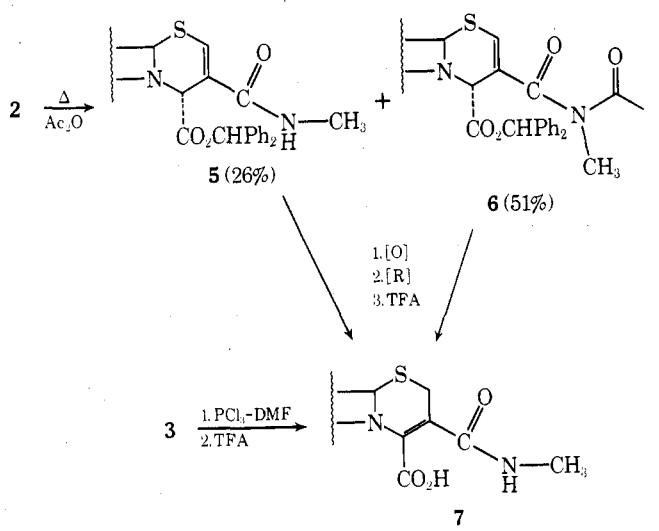
(*m*-CPBA) with concomitant double bond isomerization then gave **3** in 90% crude yield.

Cycloaddition reactions of **3** with dimethyl acetylenedicarboxylate gave what we believe to be the 4′-oxazoline **4a** (70%) via the 4′-isoxazoline by thermal rearrangement via the acyl aziridine.[5] Reaction of **3** with phenyl isocyanate gave a single product (52%) believed to be the 1′,2′,4′-oxadiazolin-5′-one (**4b**), while methyl acrylate gave two different products (**4c**, 32 and 20%). Structural assignments in the latter reaction are complicated by the fact that the mechanism of such cycloaddition reactions is not known with certainty but can be subject to both kinetic and thermodynamic control. The conditions of the reaction (80°, 1 hr) should favor conjugate addition, thus leaving the question of whether the process is stereospecific cis addition as well as the obvious creation of two new asymmetric centers.

The sulfoxides **4a–c** were reduced (PCl_3–DMF) and the esters cleaved to give the corresponding acids. The acids retain gram positive, but show loss in gram negative activity relative to sodium cephalothin.

The 3-*C*-*N*-methyl carboxamides were synthesized via the PCl_3–DMF reaction on **3** (21%) followed by ester cleavage to give **7** or alternatively by the reaction of **2** with acetic anhydride to give the amide **5** (26%) and the imide **6** (51%) (Scheme II). Although the presence of acetic acid reverses the amide/imide ratio (26:51 to 52:27), double bond isomerization followed by ester cleavage with strong acid (TFA) results in deacetylation of the imide to give the corresponding *N*-methyl amide.

Scheme II



Biological tests show that the *N*-methyl amide **7** retains gram positive, but shows reduced gram negative activity relative to sodium cephalothin.

Although aldonitrones can theoretically exist in two different geometric configurations, it is known that under thermodynamic conditions the trans or *Z* form exists exclusively.[4b,6] Consequently the nitrone oxygen in **2** is oriented correctly for an intramolecular 1,3-dipolar cycloaddition. Pyrolysis of **2** in toluene at 110° for 3 hr results in the formation of two products (**8a**, isomer I, and **8b**, isomer II) (72%) (Scheme III) which are isomeric with starting material. Similar pyrolysis on **3** gave starting material, thus showing the necessity of a Δ^2 double bond and corroborating an intramolecular 1,3-dipolar type reaction. Changing the 4-C ester changed the ratio of isomer I to II as shown: CH_3 (74%), I:II = 7:1; $CHPh_2$ (72%), I:II = 2.3:1.0; $CH_2C_6H_4NO_2$-*p* (58%), I:II = 1.2:1.0.

Ir studies of **8a** and **8b** show that both rearrangement products contain the β-lactam, while the NMR spectra were characterized in both cases by an *N*-methyl doublet (ca. δ 2.9, J = 4 Hz) and two low-field protons, one a singlet at ca. δ 8.9 and the other a multiplet at ca. δ 11.5. D_2O wash caused the *N*-methyl doublet to become a singlet and showed the δ 11.5 peak to be an NH, thus ruling out a tricyclic isoxazoline.

