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Chemistry of Cephalosporin Antibiotics. 22. Chemistry and Biological Activity of 3-Alkoxymethyl Cephalosporins

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The 3-methoxymethyl cephem nucleus was prepared by methanolysis of the Δ^2-allylic bromide **4**. Oxidation and reduction at the S atom provided the Δ^3 isomer. A series of 3-methoxymethyl-7-acylamino cephalosporin acids was prepared and evaluated for biological activity. The D-phenylglycyl derivative gave significant blood levels when administered orally in mice. A series of 3-alkoxymethyl-7-phenoxyacetamido cephalosporin acids was also prepared. Some of these were potent inhibitors of penicillin-resistant *Staphylococcus aureus*.

Early studies of structure–activity relationships in cephalosporin antibiotics included an examination of antibacterial activity as a function of the 7-acylamino group when attached to the naturally occurring 3-acetoxymethyl cephem nucleus. Shortly thereafter, the semisynthetic 3-methyl cephem nucleus became available for similar modifications. Attempts to maximize oral absorption culminated in the preparation of cephaloglycin (**1**)[1] and cephalexin (**2**)[2] and the resulting conclusion that incorporation of the D-2-amino-2-phenylacetamido (phenylglycyl) side chain led to compounds which produced significant blood levels when administered orally.[3,4] We were interested in preparing a new cephalosporin system, the 3-methoxymethyl cephem nucleus, in order to evaluate the antibacterial activity of its 7-acylamino variants. We particularly wanted to examine the ability of the phenylglycyl side chain to confer oral absorption to this cephalosporin.

A key intermediate in our functionalization of the deacetoxycephalosporin system was *p*-methoxybenzyl 3-bromomethyl-7-phenoxyacetamido-2-cephem-4-carboxylate (**4a**), which was subsequently converted into the cephalosporanic acid.[5] This allylic bromide seemed a good candidate for conversion into the 3-methoxymethyl cephem nucleus.

Δ^2-Deacetoxycephalosporin ester (**3**), the starting material for our synthesis, was prepared by our previously published methods,[5] or through the Δ^2-ketene route developed by Murphy and Koehler.[6] Reaction of **3** with NBS, catalyzed by azobisisobutyronitrile, in hot CCl_4 provided the crude allylic bromide **4**. Although the Δ^2-allylic bromide system undergoes displacement with acetate,[5] MeO^- would be expected to react with the sensitive β-lactam system. Upon dissolving **4** in MeOH, however, a nearly instantaneous reaction provides the Δ^2-3-methoxymethyl cephalosporin ester **5**. No base is required for this reaction, although $CaCO_3$ or $PhNMe_2$ are sometimes included as an HBr scavenger. The ease of this conversion may be explained as the solvolysis of a highly reactive vinylogous α-bromosulfide by MeOH. Column chromatography on silica gel separated ester **5a** in 40% yield from recovered starting deacetoxycephalosporin **3** (15%). Alternatively, **5a** could be obtained in 20% yield by crystallizing the crude solvolysis mixture from methyl isobutyl ketone.

The Δ^2-3-methoxymethyl ester **5** was converted into its Δ^3 isomer by the process used in the acetoxymethyl series,[5] *i.e.*, oxidation and then reduction at the S atom. Oxidation of ester **5a** with *m*-chloroperbenzoic acid in $CHCl_3$ gave a mixture which, from tlc analysis, appeared to contain unreacted **5a** and sulfone, in addition to the desired sulfoxide **6a**. Oxidation in *i*-PrOH[7] afforded not only a much cleaner reaction, but also allowed the direct crystallization of pure **6a** from the reaction mixture in good yield. Reduction of **6a**, using either sodium dithionite or $SnCl_2$, together with AcCl, provided Δ^3-ester **7a** in fair yield. The two steps in this crucial $\Delta^2 \rightarrow \Delta^3$ conversion developed in these laboratories have been discussed in detail elsewhere.[8]

The phenoxyacetyl group was removed from ester **7a** by consecutive treatment with PCl_5–pyridine in PhH, MeOH, and H_2O.[9] The resultant amine was isolated as its crystalline tosylate salt **8a**. Although the intermediates in the *p*-methoxybenzyl ester series were isolated and characterized as crystalline species, the sequence involving the *t*-Bu ester afforded no crystalline intermediates. Nevertheless, Δ^2-ester **3b**, using a route analogous to that described for **3a**, could be converted into crystalline tosylate **8b** without purification by chromatography. The crystalline salt did not contain observable (by nmr) contamination with deacetoxycephalosporin.

