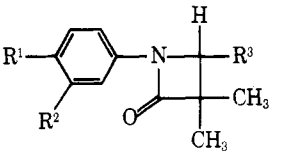
Table I



Compd no.	R^1	R^2	R^3	$\bar{\nu}$, cm^{-1}, β-lactam C=O	$\delta_{TMS}^{CDCl_3}$ CH	$\delta_{TMS}^{CDCl_3}$ $(CH_3)_2$	Formula	Yield, %	Microorganism	MIC, μg/ml
3a	H	CF_3	NMe_2	1765	4.53 (s)	1.33 (s)	$C_{14}H_{17}F_3N_2O$	100	*Staphylococcus aureus* 3055	10
									S. aureus 3074	10
									Streptococcus fecalis X66	100
									Bordetella bronchiseptica	100
3b	H	Cl	NMe_2	1765	4.43 (s)	1.30 (s)	$C_{13}H_{17}ClN_2O$	100	*S. aureus* 3055	10
									S. aureus 3074	100
									S. fecalis X66	100
									B. bronchiseptica	100
3c	H	CF_3		1765	4.45 (s)	1.37 (s)	$C_{16}H_{19}F_3N_2O_2$	96.2	*S. aureus* 3055	10
									S. aureus 3074	100
									S. fecalis X66	100
3d	CH_3	Cl		1765	4.40 (s)	1.33 (s)	$C_{16}H_{21}ClN_2O_2$	95.0	*S. aureus* 3055	10
3e	H	Cl		1765	4.42 (s)	1.33 (s)	$C_{15}H_{19}ClN_2O_2$	93.0	*S. aureus* 3074	10
									S. fecalis X66	100
									B. bronchiseptica	100
3f	Cl	Cl		1765	4.44 (s)	1.33 (s)	$C_{15}H_{18}Cl_2N_2O_2$	91.3	*S. aureus* 3055	10
									S. aureus 3074	10
									B. bronchiseptica	100

by 5.0 ml of dimethyl sulfate. The mixture was stirred vigorously for 16 hr during which time the methylammonium sulfate salt precipitated. The precipitate was filtered, washed with 2-propanol, and dried: yield 8.55 g; mp 169–170°; δ_{TMS}^{DMSO} 7.4 (br s, 4, aryl), 5.95 (br s, 1), 3.5 (s, 3, $-CH_3$), 3.2 (s, 9, *n*-CH_3), 2.4 (s, 3, Ar-CH_3), 1.6 (d, 6, CH_3); ir (Nujol) 1785, 1418, 1240–1215 hood, 1195, 1060, 1015, and 750 cm^{-1}. Anal. ($C_{16}H_{26}N_2O_5S$) N.

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7-*N*-Amidinocephalosporins

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7-Aminocephalosporanic acid *tert*-butyl ester reacts quantitatively at −20° with iminium chlorides to give amidino derivatives. Removal of the *tert*-butyl protecting group with trifluoroacetic acid and treatment with 1 equiv of triethylamine yield the corresponding zwitterions. These compounds were less active than their penicillin analogs.

Amidino derivatives of penicillins have been recently synthesized[1] and are found to exhibit enhanced activity toward gram-negative microorganisms. Amidino analogs of cephalosporins have not previously been reported.

Several approaches to amidine synthesis are available: reaction of an amine with (i) an iminoether hydrochloride;[2] (ii) with an iminochloride;[3] or (iii) with an N-substituted iminium chloride.[4] The first two routes failed when applied to 7-aminocephalosporanic acid (7-ACA) *tert*-butyl ester. This failure was attributed to the fact that the amino group of 7-ACA is weakly basic. Therefore, the iminoether hydrochlorides in alcoholic solution underwent alcoholysis rather than the desired amidine formation.[5]