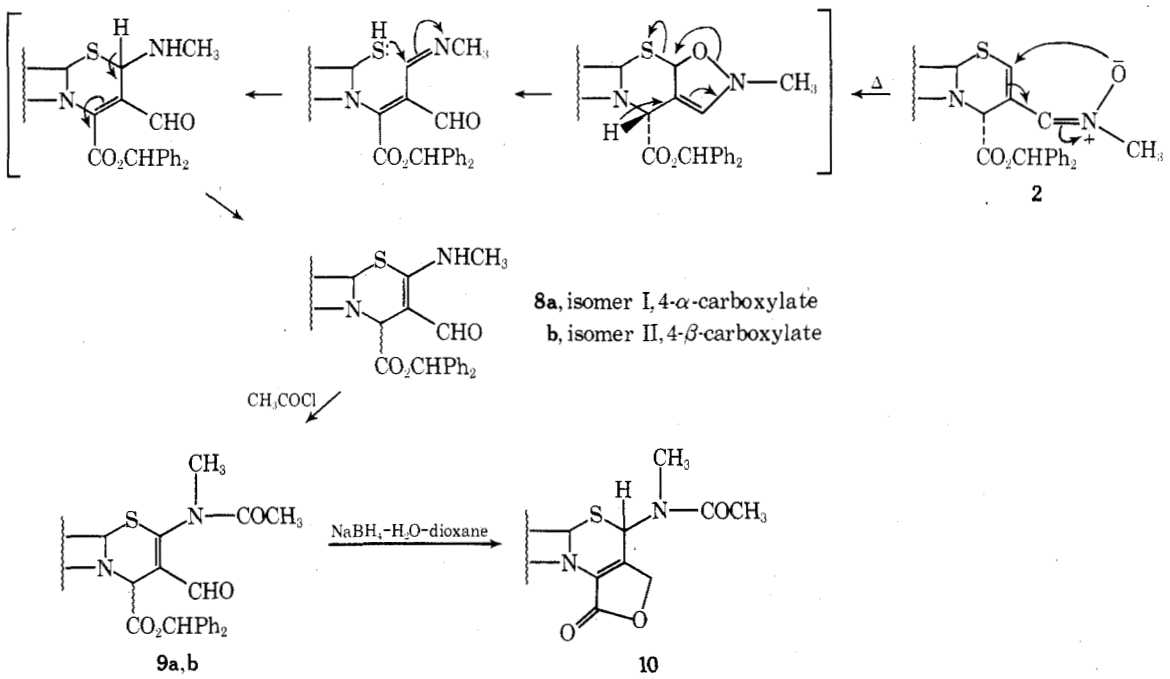
Both rearrangement products **8a** and **8b** can be acylated with either CH_3COCl or $ClCO_2CH_2CCl_3$ (isomer I, mp 166–168°) to give different acyl derivatives. Borohydride reduction of the *N*-acetyl derivatives **9a** and **9b**, however, gave a common lactone, thereby explaining the δ 8.9 peak in the NMR as belonging to the hydrogen of a 3-*C*-aldehyde.

We believe that the intramolecular dipolar addition products have structure **8**, being isomeric at 4-C (isomer I is thought to have the α-carboxylate while isomer II is the β) and are derived by fragmentation of the intermediate tricyclic isoxazoline (O–N fragmentation, rotation about 3-C–4-C, followed by abstraction of the 4-H to give the conjugated imine.)

That the double bond in **8** is Δ^2 is indicated by the NMR, which shows the NH in isomer I to have an AB pattern and the 4-C proton to be a singlet. The NMR of isomer II shows H_4 to H_7 coupling (2 Hz) which has previously been used to distinguish abnormal (β-carboxylate) stereochemistry at 4-C.[7] The uv absorption, showing λ_{max} at 325 (**8a**) and 332 nm (**8b**), confirms the double bond assignment. Similar uv data on the *N*-acyl derivatives show that acylation does not shift the double bond.

