stirred at reflux for 7 h. The bulk of the solvent was then removed in vacuo and the residue acidified with dry ice. The precipitate was taken up in Et_2O. The organic layer was washed with H_2O and brine and taken to dryness. The residue was recrystallized from Et_2O–SSB containing a few drops H_2O to give 8.55 g (81%) of product: mp 98–100 °C; m/e^+ 229. Anal. ($C_{15}H_{19}NO$) C, H, N.

endo-**5-Phenylbicyclo[3.3.1]nonyl-2-amine Hydrochloride (12).** A solution of 4.0 g (0.0175 mol) of the oxime and 8 ml of Ac_2O in 20 ml of pyridine was allowed to stand at room temperature for 5 h. The mixture was then poured into ice–H_2O and the precipitate taken up in Et_2O–C_6H_6. The organic layer was washed in turn with H_2O, ice-cold 2.5 N HCl, H_2O, and brine and taken to dryness. The NMR of the residue was in agreement with the structure.

To an ice-cooled solution of the residue in 50 ml of THF there was added 25 ml of 1 N B_2H_6 in THF. Following 17 h of standing in the cold 1 ml of H_2O was added dropwise and the bulk of the solvent removed in vacuo. The residue was stirred with 100 ml of 2.5 N HCl covered with Et_2O. At the end of 3 h the mixture was made strongly basic and extracted with Et_2O. This extract was washed with H_2O and brine and taken to dryness. The residue was dissolved in a small amount of Et_2O and treated with HCl in Et_2O. The precipitated solid was recrystallized twice from MeOH–EtOAc to give 1.30 g (30%) of product: mp 290–295 °C; m/e^+ 215. Anal. ($C_{15}H_{22}ClN$) H, N; C, calcd, 71.54; found, 72.13.

endo-**4′-Fluoro-4-(5-phenylbicyclo[3.3.1]non-2-ylamino)-butyrophenone Hydrochloride (13).** A mixture of the free base from 1.30 g (0.0052 mol) of the HCl salt, 1.04 g of KI, 1.61 g of K_2CO_3, and 1.50 g of the neopentylglycol ketal of 4′-chloro-*p*-fluorobutyrophenone in 30 ml of DMF was stirred for 17 h at 90 °C. The solvent was then removed in vacuo and the residue diluted with H_2O and C_6H_6. The organic layer was washed with H_2O and brine and taken to dryness.

A solution of the residue in 5 ml of 2.5 N HCl and 10 ml of MeOH was stirred at room temperature for 3 h. The bulk of the solvent was removed in vacuo. The residue was washed with Et_2O and then extracted with CH_2Cl_2. This last extract was taken to dryness and the residue recrystallized twice from CH_2Cl_2–Me_2CO. There was obtained 0.68 g (27%) of product: mp 197–198 °C. Anal. ($C_{25}H_{31}ClFNO$) C, H, N.

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Synthesis of Cephalosporin-4-aldehydes[1]

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The first reported synthesis of cephalosporin-4-aldehyde derivatives has been achieved via Moffatt oxidation of the corresponding 4-hydroxymethylcephalosporins. The aldehyde **1** was converted into a number of polar derivatives, in particular the acrylic acid derivative **13** which is the 4-vinylogue of sodium cephalothin. None of the new cephalosporin derivatives possessed useful antibacterial activity.

Although the synthesis of the penicillin-3-aldehyde system was achieved a number of years ago,[2] the corresponding cephalosporin-4-aldehyde system has not to date been described. In connection[3,4] with work involving total synthesis of cephalosporin antibiotics carried out in our laboratories, a convenient synthesis of 3-acetoxymethyl-7β-[2-(2-thienyl)acetamido]ceph-3-em-4-carboxaldehyde (**1**) was required, and we now report the achievement of this objective. In addition, with the ceph-3-em-4-carboxaldehyde system available, we were able to prepare a number of new cephalosporin derivatives in which the carboxylic acid function is replaced by other polar groups.

