Structure-Activity Relationships in Cephalosporins Prepared from Penicillins. 1. 7β-Acylamino Derivatives of 3-Benzyl- and 3-(3-Pyridylmethyl)ceph-3-em-4-carboxylic Acids

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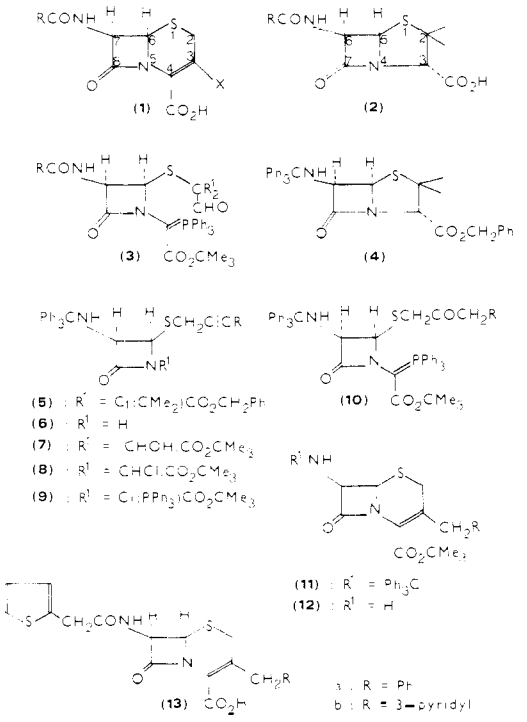
tert-Butyl 7β-aminoceph-3-em-4-carboxylates carrying either benzyl or 3-pyridylmethyl substituents at position 3 have been prepared by a multistep modification of the penicillin nucleus. Acylation of either amine, followed by deprotection, gave a range of new cephalosporins. The relationship between structure and antibacterial activity is discussed. D-Phenylglycine proved to be a preferred side chain in both series.

The very large number of cephalosporins (1) which have been described[1] includes many in which the 3-substituent has been subjected to chemical manipulation. In addition, certain cephalosporins have been prepared by chemical transformation of penicillins (2) utilizing reaction sequences which preserve the β-lactam ring and its associated stereochemistry. Thus Morin and his co-workers[2] devised an elegant route to 3-methylceph-3-ems (1, X = Me) based on a rearrangement of penicillin sulfoxides in which the 1,2 bond suffers cleavage. This route can be extended to yield ceph-3-ems in which functionality is introduced into the 3-methyl substituent, but it then becomes much more cumbersome.[3] A different multistep modification of the penicillin nucleus (2) involving initial cleavage of the 3,4 bond and subsequent cyclization of an aldehydophosphorane (3, R^1 = H or Me) provides 3-unsubstituted cephalosporins (1, X = H).[4]



We have developed a versatile route to a variety of 3-substituted cephalosporins based on the readily available penicillin derivative, benzyl 6β-(triphenylmethylamino)-penicillanate (4). Treatment of the latter with 3-substituted prop-2-ynyl bromides in the presence of strong base leads to 1,2-secopenicillanates[5] (5) which may be further modified via the stages 6, 7, 8, 9, and 10 to yield the ceph-3-ems 11 and 12. We have previously illustrated the route by describing[6] the synthesis of a 3-benzyl isostere (13a) of cephaloridine (13, R = pyridinium). In the work reported here we have used this general route to prepare a range of *N*-acyl derivatives of the 3-benzylceph-3-em nucleus and a further range of *N*-acyl derivatives of the novel 3-(3-pyridylmethyl)ceph-3-em nucleus. Acyl side chains were chosen so as to provide a variety of structural types, while including a reasonable selection of groups previously shown to confer useful antibacterial activity on semisynthetic penicillins[7] or cephalosporins.[1]

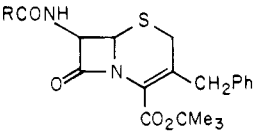
Chemistry. The amines **12a** and **12b** were treated with standard acylating agents (e.g., acid chloride, symmetrical or mixed anhydride, or carboxylic acid and dicyclohexylcarbodiimide) to give the acylamino *tert*-butyl esters listed in Tables I and II. The free cephalosporins were then liberated by treating the *tert*-butyl esters with trifluoroacetic acid. In those cases where the side chains were derived from amino acids, the amino group of the latter was protected by the *tert*-butoxycarbonyl group which was then removed at the same time as the nuclear ester group.