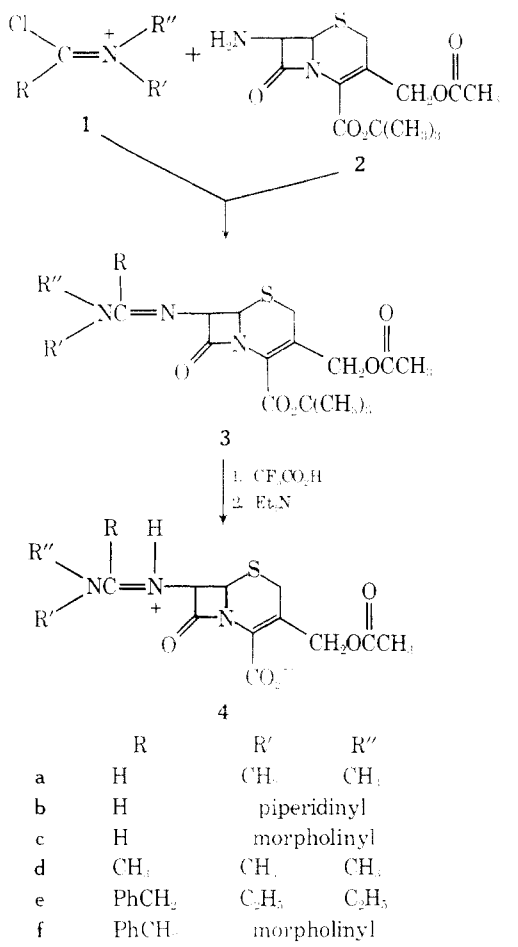
N-Substituted formiminium chlorides (**1**, R = H) are better species and react quantitatively with 7-ACA *tert*-butyl ester (**2**) under very mild conditions. Indeed, the reaction of **1** (R = H) with amine **2** yielded the amidinocephalosporin esters **3** (R = H) which were isolated as free

Table I. 7-Amidinocephalosporanic Acids and Esters

Compd	R	R′	R″	Mp, °C (dec)	Formula	Analyses
3a	H	CH_3	CH_3	114	$C_{17}H_{23}N_5O_5S$	C, H, N, S
3b	H	Piperidinyl		93–94	$C_{21}H_{29}N_5O_5S$	C, H, N, S
3c	H	Morpholinyl		60	$C_{20}H_{27}N_5O_6S$	C, H, N, S
3f	Benzyl	Morpholinyl		147–150	$C_{27}H_{33}O_6N_5S$	C, H, N, S
4a (CF_3CO_2H salt)	H	CH_3	CH_3	144	$C_{19}H_{24}F_3N_5O_7S$	C, H, N, S
4b (CF_3CO_2H salt)	H	Piperidinyl		141	$C_{23}H_{32}F_3N_5O_7S$	C, H, N
4c (CF_3CO_2H salt)	H	Morpholinyl		106	$C_{22}H_{30}F_3N_5O_8S$	C, H, N
4a	H	CH_3	CH_3	158	$C_{19}H_{25}N_5O_5S$	C, H, N, S
4b	H	Piperidinyl		145	$C_{23}H_{31}N_5O_5S \cdot 0.5H_2O$	C, H, N, S
4c	H	Morpholinyl		131	$C_{22}H_{31}N_5O_6S$	C, H, N, S
4f	Benzyl	Morpholinyl		155–158	$C_{29}H_{35}N_5O_6S$	N, S

bases (Scheme I and Tables I and II). The same method was also applied unsuccessfully to acetiminium chloride (**1d**, R = R′ = R″ = CH_3).

Scheme I



	R	R′	R″
a	H	CH_3	CH_3
b	H	piperidinyl	
c	H	morpholinyl	
d	CH_3	CH_3	CH_3
e	$PhCH_2$	C_2H_5	C_2H_5
f	$PhCH_2$	morpholinyl	

When a more highly substituted iminium chloride, such as phenylacetiminium chloride (**1e**, R = $C_6H_5CH_2$; R′ = R″ = C_2H_5), reacted under the above reaction conditions, no amidine was formed. Thus the amidino compound **3f** had to be prepared by reacting the iminochloride of cephaloram *tert*-butyl ester with morpholine, followed by trifluoroacetic acid and triethylamine treatment to give the zwitterion **4f**.