Chemistry. It was felt that on account of the α,β-unsaturation present in ceph-3-em derivatives, the chemistry involved would not necessarily parallel that previously described[2] for the penam system. As there are a large number of methods available for the oxidation of primary alcohols to the corresponding aldehydes, the known alcohol **2**[5] was selected for study.

Initial attempts at oxidizing the alcohol **2** to the corresponding aldehyde **1** using a number of standard procedures were discouraging. Since it was suspected that sensitivity of the desired aldehyde **1** was the problem, the alcohol **9** was prepared via *m*-chloroperbenzoic acid treatment of the alcohol **2** with the hope that the corresponding aldehyde **10** would be more easily handled. This indeed turned out to be the case, when application of the particularly mild Moffatt oxidation[6] to the alcohol **9** led to the aldehyde **10** in 80% yield.

When similar conditions were applied to the alcohol **2**, the reaction appeared to have proceeded (precipitation of dicyclohexylurea, darkening of color), but the desired aldehyde **1** could not be isolated from the crude product using chromatography. Examination of the crude product using NMR showed that it was essentially a mixture of the aldehyde **1** and dicyclohexylurea. The problem of isolating **1** was solved by treating the crude product with EtOH and *p*-TsOH and chromatographing the resulting material on silica gel to give the diethyl acetal **3** (62% yield based on **2**). Similarly, treatment of the crude aldehyde in THF solution with ethylene glycol and *p*-TsOH afforded the ethylene acetal **4** (45% yield based on **2**).

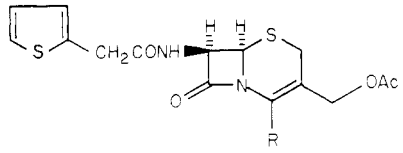
Conversion of the acetal **3** to the aldehyde **1** was readily achieved by exposing **3** in dioxane to dilute hydrochloric acid, whereupon the aldehyde **1** was obtained in 45% yield. The oxime **5**, methoxime **6**, semicarbazone **7**, and carboxymethoxime **8** derivatives of **1** were readily prepared by reacting the aldehyde briefly with an excess of the appropriate reagent.

Upon treatment with diphenylmethoxycarbonylmethylenetriphenylphosphorane, the aldehyde **1** afforded the olefin **11** in 40% yield. The trans configuration was assigned on account of the observed coupling constant of 15 Hz for the olefinic protons. Removal of the carboxyl protecting group of **11** afforded the acid **12** which was converted to the sodium salt (**13**) for biological evaluation.

Table I

Microorganism	MIC, μg/ml[a]							
	1	4	5	6	7	8	13	Cephalothin
Staph. aureus[b]	30	>100	>100	>100	>100	>100	>100	0.3
Str. pyogenes[c]	30	>100	>100	>100	>100	>100	>100	<0.1
E. coli[d]	>100	>100	>100	>100	>100	>100	>100	30.0
K. pneumoniae[e]	>100	>100	>100	>100	>100	>100	>100	1.0
Pr. vulgaris[f]	>100	>100	>100	>100	>100	>100	>100	>100.0

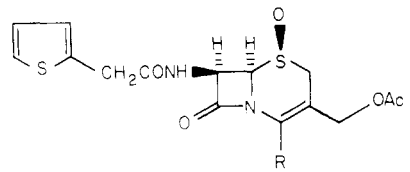
[a] The in vitro antibacterial activities are reported as minimum inhibitory concentrations (MIC's) in μg/ml. The MIC's were determined in threefold dilution by the agar inclusion method. [b] ATCC No. 6538P. [c] ATCC No. 8668. [d] ATCC No. 25922-1. [e] ATCC No. 10031-2. [f] ATCC No. 9484.