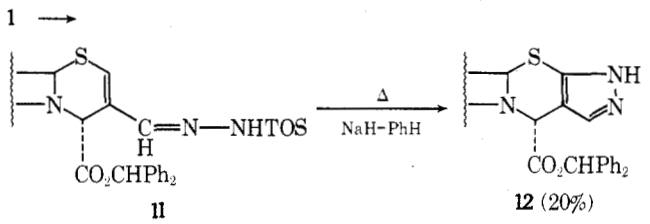
Running the intramolecular dipolar addition rearrange-

Scheme III



ment at lower temperatures failed to allow isolation of the fused isoxazoline, apparently a result of the propensity of the N–O bond to thermally fragment. This type of approach to 2-C–3-C triheterocyclic derivatives, however, has been successfully demonstrated by treatment of the tosylhydrazone **11** with NaH in a Bamford–Stevens[8] type reaction to give the tricyclic pyrazole **12** (198–199°) in 20% yield (Scheme IV). (Double bond orientation has not been determined.)

Scheme IV



Experimental Section

Diphenylmethyl-3-[(dehydroxymethyl-*aci*-nitro)methyl]-7-[2-(2-thienyl)acetamido]-2-cephem 4α-Carboxylate (2). The Δ^2-aldehyde (1) (0.519 g, 1.0 equiv), 0.184 g (2.2 equiv) of *N*-methylhydroxyamine hydrochloride, and 0.237 g (3.0 equiv) of pyridine in 2 ml of CH_2Cl_2 and 40 ml of 2B EtOH was refluxed for 6 hr and then evaporated to dryness. It was taken up in EtOAc, washed with 1 *N* HCl and brine, dried (Na_2SO_4), and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.347 g (63.5%) of nitrone as a pale yellow froth: ir ($CHCl_3$) 1780 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 3.52 (s, 3, *N*-Me), 3.85 (s, 2, thiophene methylene), 5.07 (s, 1, H_4), 5.20 (d, J = 4 Hz, 1, H_6), 5.59 (q, J = 4, 8 Hz, 1, H_7), 6.87 (s, 1, H_2), 9.12 (s, 1, nitrone proton).

Cephem-*N*-methylnitrone Sulfoxide (3). Oxidation was done in $CHCl_3$ at 5° by dropwise addition of 1.1 equiv of *m*-chloroperbenzoic acid. After 1 hr the solution was washed with $NaHCO_3$, H_2O, and brine, dried, and evaporated to 98% of an amorphous gel: NMR (DMSO-d_6) δ 3.35 (s, 3, *N*-Me), 3.90 (s, 2, thiophene methylene), 3.72, 4.43 (AB, J = 18 Hz, 2, H_2), 5.00 (d, J = 5 Hz, 1, H_6), 6.00 (q, J = 5, 8 Hz, 1, H_7), 7.60 (s, 1, nitrone proton).

Cephem-3-(4′-oxazoline) (4a). A solution of the nitrone (0.282 g, 5.0 mmol) and 1 ml (ca. 20 equiv) of dimethyl acetylenedicarboxylate in 30 ml of benzene was refluxed for 45 min and then evaporated to dryness and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.248 g (70.2%) of pale yellow froth: ir ($CHCl_3$) 1800 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.85 (s, 3, *N*-Me), 3.00, 4.15 (AB, J = 18 Hz, 2, H_2), 3.43 (s, 3, CO_2CH_3), 3.86 (s, 3, CO_2CH_3), 3.90 (s, 2, thiophene methylene), 4.45 (d, J = 4 Hz, 1, H_6), 5.75 (s, 1, 2′-oxazoline proton), 6.00 (q, J = 4, 9 Hz, 1, H_7).

Cephem-3-(1′,2′,4′-oxadiazolin-5′-one) (4b). A solution of the nitrone (0.564 g, 1.0 mmol) and 2 ml of phenyl isocyanate in 40 ml of ethylene dichloride and 10 ml of DMF was refluxed for 1 hr. It was then evaporated to dryness and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.351 g (51.3%) of froth: ir ($CHCl_3$) 1808 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.67, 4.12 (AB, J = 18 Hz, 2, H_2), 2.95 (s, 3, *N*-Me), 3.78 (s, 2, thiophene methylene), 4.17 (d, J = 4 Hz, 1, H_6), 5.90 (q, J = 4, 9 Hz, 1, H_7), 6.16 (s, 1, 3′-oxadiazoline ring proton).

Cephem-3-(isoxazolidine) (4c). A solution of the nitrone (1.18 g, 2.09 mmol) in 60 ml of methyl acrylate was gently refluxed for 1 hr. It was then evaporated to dryness and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.429 g (32%) of isomer I and 0.265 g (20%) of isomer II.