Pure samples of formamidinocephalosporin esters are stable at room temperature. More highly substituted amidinocephalosporins are less stable. We were unable to isolate a pure acetamidino derivative **4d** as a free base.

All amidinocephalosporin esters show a characteristic strong ir band in the 1630–1600-cm^{-1} region, assigned to the NC=N group.

The NMR spectra of 7-*N*-amidinocephalosporins are different from those of 7-amidocephalosporins. In the amido series the C_7H has a chemical shift at ~5.8 ppm, while in the amidino series this proton appears at ~5.3 ppm and is less separated from the chemical shift of the C_6H.

In the mass spectral analysis the formamidinocephalosporin esters **3a–c** yield the molecular ions. The most abundant ion originates from a fragmentation across the β-lactam and thiazine rings (i) (Table III).

Treatment of **3** with trifluoroacetic acid (TFA) cleaves the *tert*-butyl group to yield trifluoroacetates. The trifluoroacetates consumed 2 equiv of tetrabutylammonium hydroxide in dimethylformamide on titration. Addition of 1 equiv of triethylamine in methanol solution enabled the isolation of the corresponding zwitterions **4**.

Both trifluoroacetates and zwitterions upon electrophoresis migrated to the negative electrode at pH 6.5.

The 7-*N*-amidinocephalosporins exhibit low biological activity and are less active than the analogous penicillins.[1] Anyhow they show the same activity toward gram-negative and gram-positive bacteria, while the amidinopenicillins are better against gram-negative bacteria than gram-positive ones. The biological activity of the amidinocephalosporins is given in Table IV.

Experimental Section

All the reactions were carried out in a dry system under an argon atmosphere. Chloroform and methylene chloride were dried over P_2O_5.

Ir spectra were recorded on a Perkin-Elmer 237B. NMR spectra were taken on a Varian A-60 instrument, TMS being used as internal standard. Mass spectra were determined on Atlas MAT CH4 instrument at a temperature of 125° and electron energy of 70 eV. Melting point determinations were conducted in sealed tubes. The elemental analyses for the compounds in Table I are within the acceptable range.

General Procedure. 7-Formamidinocephalosporanic Acid *tert*-Butyl Esters (3a–c). 7-ACA *tert*-butyl ester[6] (4 mmol) and triethylamine (8 mmol) in chloroform (100 ml) were cooled to −20°. Iminium chloride (**1**,[4] 8 mmol) was introduced in one lot, the mixture stirred for 1 hr and washed with a cold saturated $NaHCO_3$ solution, and the organic layer dried ($MgSO_4$). The solvent was evaporated in vacuo at 30–35° bath temperature and the excess of amide removed in high vacuum. The resulting crude light yellow product was used for the next step to prepare **4**.

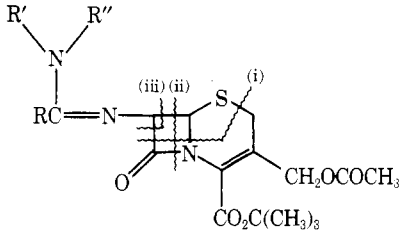
Analytical samples were obtained by recrystallization from ether–hexane (Tables I and II).

7-Amidinocephalosporanic Acid Trifluoroacetates. The ester **3** was treated with dry trifluoroacetic acid (5 ml) at room temperature for 0.5 hr. The acid was removed in vacuo and the product triturated several times with dry ether to yield the pure trifluoroacetate (Tables I and II).