Biological Results and Discussion. The new cephalosporins were tested in vitro against a range of gram-positive and gram-negative bacteria in comparison with three clinically established cephalosporins, and results for representative organisms are given in Tables III and IV. All the compounds showed considerable activity against *Staphylococcus aureus* Oxford, as do the great majority of β-lactam antibiotics. Activity against the β-lactamase-producing *Staphylococcus aureus* Russell was inferior to that against the Oxford staphylococcus, sometimes considerably so. The differing ratios between the MIC values for these two strains indicate that some compounds are more susceptible than others to inactivation by staphylococcal β-lactamase.

Most of the 3-benzylcephalosporins (Table III) showed little or no activity against gram-negative bacteria, although the D-phenylglycyl compound **53** was moderately active and its *p*-hydroxy analogue **54** was about as active as cephalexin. The general level of activity against gram-negative bacteria was higher among the 3-(3-pyridylmethyl)cephalosporins (Table IV), which is in line with the general tendency among β-lactam antibiotics[1,7] for the more hydrophilic compounds to have a broader spectrum.

Compound **13b** and cephaloridine (13, R = pyridinium) are position isomers, although the former is a tertiary amine and the latter (which has better activity) a quaternary pyridinium salt. The D-phenylglycyl derivative **62** has the best broad-spectrum activity of all the new compounds, being more active than cephalexin and as active as cephalothin and cephaloridine against gram-negative bacilli. Two other compounds which are almost as active as **62** are the 2-thienyl analogue **64** and the D-mandelic acid derivative **57**.

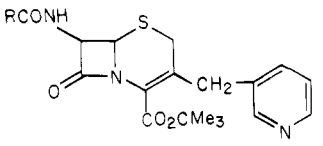
Table I. *tert*-Butyl 7β-Acylamino-3-benzylceph-3-em-4-carboxylates

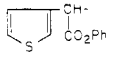
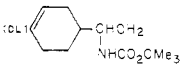


Compd	R	Acylation method	Mp, °C (solvent[a])	Formula	Analyses
14	Me	C	194-195 (E)	$C_{20}H_{24}N_2O_4S$	C, H, N
15	CF_3	C	157-158 (EA-P)	$C_{20}H_{21}F_3N_2O_4S$	M⁺
16	$NCCH_2$	B	Amorphous	$C_{21}H_{23}N_3O_4S$	C, H, N
17	$PhOCH_2$	A	Amorphous	$C_{26}H_{28}N_2O_5S$	M⁺
18	$EtSCH_2$	A	97-99 (E)	$C_{22}H_{28}N_2O_4S_2$	M⁺
19	$HO_2CCH_2SCH_2$	D	120-121 (EA-P)	$C_{22}H_{26}N_2O_6S_2$	C, H, N
20	(D)PhCHOH	E	Amorphous	$C_{26}H_{28}N_2O_5S$	M⁺
21	$PhCH(CO_2Ph)$	A	153-160 (EA-P)	$C_{33}H_{32}N_2O_6S$	C, H, N
22	C_5H_4N-*p*-CH_2	A	102 (E)	$C_{25}H_{27}N_3O_4S$	M⁺
23	C_5H_4N-*p*-SCH_2	B	207-208 (EA)	$C_{25}H_{27}N_3O_4S_2$	C, H, N
24		A	138-144 (B-P)	$C_{21}H_{24}N_6O_4S$	C, H, N, S
25	(D)$MeCH(NHCO_2CMe_3)$	F	80-85 (P)	$C_{26}H_{35}N_3O_6S$	M⁺
26	(D)c-C_3H_5-$CH(NHCO_2CMe_3)$	F	92-95 (P)	$C_{28}H_{37}N_3O_6S$	M⁺
27	(D)$PhCH(NHCO_2CMe_3)$	F	152-153 (E-P)	$C_{31}H_{37}N_3O_6S$	C, H, N, S
28	(D)*p*-$HOC_6H_4CH(NHCO_2CMe_3)$	F	Amorphous	$C_{31}H_{37}N_3O_7S$	C, H, N

[a] B = benzene, E = ether, EA = ethyl acetate, P = petroleum ether (bp 60-80 °C). All compounds gave satisfactory NMR spectra and were homogeneous by TLC.