Isomer I: ir ($CHCl_3$) 1800 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.55 (s, 3, *N*-Me), 3.42 (s, 3, CO_2CH_3), 3.85 (s, 2, thiophene methylene), 3.0–4.5 (m, 5), 5.30 (d, J = 9 Hz, 1), 6.02 (q, J = 4, 10 Hz, 1, H_7).

Isomer II: ir ($CHCl_3$) 1800 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.59 (s, 3, *N*-Me), 3.76 (s, 3, CO_2CH_3), 3.86 (s, 2, thiophene methylene), 2.0–3.0 (m, 2), 4.0–4.7 (m, 4), 6.0 (q, J = 4, 10 Hz, 1, H_7).

Sulfides of 4a–c. The sulfoxides were reduced using 2–3 equiv of PCl_3 in DMF at room temperature for 45 min. Ethyl acetate was then added and the solution was washed with $NaHCO_3$ and NaCl, dried (Na_2SO_4), evaporated, and chromatographed on silica gel using a toluene–ethyl acetate gradient to give the corresponding sulfides.

Cephem-3-(4′-oxazoline) (30%): ir ($CHCl_3$) 1790 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.86 (s, 3, *N*-Me), 3.65 (s, 3, CO_2CH_3), 3.85 (s, 3, CO_2CH_3), 3.99 (s, 2, thiophene methylene), 5.00 (d, J = 4 Hz, 1, H_6), 5.65 (s, 1, oxazoline proton), 5.88 (q, J = 5, 9 Hz, 1, H_7).

Cephem-3-(oxadiazolin-5′-one) (35%): ir ($CHCl_3$) 1800 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 3.00 (s, 3, *N*-Me), 3.10, 3.74 (AB, J = 18 Hz, 2, H_2), 3.81 (s, 2, thiophene methylene), 4.70 (d, J = 4 Hz, 1, H_6), 5.80 (q, J = 4, 9 Hz, 1, H_7), 6.08 (s, 1, 3′-oxadiazoline ring proton), 6.78 (d, J = 9 Hz, 1, NH).

Cephem-3-(isoxazolidine). Isomer I (82%): ir ($CHCl_3$) 1790 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.54 (s, 3, *N*-Me), 3.44 (s, 3, CO_2CH_3), 3.80 (s, 2, thiophene methylene), 3.3–4.3 (m, 5), 4.85 (d, J = 4 Hz, 1, H_6), 5.20 (d, J = 9 Hz, 1), 5.80 (q, J = 4, 8 Hz, 1, H_7).

Isomer II (76%): ir ($CHCl_3$) 1788 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 3.80 (s, 3, CO_2CH_3), 3.59 (s, 2, H_2), 3.87 (s, 2, thiophene methylene), 4.0–4.7 (m, 2), 4.99 (d, J = 4 Hz, 1, H_6), 5.80 (q, J = 4, 9 Hz, 1, H_7), 6.80 (d, J = 9 Hz, 1, NH).

Cephem-3-*C*-carboxamide (5) and Imide (6). The nitrone **2** (0.548 g) was dissolved in 30 ml of distilled acetic anhydride, acetic acid (4 drops) was added, and the solution was heated at 80° for 10 min and then cooled in an ice bath. Evaporation to dryness followed by chromatography on silica gel using a toluene–ethyl acetate gradient gave 0.161 g (27%) of the faster moving imide **6** and 0.287 g (52%) of the amide **5**.

5: needles from CH_2Cl_2–hexane; mp 196–197°; ir ($CHCl_3$) 1788 cm^{-1} (β-lactam); NMR (DMSO-d_6) δ 2.73 (d, J = 4 Hz, 3, N-Me), 3.85 (s, 2, thiophene methylene), 5.09 (d, J = 4 Hz, 1, H_6), 5.55 (q, J = 4, 8 Hz, 1, H_7), 5.70 (s, 1, H_4), 8.21 (d, J = 4 Hz, 1, NHMe). Anal. Calcd for $C_{28}H_{25}N_3O_5S_2$: C, 61.41; H, 4.60; N, 7.67. Found: C, 61.20; H, 4.42; N, 7.54.