Table II. Spectral Data on 7-Amidinocephalosporins

Compd	Uv λ_{max}^{MeOH}, nm (ϵ)	Ir, cm^{-1}	NMR (δ, ppm)
3a	232 (17,000), 253 sh (9,750)	1775, 1770–1750, 1635 ($CHCl_3$)	1.54 (s, 9, CH_3), 2.08 (s, 3, $COCH_3$), 2.88 (s, 6, NCH_3), 3.37–3.47 (2, CH_2S), 4.58–5.26 (m, CH_2O, C_6H, and C_7H), 7.58 (s, 1, CH=N)($CDCl_3$)
3b	239 (17,000)	1780, 1720, 1630 ($CHCl_3$)	1.4–1.7 (m, CH_2, and s, CH_3), 2.07 (s, 3, $COCH_3$), 3.2–3.5 (m, 4, CH_2N and CH_2S), 4.8–5.2 (m, CH_2O, C_6H, and C_7H), 7.51 (s, 1, CH=N)($CDCl_3$)
3c	238 (14,000)	1775, 1740, 1720, 1630 ($CHCl_3$)	1.54 (s, 9, CH_3), 2.08 (s, 3, $COCH_3$), 3.28–3.48 (m, 6, CH_2N and CH_2S), 3.54–3.80 (m, 4, CH_2O), 4.6–5.2 (m, 4, CH_2O, C_6H, and C_7H), 7.62 (s, 1, CH=N) ($CDCl_3$)
3f	244 (9,800), 256 (9,800)	1770, 1730 sh, 1720 1630 sh, 1600 ($CHCl_3$)	1.5 [s, 9, $C(CH_3)_3$], 2.1 (s, 3, $COCH_3$), 2.9–4.2 (m, CH_2S, CH_2N, CH_2O, and CH_2Ph), 4.7–5.2 (m, 4, CH_2O, C_6H, and C_7H), 7.3 (s, 5, aromatic)($CDCl_3$)
4a (CF_3CO_2H salt)	232 (14,000), 260 sh (7,500)	1790–1750, 1740–1720, 1640 (KBr)	2.05 (s, 3, $COCH_3$), 3.10 (s, NCH_3), 3.30 (s, 3, NCH_3), 3.68 (s, 2, CH_2S), 4.72–5.03 (q, J = 12 Hz, 2, CH_2O), 5.21, 5.70 (q, J = 5 Hz, C_6H and C_7H), 8.22 (s, 1, CH=N)(DMSO-d_6)
4b (CF_3CO_2H salt)	223 (16,000), 267 (7,500)	1780, 1740, 1700, 1640 (KBr)	1.30–1.80 (m, 6, CH_2), 2.05 (s, 3, $COCH_3$), 3.4–3.8 (m, 6, CH_2N, CH_2S), 4.75, 5.08 (q, J = 12 Hz, 2, CH_2O), 5.26, 5.72 (q, J = 5 Hz, 2, C_6H and C_7H), 7.87 (s, 1, CH=N)(DMSO-d_6)
4c (CF_3CO_2H salt)	227 (16,000), 265 sh (7,500)	1780, 1740, 1700, 1640 (KBr)	2.04 (s, 3, $COCH_3$), 3.4–3.9 (m, 10, CH_2, CH_2N, CH_2S), 4.74, 5.08 (q, J = 12 Hz, 2, CH_2O), 5.24, 5.74 (q, J = 5 Hz, 2, C_6H and C_7H), 8.40 (s, 1, CH=N) (DMSO-d_6)
4a	225 (16,400), 265 sh (7,200)	1770, 1730, 1700, 1610 (KBr)	2.05 (s, 3, $COCH_3$), 2.99 [s, 6, $N(CH_3)_2$], 3.43, 3.50 (2, CH_2S), 4.68, 5.04 (q, J = 12 Hz, 2, CH_2O), 5.10, 5.27 (q, J = 5 Hz, 2, C_6H and C_7H), 7.75 (s, 1, CH=N) (DMSO-d_6)
4b	223 (18,000), 267 (12,200)	1820, 1730, 1710, 1615 (KBr)	1.2–1.7 (m, 6, CH_2), 2.02 (s, 3, $COCH_3$), 3.10–3.60 (m, 4, CH_2N, CH_2S), 4.70, 5.00 (q, J = 12 Hz, 2, CH_2O), 5.10, 5.26 (q, J = 5 Hz, 2, C_6H and C_7H), 7.76 (s, 1, CH=N)(DMSO-d_6)
4c	235 (15,500), 265 sh (7,500)	1770, 1730, 1700, 1600 (KBr)	2.02 (s, 3, $COCH_3$), 3.2–3.8 (m, 10, CH_2N, CH_2O, CH_2S), 4.68, 4.97 (q, J = 12 Hz, 2, CH_2O), 5.10, 5.27 (q, J = 5 Hz, C_6H and C_7H), 7.68 (s, 1, CH=N) (DMSO-d_6)
4f	232 (13,800), 254 sh (11,400)	1780, 1730, 1640, 1600 (KBr)	2.05 (s, 3, $COCH_3$), 3.3–4.0 (m, 12, CH_2N, CH_2O, CH_2S, CH_2Ph), 4.2–5.4 (m, 4, CH_2O, C_6H, and C_7H), 7.3 (s, 5, C_6H_5)(DMSO-d_6)