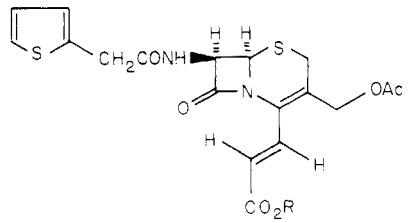
1, R = CHO
2, R = CH_2OH
3, R = $CH(OEt)_2$

4, R = 

5, R = CH=NOH
6, R = CH=NOMe
7, R = $CH=NNHCONH_2$
8, R = $CH=NOCH_2CO_2H$



9, R = CH_2OH
10, R = CHO



11, R = $CHPh_2$
12, R = H
13, R = Na

Biological Activities. The new cephalosporins **1**, **4–8**, and **13** were tested in vitro against several strains of gram-positive and gram-negative bacteria, and the results are shown in Table I. All exhibited considerably reduced antibacterial activity compared with the reference compound, cephalothin. This result was particularly noteworthy in the case of **13**, which differs from sodium cephalothin only by the insertion of a double bond between the cephem nucleus and the carboxylate group. Modification of the 4-carboxyl group by other workers led to compounds exhibiting similarly disappointing biological results.[5,7] Thus our findings further support the conclusion that a carboxylic acid function, directly attached at the 4 position of the cephalosporin nucleus, is necessary if useful antibacterial activity is to be observed.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 237B spectrometer, and ultraviolet spectra were determined with a Cary 14 instrument. NMR spectra were obtained with Varian A-60 and HA-100 instruments, and chemical shifts are given in parts per million from Me_4Si. For AB quartets, the chemical shift given is for the middle of the respective doublet, rather than the correct chemical shift. Elemental analyses were performed by the analytical department of Syntex Research, Institute of Organic Chemistry, and are within ±0.4% of calculated values.

3-Acetoxymethyl-4-hydroxymethyl-7β-[2-(2-thienyl)-acetamido]ceph-3-em 1-Oxide (9). A solution of the alcohol **2**[5] (1 g, 2.63 mmol) in CH_2Cl_2 (40 ml) was stirred at 0 °C and *m*-chloroperbenzoic acid was added in portions, with TLC examination between additions. When optimal conversion was observed (about 1.2 equiv of reagent added), the organic layer was washed with saturated sodium bicarbonate solution and dried (Na_2SO_4) and the solvent was evaporated to give 1.1 g (72%) of a white solid. This was chromatographed on silica gel eluting with CH_2Cl_2–acetone (7:3), giving 0.75 g (49%) of the sulfoxide **9** as a white solid: mp 207–208 °C; $[\alpha]_D$ +54° (*c* 0.5, Me_2SO); ir (KBr) 1765 cm^{-1}. Anal. ($C_{16}H_{18}N_2O_6S_2$) C, H, N.

3-Acetoxymethyl-7β-[2-(2-thienyl)acetamido]ceph-3-em-4-carboxaldehyde 1-Oxide (10). A solution of the alcohol **9** (200 mg, 0.51 mmol) and DCC (360 mg, 1.75 mmol) in Me_2SO (5 ml) was stirred under N_2 at 20 °C and 50 μl (0.60 mmol) of dichloroacetic acid was added. After 5 min the mixture was diluted with EtOAc and washed twice with water and with brine, dried (Na_2SO_4), and filtered and the solvent was evaporated. The residue was chromatographed on silica gel eluting with CH_2Cl_2–acetone (7:3), giving 157 mg (80%) of the aldehyde **10** as a white solid: mp 186–188 °C dec; $[\alpha]_D$ +162° (*c* 0.5, dioxane); ir (KBr) 1785 cm^{-1}; NMR ($CDCl_3$) 2.03 (3 H, s, OAc), 3.67, 4.01 (2 H, AB q, *J* = 19 Hz, 2-CH_2), 3.75, 3.94 (2 H, AB q, *J* = 15 Hz, thiophene methylene), 4.87 (1 H, d, *J* = 4.5 Hz, 6-H), 4.88, 5.23 (2 H, AB q, *J* = 13 Hz, CH_2OAc), 5.82 (1 H, dd, *J* = 4.5, 8 Hz, 7-H), 6.8–7.0 (2 H, m, thiophene H_2), 7.2–7.5 (1 H, m, thiophene H), 8.4 (1 H, d, *J* = 8 Hz, NH), 10.01 (1 H, s, CHO). Anal. ($C_{16}H_{16}N_2O_6S_2$) C, H, N.