Table II. *tert*-Butyl 7β-Acylamino-3-(3-pyridylmethyl)ceph-3-em-4-carboxylates



Compd[a]	R	Acylation method	Formula	Analyses
29	$PhOCH_2$	A	$C_{25}H_{27}N_3O_5S$	M⁺
30	$EtSCH_2$	A	$C_{21}H_{27}N_3O_4S_2$	M⁺
31	(D)PhCHOH	E	$C_{25}H_{27}N_3O_5S$	C, H, N
32	C_4H_3S-*o*-CH_2	A	$C_{23}H_{25}N_3O_4S_2$	M⁺
33	C_5H_4N-*p*-CH_2	B	$C_{24}H_{26}N_4O_4S$	M⁺
34	C_5H_4N-*p*-SCH_2	B	$C_{24}H_{26}N_4O_4S_2$	M⁺
35		A	$C_{30}H_{29}N_3O_6S_2 \cdot H_2O$	C, H, N
36	(D)c-C_3H_5-$CH(NHCO_2CMe_3)$	F	$C_{27}H_{36}N_4O_6S$	M⁺
37	(D)$PhCH(NHCO_2CMe_3)$	F	$C_{30}H_{36}N_4O_6S$	M⁺
38		F	$C_{31}H_{42}N_4O_6S$	M⁺
39	(DL)C_4H_3S-*o*-$CH(NHCO_2CMe_3)$	F	$C_{28}H_{34}N_4O_6S_2$	M⁺

[a] These esters were amorphous apart from 31 (mp 157-159 °C, from EtOAc-petroleum ether) and 35 (mp 105-107 °C from $CHCl_3$-Et_2O). However, all gave satisfactory NMR spectra and were homogeneous by TLC.

It is noteworthy that D-phenylglycine constitutes a preferred side chain in both the 3-benzyl series (Table III) and the 3-(3-pyridylmethyl) series (Table IV). In each series derivatives of aliphatic or cycloaliphatic amino acids are less active. D-Phenylglycine is, of course, the side chain of the leading semisynthetic penicillin, ampicillin, and of the orally effective cephalosporin, cephalexin.

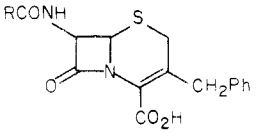
Experimental Section

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian A-60 instrument for solutions in $CDCl_3$ with $SiMe_4$ as internal standard unless stated otherwise. Mass spectra were determined with an AEI MS9 machine. Compounds shown as having been analyzed either gave figures for the elements cited correct to within ±0.4% of the theoretical values or else gave accurate mass measurements correct to within ±5 ppm. Merck silica gel GF 254 was used for TLC and Merck silica gel H for column chromatography, with ethyl acetate–petroleum ether as eluent. Petroleum ether refers to the fraction of bp 60–80 °C.

***tert*-Butyl 7β-Amino-3-benzylceph-3-em-4-carboxylate Toluene-*p*-sulfonic Acid Salt (12a).** This was prepared as described by Nayler et al.[6]

***tert*-Butyl 7β-Amino-3-(3-pyridylmethyl)ceph-3-em-4-carboxylate (12b).** *tert*-Butyl glyoxylate monohydrate (1.93 g, 13 mmol) and dry benzene (20 mL) were refluxed under nitrogen in a Dean-Stark apparatus until all the water had been removed; then (3*R*,4*R*)-4-[3-(pyridyl)prop-2-ynylthio]-3-(triphenylmethylamino)azetidin-2-one (**6b**)[5] (620 mg, 1.3 mmol) was added and the mixture refluxed under nitrogen for 3 h more, cooled, washed, dried, and evaporated. Chromatography gave the mixed

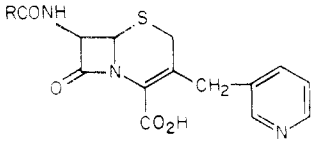
Table III. Antibacterial Activity of 7β-Acylamino-3-benzylceph-3-em-4-carboxylic Acids

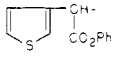
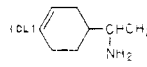