6: ir ($CHCl_3$) 1792 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 2.07 (s, 3, $COCH_3$), 2.87 (s, 3, N-Me), 3.75 (s, 2, thiophene methylene), 5.10 (d, J = 4 Hz, 1, H_6), 5.50 (q, J = 4, 7 Hz, 1, H_7), 5.70 (s, 1, H_4).

3-Formyl-2-(methylamino)-2-cephem (8). The nitrone **2** (2.45 g, 4.48 mmol) in 100 ml of dry toluene was refluxed for 3 hr, evaporated to dryness, and chromatographed on silica gel using a hexane–toluene–ethyl acetate gradient to give 1.22 g of isomer I (eluted first) and 0.54 g of isomer II.

8a isomer I: needles from toluene–hexane; mp 176–177° (4-*C*-PNB, mp 192–193°); ir ($CHCl_3$) 1782 cm^{-1} (β-lactam); NMR (60 and 220 MHz) ($CDCl_3$) δ 2.90 (d, J = 4 Hz, 3, N-Me), 3.91 (s, 2, thiophene methylene), 5.27 (s, 1, H_4), 5.44 (d, J = 4 Hz, 1, H_6), 5.52 (q, J = 4, 8 Hz, 1, H_7), 8.86 (s, 1, CHO), 11.53, 11.62 (AB, J = 4 Hz, 1, NH); λ_{EtOH} 325 nm (ϵ 14,700). Anal. Calcd for $C_{28}H_{25}N_3O_5S_2$: C, 61.40; H, 4.60; N, 7.67. Found: C, 61.65; H, 4.38; N, 7.77.

8b isomer II: ir ($CHCl_3$) 1780 cm^{-1} (β-lactam); NMR (60 and 100 MHz) ($CDCl_3$) δ 2.86 (d, J = 4 Hz, 3, N-Me), 3.75 (s, 2, thiophene methylene), 4.97 (d, J = 2 Hz, 1, H_4), 5.02 (d, J = 4 Hz, 1, H_6), 5.40 (m, 1, H_7), 8.90 (s, 1, CHO) (220 MHz on D_2O shake shows the multiplet at 5.40 as a q, J = 2, 4 Hz, and shows H_4 to H_7 coupling); λ_{EtOH} 332 nm (ϵ 11,000).

2-(*N*-Methyl,*N*-acetyl)-3-formyl-2-cephem (9). Acetylation of **8a** and **8b** was accomplished in cold (5°) THF using 1.1 equiv of acetyl chloride and 2.0 equiv of $NaHCO_3$ for 40 min. The reaction mixture was combined with ETOAc, washed with $NaHCO_3$, H_2O, and brine, evaporated, and chromatographed on silica gel to acetylated derivatives **9a** (79%) from **8a** and **9b** (69%) from **8b**. The NMR spectra are similar, both showing N-methyl singlets, the major difference being the H_4 proton (**9a** δ 5.67, **9b** δ 5.15).

2-(*N*-Methyl,*N*-acetyl)-3-cephem Lactone (10). 9a (0.325 g) in 15 ml of dioxane plus 8 ml of water was cooled to ca. 5° and treated with 4 equiv of $NaBH_4$ in 2 ml of water for 15 min; 1 ml of 1 N HCl was added and when the reaction had ceased the mixture was diluted with EtOAc, washed with 1 N HCl and brine, evaporated, and chromatographed on silica gel to give 0.095 g (42%) of lactone. A similar run on **9b** gave 51% identical lactone: ir ($CHCl_3$) 1810 cm^{-1} (β-lactam); mass 407 (theory 407.46); NMR ($CDCl_3$) δ 2.12 (s, 3, N-Ac), 2.93 (s, 3, N-Me), 3.87 (s, 2, thiophene methylene), 4.85 (br s, 2, lactone methylene), 5.20 (d, J = 4 Hz, 1, H_6), 6.02 (q, J = 4, 9 Hz, 1, H_7), 6.70 (s, 1, H_2); λ_{EtOH} 255 nm (ϵ 10,500).