Amide derivatives of the 3-methoxymethyl cephalosporin nucleus were prepared by either acylation of the nucleus tosylate ester **8**, followed by ester cleavage, or by ester cleavage of **8** to give 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid and subsequent mixed anhydride acylation.

As described in the Experimental Section, the route to the 3-methoxymethyl cephalosporin system could be

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(1) 3-Acetoxymethyl-7-(D-2-amino-2-phenylacetamido)-3-cephem-4-carboxylic acid.

(2) 7-(D-2-Amino-2-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid.

(3) (a) W. E. Wick and W. S. Boniece, *Appl. Microbiol.*, **13**, 248 (1965). (b) J. L. Spencer, E. H. Flynn, R. W. Roeske, F. Y. Siu, and R. R. Chauvette, *J. Med. Chem.*, **9**, 746 (1966).

(4) C. W. Ryan, R. L. Simon, and E. M. Van Heyningen, *ibid.*, **12**, 310 (1969).

(5) J. A. Webber, E. M. Van Heyningen, and R. T. Vasileff, *J. Amer. Chem. Soc.*, **91**, 5674 (1969).

(6) C. F. Murphy and R. E. Koehler, *J. Org. Chem.*, **35**, 2429 (1970).

(7) F. Montanari, M. Cinquini, and U. Folli in "Mechanisms of Reactions of Sulfur Compounds," Vol. 3, N. Kharasch, Ed., Intra-Science Research Foundation, Santa Monica, Calif., p 123.

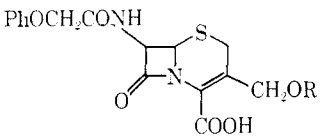
(8) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heyningen, *J. Org. Chem.*, **35**, 2430 (1970).

(9) For discussion and other uses of this interesting reaction see R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, submitted for publication.

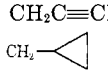
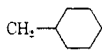
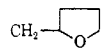
altered by substituting other liquid alcohols for MeOH in the alcoholysis of Δ^2-allylic bromide **4b**. The Δ^3-esters obtained by oxidation and reduction at the S atom were cleaved to the corresponding 7-phenoxyacetamido-3-alkoxymethyl cephalosporin acids. Structures and *in vitro* activities for this series are indicated in Table I. Although these cephalosporins are essentially devoid of Gram-negative activity, a few have excellent *in vitro* activity against penicillin-resistant *Staphylococcus aureus* (**9c**, **9f**, and **9t**).

TABLE I

BIOLOGICAL ACTIVITIES OF PHENOXYACETAMIDOCEPHALOSPORIN ETHERS



9

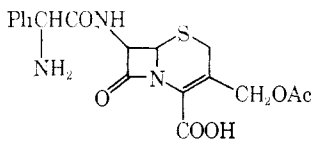
Compd	R	Resistant[a] *S. aureus*
9a	CH_3	0.2
9b	C_2H_5	0.3
9c	$CH(CH_3)_2$	0.1
9d	$(CH_2)_3CH_3$	0.2
9e	$C(CH_3)_3$	0.7
9f	$CH_2CH{=}CH_2$ (Na^+ salt)	0.1
9g	$CH_2C{\equiv}CH$	0.2
9h		0.2
9i		0.4
9j		0.2
9k	CH_2Ph	0.4
9l	$CH_2CH_2OCH_3$	0.6
9m		0.5
9n		0.6
9o	CH_2COCH_3	0.6
9p	CH_2CO_2Et	0.5
9q	(DL)—$CHCO_2Et$ | CH_3	0.7
9r	$(CH_2)_2OCOCH_3$	0.4
9s	CH_2CH_2Cl	0.3
9t	CH_2CH_2Br	0.1
9u	CH_2CH_2CN	0.2

[a] MIC in μg/ml by gradient plate assay. Each figure is the av value obtained using 3 penicillin-resistant, coagulase-positive *S. aureus* strains.

We concentrated our attention upon derivatives of the 3-methoxymethyl cephem nucleus; this 3-alkoxymethyl cephalosporin is more readily obtained using our synthetic route than the other ethers mentioned in Table I. In addition, Tables II and III each contain a 3-ethoxymethyl cephem derivative for comparison.

Table II provides the biological activity of a series of 7-acylamino-3-methoxymethyl cephalosporin derivatives. Those selected for preparation reflect side chains which have appeared promising in the 3-acetoxymethyl and 3-methyl series. The mandelic derivative **10f** provides the only noteworthy *in vitro* activity against Gram-negative organisms. From a comparison of oral ED_{50} values in mice against *Streptococcus pyogenes* with *in vitro* antibiotic potency, we concluded that none of the compounds in Table II have significant oral absorption.