Compd	R	Minimum inhibitory concentration, μg/mL[a]						
		S. aureus Oxford	*S. aureus* Russell[b]	*E. coli*	*S. typhi*	*Sh. sonnei*	*K. aerogenes*	*P. mirabilis*
13a	C_4H_3S-*o*-CH_2	0.05	10	200	200	200	>200	>200
40	Me	0.5	2.5	>500	500	>500	>500	>500
41	CF_3	2.5	12.5	>500	>500	>500	>500	500
42	$NCCH_2$	0.12	0.5	500	250	500	>500	>500
43	$PhOCH_2$	0.02	0.12	>500	>500	>500	>500	500
44	$EtSCH_2$	0.12	1.25	>125	125	>125	>125	>125
45	$HO_2CCH_2SCH_2$	5	25	>500	250	250	>500	125
46	(D)PhCHOH	0.12	12.5	125	50	50	50	>500
47	$PhCH(CO_2Ph)$	2.5	25	>100	>100	>100	>100	50
48	C_5H_4N-*p*-CH_2	0.05	5	50	50	50	100	100
49	C_5H_4N-*p*-SCH_2	0.05	2.5	250	250	250	>500	250
50		0.12	1.25	>500	>500	125	500	125
51	(D)$MeCH(NH_2)$	5	10	>100	>100	>100	>100	>100
52	(D)c-C_3H_5-$CH(NH_2)$	5	12.5	>250	>250	>250	>250	>250
53	(D)$PhCH(NH_2)$	0.1	2.5	25	25	25	25	50
54	(D)*p*-$HOC_6H_4CH(NH_2)$	0.12	1.25	12.5	5	12.5	5	25
Cephalothin		0.12	0.5	5	12.5	5	5	5
Cephaloridine		0.02	1.25	5	1.25	1.25	2.5	5
Cephalexin		1.25	5	12.5	5	5	5	12.5

[a] Determined by serial dilution on nutrient agar using an inoculum of 0.001 mL of an undiluted overnight broth culture. MIC values were read after incubation at 37 °C for 18 h. [b] β-Lactamase-producing benzylpenicillin-resistant strain.

Table IV. Antibacterial Activity of 7β-Acylamino-3-(3-pyridylmethyl)ceph-3-em-4-carboxylic Acids



Compd	R	Minimum inhibitory concentration, μg/mL[a]						
		S. aureus Oxford	*S. aureus* Russell[b]	*E. coli*	*S. typhi*	*Sh. sonnei*	*K. aerogenes*	*P. mirabilis*
13b	C_4H_3S-*o*-CH_2	0.05	10	25	5	25	25	25
55	$PhOCH_2$	0.02	0.12	500	500	500	500	125
56	$EtSCH_2$	0.05	1.25	50	50	50	50	25
57	(D)PhCHOH	0.25	12.5	2.5	2.5	2.5	2.5	5
58	C_5H_4N-*p*-CH_2	0.12	25	25	10	25	10	10
59	C_5H_4N-*p*-SCH_2	<0.02	1	25	10	25	5	100
60		12.5		12.5	50	12.5	12.5	12.5
61	(D)c-C_3H_5-$CH(NH_2)$	5	12.5	500	250	250	250	500
62	(D)$PhCH(NH_2)$	0.25	2.5	2.5	1.25	2.5	2.5	5
63	 (DL)	0.5	1.25	125	125	125	125	250
64	C_4H_3S-*o*-$CH(NH_2)$	0.5	5	12.5	2.5	5	5	12.5
Cephalothin		0.12	0.5	5	12.5	5	5	5
Cephaloridine		0.02	1.25	5	1.25	1.25	2.5	5
Cephalexin		1.25	5	12.5	5	5	5	12.5

[a] Determined by serial dilution on nutrient agar using an inoculum of 0.001 mL of an undiluted overnight broth culture. MIC values were read after incubation at 37 °C for 18 h. [b] β-Lactamase-producing benzylpenicillin-resistant strain.