Tricyclic Pyrazole 12. The 3-formyl-2-cephem **1** was combined with 1.1 equiv of tosylhydrazine in 2B EtOH and refluxed for 1 hr. It was then evaporated to dryness and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 88% tosylhydrazone as a white froth: 0.609 g (0.89 mmol) of tosylhydrazone in 50 ml of dry benzene was treated with 1.2 equiv of 50% NaH and refluxed for 15 min. It was then cooled to room temperature, washed with 1 N HCl and brine, evaporated, and chromatographed on silica gel using a toluene–ethyl acetate gradient to give 0.092 g (20%) of pyrazole as a crystalline white solid: needles from acetone–hexane: mp 198–199°; ir ($CHCl_3$) 1765 cm^{-1} (β-lactam); NMR (DMSO-d_6) δ 3.80 (s, 2, thiophene methylene), 5.37 (d, J = 4 Hz, 1, H_6), 5.57 (q, J = 4, 8 Hz, 1, H_7), 5.93 (s, 1, H_4), 7.79 (br s, 1, olefinic proton of pyrazole), 13.15 (br s, 1, NH of pyrazole). Anal. Calcd for $C_{27}H_{22}N_4O_4S_2$: C, 61.12; H, 4.18; N, 10.56; S, 12.09. Found: C, 60.96; H, 4.11; N, 10.53; S, 12.00.

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Registry No.—**1**, 55331-32-3; **2**, 55569-95-4; **3**, 55569-96-5; **4a**, 55569-97-6; **4a** sulfide, 55569-98-7; **4b**, 55569-99-8; **4b** sulfide, 55570-00-8; **4c**, 55570-01-9; **4c** sulfide, 55570-02-0; **5**, 55570-03-1; **6**, 55570-04-2; **7**, 55570-05-3; **8a**, 55570-06-4; **8b**, 55570-07-5; **9a**, 55570-08-6; **9b**, 55570-09-7; **10**, 55570-10-0; **11**, 55570-11-1; **12**, 55570-12-2.

References and Notes

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Nucleophilic Adducts of *N*-*tert*-Butyloxycarbonyl-1,1,1,3,3,3-hexafluoroisopropylimine. Facile Hydrolysis of Imidazole-Based Adducts[1,2]

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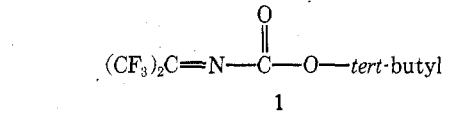
During the course of studies toward new blocking groups for the imidazole moiety of histidine,[3] we synthesized *N*-*t*-Boc-hexafluoroisopropylimine (**1**) and prepared its adducts with various nucleophiles including imidazole (adduct **2a**), N^{α}-Z-L-his-OCH_3 (adduct **2b**), water (adduct **3a**), methanol (adduct **3b**), and *tert*-butyl mercaptan (adduct **3c**). It



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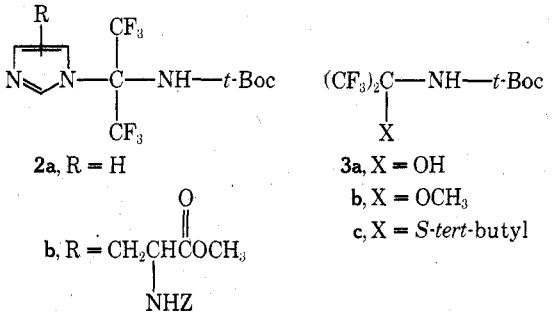

2a, R = H

3a, X = OH
b, X = OCH_3
c, X = *S*-*tert*-butyl

b, R = $CH_2CHCOCH_3$ (NHZ)

was found that although **3b** and **3c** are hydrolytically stable, the imidazole-based adducts **2a** and **2b** undergo facile hydrolysis; **2a** decomposes upon standing in air giving *O*-*tert*-butyl carbamate and **2b** cleaves in acetonitrile solution to which a small amount of water is added giving the carbamate and N^{α}-Z-his-OCH_3. This is surprising in view of the stability of many 1,1,1,3,3,3-hexahalopropanes bearing two heteroatoms at carbon 2 including **3b** and **3c** (unchanged after 124 and 179 hr in an aqueous environment), the incredible stability in both acid and base of ketals and *gem*-amino ethers of fluorinated ketones,[3-5] and the stability of analogs of **2b** containing a single trifluoromethyl group derived from trifluoroacetaldehyde.[6] Simple *gem*-diamines based on hexafluoroacetone have been reported to decompose with HCl in ether.[7] Details of the hydrolysis of **2b** were examined by NMR spectroscopy.