Preparation of a 3-methoxymethyl cephalosporin bearing the D-phenylglycyl side chain resulted in an antibiotic with desirable properties. This 7-(D-2-amino-2-phenylacetamido) moiety has been shown previously to contribute to the oral absorption of other cephem systems.[3a,4] The biological activities of cephaloglycin (**1**) and cephalexin (**2**) and two new 3-alkoxymethyl phenylglycyl cephalosporins (**10k** and **10l**) are summarized in Table III. These data provide further evidence for the unique character of the phenylglycyl side chain; this derivative of the 3-methoxymethyl and 3-ethoxymethyl cephem nuclei shows oral ED_{50} values indicative of significant blood levels. The *in vitro* Gram-positive and Gram-negative activities of **10k** and **10l** are comparable to those of the two older phenylglycyl cephalosporins.[3a,4] We interpret the inferior *in*



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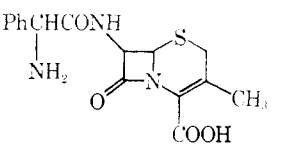

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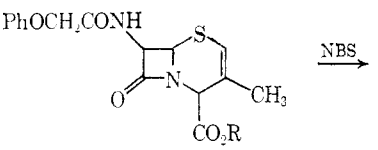
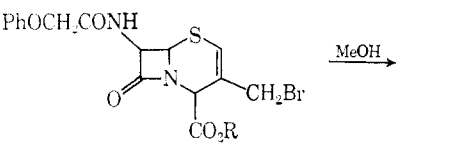


3

a, R = $CH_2C_6H_4OCH_3(p)$

b, R = *t*-Bu



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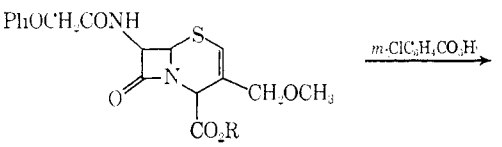
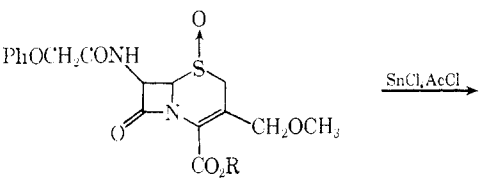


5



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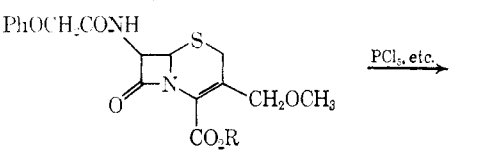

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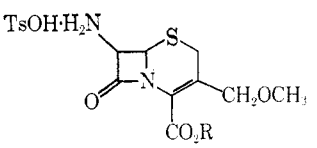

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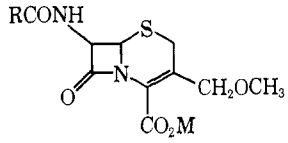
TABLE II

BIOLOGICAL ACTIVITIES OF 3-METHOXYMETHYL CEPHALOSPORIN DERIVATIVES



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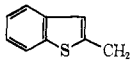
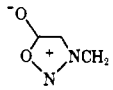
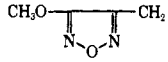
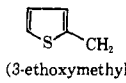
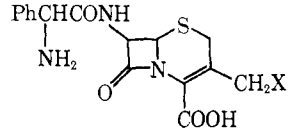
Compd	R	M	Resistant[a] S. aureus	Gram negative[b] N-9	N-10	N-26	X-26	X-68	K-1	X-528	Cephalothin[c] assay	Oral[d] ED_{50}
10a		K	0.4	>50	39.0	38.0	43.4	12.4	22.1		280	12.7
10b		Na	0.2	>50	>50	>50	7.6	>50	>50	>50	840	13.8
10c	$4\text{-}NO_2C_6H_4CH_2$	Na	0.4	>50	>50	>50	35.5	>50	>50	>50	500	6.7
10d	$3\text{-}ClC_6H_4CH_2$	Na	0.1	>50	>50	>50	13.0	>50	>50	>50	>500	8.6
10e	$3\text{-}ClC_6H_4SCH_2$	Na	0.1	>50	>50	>50	10.1	>50	>50	>50	>1000	10.3
10f	PhCHOH	Na	0.5	1.1	4.4	5.3	5.8	1.0	1.0	>50	>200	12.8
10g	$PhCHCO_2H$	H	8.8	31.0	33.0	36.0	39.0	38.0	>50	>50	4	
10h		H	0.9	20.0	32.5	33.0	29.0	32.0	31.5	50	64	19.5
10i		Na	0.5	>50	>50	>50	22.9	34.0	32.0	50	64	>20.8
10j	 (3-ethoxymethyl)	Na	0.7	>50	>50	>50	31.0	>50	>50	>50	480	>20.8
Cephalothin			0.4	7.5	8.7	10.5	0.7	3.0	4.1	>50	1000	26.0