3-Acetoxymethyl-7β-[2-(2-thienyl)acetamido]-ceph-3-em-4-carboxaldehyde Diethyl Acetal (3). A solution of the alcohol **2** (200 mg, 0.53 mmol) and DCC (360 mg, 1.75 mmol) in Me_2SO (5 ml) was stirred under N_2 at 20 °C and 30 μl (0.37 mmol) of dichloroacetic acid was added. After 5 min the mixture was diluted with EtOAc and washed twice with water and brine, dried (Na_2SO_4), and filtered and the solvent was evaporated. The residue was dissolved in a mixture of EtOAc (2 ml) and EtOH (10 ml), and *p*-TsOH (50 mg, 0.37 mmol) was added. After stirring at 20 °C for 4 h, the mixture was diluted with water and extracted twice with EtOAc, the combined extracts were washed with dilute $NaHCO_3$ solution and brine, dried (Na_2SO_4), and filtered, and the solvent was evaporated to give a brown oily residue. This was purified using preparative TLC on silica gel developing with CH_2Cl_2–acetone (19:1), giving 140 mg (62%) of the acetal **3** as an oil: $[\alpha]_D$ −35° (*c* 0.5, $CHCl_3$); ir ($CHCl_3$) 1775 cm^{-1}; NMR ($CDCl_3$) 1.19 (6 H, t, *J* = 7 Hz, CH_2CH_3), 2.04 (3 H, s, OAc), 3.18, 3.47 (2 H, AB q, *J* = 17.5 Hz, 2-CH_2), 3.4–3.9 (4 H, m, CH_2CH_3), 3.85 (2 H, s, thiophene methylene), 4.85, 5.08 (2 H, AB q, *J* = 12 Hz, CH_2OAc), 4.92 (1 H, d, *J* = 5 Hz, 6-H), 5.53 [1 H, s, $CH(OEt)_2$], 5.77 (1 H, dd, *J* = 5, 9 Hz, 7-H), 6.35 (1 H, d, *J* = 9 Hz, NH), 6.9–7.4 (3 H, m, thiophene H).

3-Acetoxymethyl-7β-[2-(2-thienyl)acetamido]ceph-3-em-4-carboxaldehyde Ethylene Acetal (4). A solution of the alcohol **2** (220 mg, 0.58 mmol) and DCC (400 mg, 2 mmol) in Me_2SO (5 ml) was stirred at 20 °C under N_2 and dichloroacetic acid (30 μl) was added. After 4 min the mixture was diluted with EtOAc and washed twice with water and brine, dried (Na_2SO_4), and filtered and the solvent was evaporated. The residue was dissolved in THF (5 ml), ethylene glycol (1 ml) and *p*-TsOH (50

mg) were added, and the mixture was stirred at 40 °C for 5 h. The mixture was diluted with EtOAc and washed with water, dilute $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and filtered and the solvent was evaporated. The residue was purified using preparative TLC on silica gel developing with benzene–EtOAc (7:3), giving 102 mg (42%) of the ethylene acetal **4** as a white solid: mp 171–172 °C; $[\alpha]_D$ −48° (*c* 1.0, $CHCl_3$); ir (KBr) 1775 cm^{-1}; NMR ($CDCl_3$) 2.03 (3 H, s, OAc), 3.20, 3.51 (2 H, AB q, J = 18 Hz, 2-CH_2), 3.82 (2 H, s, thiophene methylene), 3.7–4.3 (4 H, m, ethylenedioxy), 4.75 (2 H, s, CH_2OAc), 4.89 (1 H, d, J = 5 Hz, 6-H), 5.19 (1 H, dd, J = 5, 9 Hz, 7-H), 5.30 (1 H, s, $CHO_2C_2H_4$), 6.30 (1 H, d, J = 9 Hz, NH), 6.8–7.4 (3 H, m, thiophene). Anal. ($C_{18}H_{20}N_2O_6S_2$) C, H, N.