Table III



m/e (rel abundance)

	M^+	i	ii	iii
3a	383 (31)	129 (100)	112 (70)	84 (50)
3b	423 (27)	169 (100)	152 (83)	124 (88)
3c	425 (27)	171 (100)	154 (81)	126 (75)

7-Amidinocephalosporanic Acids. The trifluoroacetates were dissolved in a minimum volume of dry methanol and treated with 1 equiv of triethylamine. The methanol was removed and the residue was stirred with dry 2-propanol (15 ml) for 0.5 hr, filtered in a drybox, washed twice with 2-propanol and then with methanol, and dried. The overall yields of the zwitterions 4 were 50–60% (Tables I and II).

Table IV. Biological Activity of the Amidinocephalosporins (MIC, γ/ml)

Bacteria	4a	4b	4c	4f	Cephalothin
S. aureus Tour	10	100	10	10	0.05
E. coli $0111B_4H_{12}$	50	10	10	50	1
Proteus mirabilis TH3333	50	50	50		10

Cephaloram *tert*-Butyl Ester. 7-Aminocephalosporanic acid *tert*-butyl ester (0.99 g, 3 mmol) was dissolved in 10 ml of methylene chloride. Phenacetyl chloride (0.618 g, 4 mmol) in 3 ml of methylene chloride was added dropwise at such a rate that the mixture was kept at room temperature. The reaction mixture was stirred for 25 min. The resulting organic solution was washed with 5% $NaHCO_3$ (25 ml) and water (2 × 25 ml), dried, filtered, and evaporated. The residue was dissolved in a minimum amount of methylene chloride and precipitated with ether, yielding 1.1 g (82%) of cephaloram *tert*-butyl ester as white crystals: mp 148–150°; mass spectrum M^+ *m/e* 446; ir ($CHCl_3$) 1780, 1730, 1675,

1625 sh, 1595 cm^{-1}; NMR δ ($CDCl_3$) 1.5 [s, 9, $C(CH_3)_3$], 2.08 (s, 3, $COCH_3$), 3.42 (d, 2, CH_2S), 3.65 (s, 2, CH_2Ph), 4.65–5.25 (m, 3, C_6H and CH_2O), 5.85 (q, 1, C_7H), 6.2–6.5 (m, 1, NH), 7.32 (s, 5, aromatic). Anal. ($C_{22}H_{26}N_2O_6S$) C, H, S.

7-(*N*-Morpholinyl)phenylacetamidinocephalosporanic Acid *tert*-Butyl Ester (3f). Phosphorus pentachloride (0.92 g, 4.3 mmol) was dissolved in 10 ml of methylene chloride. Pyridine (0.7 ml, 8.6 mmol) was added and the reaction mixture cooled to −10°. Cephaloram *tert*-butyl ester (0.96 g, 2.15 mmol) was added and stirred at this temperature for 45 min and then at 0° for another 3 hr.

The reaction mixture was poured into 50 ml of 5% $NaHCO_3$ at 0° and the layers were separated. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give the imino chloride[7] of the cephaloram ester as a dark oil: ir ($CHCl_3$) 1780, 1725, 1670 sh, 1630 cm^{-1}; NMR δ ($CDCl_3$) 1.5 [s, 9, $C(CH_3)_3$], 2.1 (s, 3, $COCH_3$), 3.45 (d, 2, CH_2S), 3.95 (s, 2, CH_2Ph), 4.65–5.6 (m, 4, CH_2O + C_6H and C_7H), 7.3 (s, 5, aromatic).