isomers of **7b** (510 mg, amorphous). This in dry dioxane (5 mL) and dry THF (5 mL) containing pyridine (202 mg) was cooled to −5 °C, treated dropwise with $SOCl_2$ (304 mg), and stirred at −5 to 0 °C for 15 min. The mixture was filtered and the filtrate and toluene washings were evaporated to give the mixed isomers of **8b** (436 mg, 0.7 mmol, amorphous). The latter in dry dioxane (10 mL) was treated with PPh_3 (368 mg, 1.4 mmol) and 2,6-lutidine (90 mg, 0.84 mmol), stirred 5 h at 50 °C under nitrogen, then cooled, diluted with ethyl acetate (100 mL), washed with brine, dried, and evaporated. Chromatography gave the phosphorane **9b** (262 mg, amorphous) which was refluxed in piperidine (5 mL) under nitrogen for 3 h and then evaporated. The gum was taken up in EtOAc, shaken with 0.1 N HCl (20 mL) for 5 min, and then basified with $NaHCO_3$ and the organic layer was separated, dried, and evaporated. Chromatography gave the ketone **10b** (197 mg, amorphous) which was refluxed in dry dioxane (5 mL) under

nitrogen for 8 h to give, after evaporation and chromatography, the cephem **11b** [95 mg (12%) from **6b**]: mp 169–171 °C (from MeOH); α^{25}_D −13.8° (*c* 1, $CHCl_3$), ν_{max} ($CHCl_3$) 1775, 1715 cm^{-1}; λ_{max} 263 nm (ε 10 500) (EtOH). Anal. ($C_{36}H_{35}N_3O_3S$) C, H, N, S. Detritylation was effected by treating **11b** (95 mg, 0.16 mmol) in acetone (1 mL) at 0 °C with toluene-*p*-sulfonic acid monohydrate (68 mg, 0.36 mmol), stirring for 2 h at 0 °C and then 4 h at room temperature, and evaporating the mixture. The residue was taken up in EtOAc, washed with $NaHCO_3$ solution, dried, and chromatographed to give *tert*-butyl 7β-amino-3(3-pyridylmethyl)ceph-3-em-4-carboxylate (**12b**) as a foam (72%): ν_{max} ($CHCl_3$) 1775, 1715 cm^{-1}; δ ($CDCl_3$) 1.55 (9 H, s), 2.7 br (2 H, exch), 3.02 and 3.48 (2 H, AB q, *J* = 18 Hz), 3.44 and 4.08 (2 H, AB q, *J* = 15 Hz), 4.76 (1 H, d, *J* = 5 Hz), 4.99 (1 H, d, *J* = 5 Hz), 7.0–8.8 (Ar multiplet); M^+ 347.1292 ($C_{17}H_{21}N_3O_3S$ requires M 347.1303).

Acylation of *tert*-Butyl 7β-Aminoceph-3-em-4-carboxylates. Acylation of the amines **12a** and **12b** gave the amides listed in Tables I and II, all of which showed the spectroscopic properties typical of Δ^3-cephalosporin esters including λ_{max} (EtOH) 263–270 nm and ν_{max} ($CHCl_3$) 1780–1790 cm^{-1} (β-lactam CO) and 1710–1720 cm^{-1} (ester CO). The following acylation procedures are representative.

Method A (Acid Chloride). The toluene-*p*-sulfonic acid salt of **12a** (0.5 g, 0.96 mmol) and $NaHCO_3$ (0.4 g) were suspended in dry acetone (30 mL) and stirred at 0 °C while ethylthioacetyl chloride[8] (0.4 g, 2.9 mmol) was added dropwise. The mixture was stirred for 1 h at 0 °C, followed by 3 h at room temperature, and then evaporated. The residue, dissolved in benzene, was washed successively with cold 5% HCl, saturated $NaHCO_3$, and brine, then dried, and evaporated. Chromatography gave the ester **18** (0.23 g, 66.5%).

Method B (Carbodiimide). The amine **12a** (115 mg, 0.33 mmol) in CH_2Cl_2 (1.5 mL) was cooled in an ice bath and treated with *N,N'*-dicyclohexylcarbodiimide (65 mg, 0.31 mmol) in CH_2Cl_2 (1.0 mL). Cyanoacetic acid (30 mg, 0.35 mmol) in DMF (0.5 mL) was added dropwise. The mixture was stirred for 2 h, then diluted with CH_2Cl_2, washed with 0.5 N HCl, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel to give the cyanoacetamido derivative **16** (125 mg, 91%).