3-Acetoxymethyl-7β-[2-(2-thienyl)acetamido]ceph-3-em-4-carboxaldehyde (1). The diethyl acetal **3** (100 mg, 0.23 mmol) was dissolved in dioxane (5 ml) and 2 N hydrochloric acid (2 ml) was added. The mixture was stirred at 20 °C under N_2 until by TLC the acetal was no longer present (ca. 2 h). The mixture was diluted with water and extracted twice with EtOAc, the combined extracts were washed with water and brine and then dried (Na_2SO_4), and the solvent was evaporated. The residue was dissolved in a minimum of CH_2Cl_2 and upon adding ether a white crystalline solid separated. The solid was collected by filtration and dried under vacuum to give 40 mg (45%) of the aldehyde **1**: mp 132–134 °C dec; $[\alpha]_D$ +42° (*c* 0.5, $CHCl_3$); uv (EtOH) 233, 276 nm (ε 12 100, 5000); ir (KBr) 1775, 1745, 1700, 1665 cm^{-1}; NMR ($CDCl_3$) 2.08 (3 H, s, OAc), 3.39, 3.63 (2 H, AB q, J = 18.5 Hz, 2-CH_2), 3.85 (2 H, s, thiophene methylene), 4.96 (1 H, d, J = 5 Hz, 6-H), 5.05 (2 H, s, CH_2OAc), 5.85 (1 H, dd, J = 5, 8.5 Hz, 7-H), 6.53 (1 H, d, J = 8.5 Hz, NH), 6.8–7.4 (3 H, m, thiophene), 9.93 (1 H, s, CHO). Anal. ($C_{16}H_{16}N_2O_5S_2$) C, H, N.

Oxime Derivative 5. The alcohol **2** (200 mg, 0.51 mmol) was oxidized as described for the preparation of **3**. The crude aldehyde was dissolved in THF (10 ml), filtered to remove some dicyclohexylurea, and then treated with hydroxylamine hydrochloride (72 mg, 1 mmol), potassium acetate (102 mg, 1 mmol), water (2 ml), and ethanol (4 ml). After stirring at room temperature for 10 min, the mixture was diluted with water and extracted twice with EtOAc. The combined EtOAc extracts were washed with brine and dried (Na_2SO_4) and the solvent was evaporated to give a residue which was purified using preparative TLC on silica gel developing with CH_2Cl_2–acetone (9:1). Obtained was 70 mg (34%) of the oxime **5**: mp 176–177 °C; $[\alpha]_D$ +53° (*c* 0.5, dioxane); ir (KBr) 1680 cm^{-1}; NMR (Me_2SO-d_6 + D_2O) 2.02 (3 H, s, OAc), 3.54 (2 H, AB q, J = 18 Hz, 2-CH_2), 3.76 (2 H, s, thiophene methylene), 4.79 (2 H, s, CH_2OAc), 5.09 (1 H, d, J = 5 Hz, 6-H), 5.61 (1 H, d, J = 5 Hz, 7-H), 6.9–7.0 (2 H, m, thiophene), 7.3–7.4 (1 H, m, thiophene), 8.04 (1 H, s, C*H*NOH). Anal. ($C_{16}H_{17}N_3O_5S_2$) C, H, N.

Methoxime Derivative 6. The preparation was carried out as described for the oxime **5**, except that an equivalent amount of methoxylamine hydrochloride was employed. Obtained was 100 mg (45%) of the methoxime **6** as needles: mp 143–144 °C; $[\alpha]_D$ −7° (*c* 0.5, $CHCl_3$); ir (KBr) 1680 cm^{-1}. Anal. ($C_{17}H_{19}N_3O_5S_2$) C, H, N.

Semicarbazone Derivative 7. The preparation was carried out as described for the oxime **5**, except that an equivalent amount of semicarbazide hydrochloride was employed. Obtained was 60 mg of a white powder: mp 222–226 °C (20%); $[\alpha]_D$ +185° (*c* 0.5, Me_2SO); ir (KBr) 1770 cm^{-1}. Anal. ($C_{17}H_{19}N_5O_5S_2$) C, H, N.