The resulting iminochloride was dissolved in 6 ml of chloroform and cooled to −30°. Morpholine (0.38 ml, 4.3 mmol) in 2 ml of chloroform was added to the reaction mixture. The temperature was kept at −30° for 30 min and then at 0° for another 3.5 hr. The solvent was evaporated and the resulting dark oil was dissolved in ethyl acetate and filtered to remove the morpholine hydrochloride. The organic layer was washed with aqueous 5% $NaHCO_3$, dried, filtered, and evaporated. The oil was dissolved in ether and precipitated with hexane to yield 0.57 g (53%) amidine ester **3f**.

Electrophoresis. All amidines, trifluoroacetates, and zwitterions were subjected to electrophoresis at pH 6.5 (pyridine–acetate buffer), 60 V/cm for 30 min on Whatman No. 1. They migrated 1.2 cm toward the cathode giving rise to pale spots on blue-purple background after consecutive spraying with 0.05 *N* iodine containing 3.5% sodium azide and 1% starch solution.[8]

Nonaqueous Titrations. The compounds **3f** and **4a–c** in DMF solutions were titrated with 0.1 *N* $HClO_4$ in acetic acid and yielded molecular weights within experimental error.

The zwitterions **4a–c** in methanol solution were also titrated with 0.05 *N* $NaOCH_3$ to give the same results.

Biological Activity Evaluation. The in vitro antimicrobial tests were done using Bacto Antibiotic Medium 1 (Difco) agar plates seeded with *Staphylococcus aureus* Tour, *Escherichia coli* $0111B_4H_{12}$, and *Proteus mirabilis* TH3333 (untitable). A zone of inhibition in agar around filter disks that had been wetted with compounds solutions was used as the indication of activity.

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Synthesis of α-1-Noracetylmethadol. A Facile N-Demethylation of α-1-Acetylmethadol

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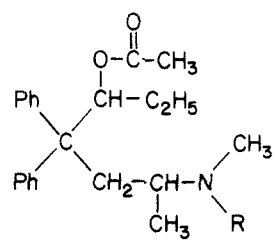
A facile N-demethylation of the narcotic analgesic, α-1-acetylmethadol, was accomplished by allowing it to react with mercuric acetate under reflux in dilute acetic acid. The product, α-1-noracetylmethadol, was isolated as the hydrochloride in 50% yield. Methadone, when allowed to react with mercuric acetate under the same conditions, did not undergo N-demethylation and was recovered unchanged.

The compound α-1-noracetylmethadol (**1a**), a biotransformation product of acetylmethadol (**1b**), has been shown to possess potent antinociceptive activity in the mouse.[2] Studies in laboratory animals[3] and in man[4–6] have suggested that the biotransformation of acetylmethadol (**1b**) is responsible for the time–action characteristics of certain of the pharmacologic effects of this compound. In particular, the relative long duration of suppression of narcotic withdrawal symptoms following administration of **1b** has stimulated both interest in its use in the maintenance treatment of opiate dependence[7,8] and the search for other long-lasting compounds for use in maintenance treatment.

Our studies on the biotransformation of **1b**[4,5] and interest in chemical N-demethylation procedures[9] prompted us to investigate a facile synthetic procedure to obtain significant quantities of **1a** from the more readily available **1b**. Further, it was of interest to us to obtain **1a** as the α-1 diastereoisomer (3*S*,6*S*) from the parent compound **1b** having the same stereochemistry. Compound **1a** could also serve as a convenient synthon for an alternative and more facile synthesis of the corresponding primary amine, which has also been shown to be an active metabolite.[3b,6]



1a, R=H
b, R=CH3

The synthetic objective has now been partially achieved by us in a reaction wherein **1b** is allowed to react with mer-