Method C (Symmetrical Anhydride). The toluene-*p*-sulfonic acid salt of the cephem **12a** (800 mg, 1.54 mmol) in dry CH_2Cl_2 (5 mL) was cooled in an ice bath and NEt_3 (0.30 mL) was added. Ac_2O (0.25 mL, 2.5 mmol) in $CHCl_3$ (15 mL) was added dropwise over 30 min, maintaining the temperature at 0–5 °C. The mixture was then allowed to warm to room temperature and washed successively with aqueous $NaHCO_3$ and brine, then dried ($MgSO_4$), and evaporated to leave a partially crystalline residue. Chromatography, followed by crystallization from ether, gave the acetyl derivative **14** (547 mg, 91%).

Method D (Cyclic Anhydride). **12a** (520 mg) in CH_2Cl_2 at 0 °C was treated with a solution of thiodiglycolic anhydride[9] (198 mg, 1.5 mmol) in CH_2Cl_2. After 2 h at room temperature the solvent was removed by evaporation to give a foam (562 mg) which on trituration with ether gave the ester **19** as a solid.

Method E (*O*-Carboxyanhydride). D-Mandelic *O*-carboxyanhydride[10] (196 mg, 1.1 mmol) was added over 5 min to a stirred solution of the amine **12b** (347 mg, 1 mmol) in dry CH_2Cl_2 (20 mL) at −20 °C; then the mixture was stirred for 2 h at −20 °C and evaporated. Chromatography of the residue gave the cephem ester **31** (318 mg, 66%).

Method F (Mixed Anhydride). Redistilled $ClCO_2Me$ (100 mg, 1.05 mmol) in dry THF (15 mL) was stirred at −10 °C while a solution of *N*-(*tert*-butoxycarbonyl)-D-α-phenylglycine (261 mg, 1.05 mmol), NEt_3 (105 mg), and $PhCH_2NMe_2$ (1 drop) in dry THF (10 mL) was added over 5 min. The mixture was stirred at −10 °C for a further 25 min to complete formation of the mixed anhydride and then treated dropwise over 5 min with the amine **12a** (330 mg, 0.95 mmol, regenerated from toluene-*p*-sulfonate salt) in dry THF (5 mL). The mixture was stirred for 2 h at −10 °C, then NEt_3HCl was removed, and the filtrate evaporated. The residue was taken up in EtOAc and washed successively with water, dilute HCl, 5% $NaHCO_3$, and water, then dried, and evaporated. Chromatography gave the ester **27** (461 mg, 77%).

Deesterification of *tert*-Butyl Esters (12). (a) The ester **15** (359 mg) was dissolved in THF (6 mL) and, after 5 min at room temperature, the solution was evaporated in vacuo. Recrystallization of the residue from EtOAc–petroleum ether gave 3-benzyl-7β-trifluoroacetamidoceph-3-em-4-carboxylic acid (**41**): mp 181–182 °C; α^{23}_D −9.4° (*c* 1, $CHCl_3$); λ_{max} (EtOH) 260 nm (ε 9650); ν_{max} 1785 and 1725 cm^{-1} Anal. ($C_{16}H_{13}F_3N_2O_4S$) C, H, N.

(b) Similar treatment of **22**, but with a reaction time of 40 min, gave the TFA salt of 3-benzyl-7β-(4-pyridylacetamido)ceph-3-em-4-carboxylic acid. This dissolved readily in water, but after some time the free cephalosporin **48** crystallized: mp 207–210 °C dec. Anal. ($C_{21}H_{19}N_3O_4S$) C, H, N.

(c) The ester **28** (662 mg) was dissolved in anhydrous TFA (10 mL), set aside at room temperature for 35 min, and evaporated in vacuo. After addition of toluene and repetition of the evaporation (three times), the residue was triturated with ether to give the TFA salt of 7β-(D-α-amino-*p*-hydroxyphenylacetamido)-3-benzylceph-3-em-4-carboxylic acid (**54**) (585 mg): mp 158–165 °C dec; α^{22}_D +47.1° (*c* 0.828, H_2O); λ_{max} (EtOH) 264.5 nm (ε 11 100). Anal. ($C_{24}H_{22}F_3N_3O_7S$) C, H, N.

(d) The other esters in Tables I and II were similarly treated to give the free cephalosporins. Due to the small quantities available the end products were not fully characterized, but spectroscopic data indicated them to be sufficiently pure for antibacterial testing (see Tables III and IV).

Supplementary Material Available: High-resolution mass spectral data, NMR data, and elemental composition data (5 pages). Ordering information is given on any current masthead page.

References and Notes

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