Carboxymethoxime Derivative 8. The preparation was carried out as described for the oxime **5**, except that an equivalent amount of carboxymethoxylamine hemihydrochloride was employed. The reaction mixture was diluted with water and acidified using dilute hydrochloric acid. The mixture was extracted twice with aqueous $NaHCO_3$ solution. The $NaHCO_3$ extracts were acidified using dilute hydrochloric acid and extracted twice with EtOAc. The combined EtOAc extracts were washed with brine, dried (Na_2SO_4), and evaporated to give a crystalline residue, which yielded 70 mg (30%) of needles when recrystallized from EtOAc–hexane: mp 139–141 °C; $[\alpha]_D$ +37° (*c* 0.5, Me_2SO); ir (KBr) 1775 cm^{-1}. Anal. ($C_{18}H_{19}N_3O_7S_2$) C, H, N.

Diphenylmethyl 3-Acetoxymethyl-7β-[2-(2-thienyl)-acetamido]ceph-3-em-4-(*trans*-acrylate) (11). The alcohol **2** (200 mg, 0.51 mmol) was oxidized as described for the preparation of **3**. The crude aldehyde was dissolved in 5 ml of CH_2Cl_2 and filtered to remove some dicyclohexylurea, and the filtrate was treated with diphenylmethoxycarbonylmethylenetriphenylphosphorane (150 mg, prepared by treating bromoacetic acid in turn with diphenyldiazomethane, triphenylphosphine, and base). After 15 min the mixture was concentrated and the residue purified using preparative TLC on silica gel, developing with CH_2Cl_2–acetone (19:1). Obtained was 180 mg of a colorless oil which deposited 120 mg of crystals of **11** (40%) from benzene–hexane: mp 95–100 °C; $[\alpha]_D$ +51° (*c* 1.0, $CHCl_3$); uv (EtOH) 287 nm (ε 11 700); ir (KBr) 1785, 1745, 1720 1665 cm^{-1}; NMR ($CDCl_3$) 2.01 (3 H, s, OAc), 3.24, 3.51 (2 H, AB q, J = 18 Hz, 2-CH_2), 3.81 (2 H, s, thiophene methylene), 4.64, 4.80 (2 H, AB q, J = 13 Hz, CH_2OAc), 4.95 (1 H, d, J = 5 Hz, 6-H), 5.77 (1 H, dd, J = 5, 9 Hz, 7-H), 6.39 (1 H, d, J = 15 Hz, vinyl), 6.68 (1 H, d, J = 9 Hz, NH), 6.8–7.5 (14 H, m, aromatic H), 7.59 (1 H, d, J = 15 Hz, vinyl). Anal. ($C_{31}H_{28}N_2O_6S_2$) C, H, N.

Sodium 3-Acetoxymethyl-7β-[2-(2-thienyl)acetamido]-ceph-3-em-4-(*trans*-acrylate) (13). A solution of the ester **11** (120 mg, 0.2 mmol) in anisole (0.5 ml) was stirred at 0 °C and trifluoroacetic acid (2.5 ml) was added. After 2 min of vigorous stirring at 0 °C, the mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc and extracted twice with dilute sodium bicarbonate solution. The combined extracts were acidified to pH 1.5 using dilute hydrochloric acid, and the mixture was extracted twice with EtOAc. The combined extracts were washed with brine and dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the acid **12**. A solution of **12** in EtOAc was treated with a solution of 2 equiv of sodium 2-ethylhexanoate in EtOAc, and a small amount of ether was added to complete the precipitation of the sodium salt, which was collected by filtration, washed with ether–EtOAc (1:1), and dried under vacuum to give 52 mg (58%) of the sodium salt **13** as a white powder: decomposed on attempted melting point determination; uv (H_2O) 276 nm (ε 10 800); ir (KBr) 1775, 1745, 1665, 1575 cm^{-1}; NMR (Me_2SO-d_6) 2.01 (3 H, s, OAc), 3.45 (2 H, brs, 2-CH_2), 3.76 (2 H, s, thiophene methylene), 4.73 (2 H, brs, CH_2OAc), 5.04 (1 H, d, J = 4.5 Hz, 6-H), 5.60 (1 H, dd, J = 4.5, 8 Hz, 7-H), 6.10 (1 H, d, J = 15 Hz, olefinic), 6.8–7.4 (4 H, m, olefinic H + thiophene), 9.10 (1 H, d, J = 8 Hz, NH).

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