[a] See footnote *a*, Table I. [b] MIC in μg/ml by gradient plate assay: N-9 = *Shigella* sp.; N-10 = *Escherichia coli;* N-26 = *E. coli;* X-26 = *Klebsiella pneumoniae;* X-68 = *Enterobacter aerogenes;* K-1 = *K. pneumoniae;* X-528 = *Pseudomonas* sp. [c] Values are expressed as μg/ml of cephalothin activity against *Bacillus subtilis.* [d] The values given are the minimum dose in mg/kg which afforded protection to 50% of mice against *S. pyogenes.* The dose was given orally 1 and 5 hr postinfection.

TABLE III

BIOLOGICAL ACTIVITIES OF PHENYLGLYCYL DERIVATIVES



Compd	X	Resistant[a] S. aureus	Gram negative[b] N-9	N-10	N-26	X-26	X-68	K-1	X-528	Cephaloglycin[c] assay	Oral[d] ED_{50}
1	OAc	2.9	3.3	3.6	3.7	1.8	1.4	0.9	>50	1000	4.5
2	H	3.6	8.7	7.8	8.3	6.2	5.8	5.4	>50	440	1.8
10k	OCH_3	0.7	3.9	4.4	5.0	3.6	2.2	3.0	>50	1300	1.1
10l	OC_2H_5	1.0	19.1	11.1	11.2	7.7	8.9	9.2	>50	1050	4.9

[a,b] See corresponding footnotes in Table II. [c] Values are expressed as μg/mg of cephaloglycin activity against *S. aureus.* [d] See footnote *d*, Table II.

vitro and oral ED_{50} values of **10j** relative to **10l** as a result of the increased size of the ether moiety (MeO → EtO). This trend is also evident in the *in vitro* and oral ED_{50} values of **10a** and **10j** in Table II.

Table IV provides uv data for derivatives **10a–l**.

It is known that the 3-acetoxymethyl cephalosporin derivatives cephalothin and cephaloglycin are metabolized to deacetyl compounds[10] which, although retaining the antibacterial spectra of their acetoxymethyl parent, have decreased potency. It has been suggested[10b] that a metabolically stable cephalosporin might be therapeutically desirable; cephaloridine and cephalexin, for example, represent confirmation of this concept. We have obtained preliminary evidence of metabolic stability in the 3-methoxymethyl cephem system in the following manner: the cephalosporin **10k** was administered to mice; their urine was collected; **10k** was the only compound detected by a bioautograph.

(10) (a) C. C. Lee, E. B. Herr, Jr., and R. C. Anderson, *Clin. Med.*, **70**, 1123 (1963). (b) E. H. Flynn, *Antimicrob. Ag. Chemother.*, 715 (1966). (c) K. Shimizu and H. Nishimura, *J. Antibiot.*, **23**, 216 (1970).

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. Uv spectra were run in EtOH or H_2O; ir spectra were taken in $CHCl_3$ or as a mull. Nmr spectra were obtained using a Varian HA-60 spectrometer in $CDCl_3$, DMSO-d_6, or D_2O

TABLE IV

3-METHOXYMETHYL CEPHALOSPORIN DERIVATIVES

Compd	Uv λ_{max} mμ (ε)	Formula[a]
10a	260 (8,600)	$C_{15}H_{15}KN_2O_5S_2$
10b	227 (17,000)	$C_{19}H_{17}NaN_2O_5S_2$
	258 (9,550)	
	297 (2,000)	
10c	217 (10,800)	$C_{17}H_{16}NaN_3O_7S$
	265 (16,300)	
10d	258 (7,000)	$C_{17}H_{16}ClNaN_2O_5S$
10e	252 (12,300)	$C_{17}H_{16}ClNaN_2O_5S_2$
10f	258 (6,800)	$C_{17}H_{17}NaN_2O_6S$[b,c,d]
10g	258 (7,550)	$C_{18}H_{18}N_2O_7S$
10h	268 (9,800)	$C_{13}H_{14}N_4O_7S$
	285 (8,000)	
10i	230 (8,400)	$C_{14}H_{15}NaN_4O_7S$
10j (3-ethoxymethyl)	260 (7,400)	$C_{16}H_{17}NaN_2O_5S_2$[e,f]
10k, R = PhCH(NH$_2$)	258 (7,700)	$C_{17}H_{19}N_3O_5S$
10l	258 (7,500)	$C_{18}H_{21}N_3O_5S$[g,h]

[a] All compds were analyzed for C, H, N. [b] Calcd: C, 50.99; found: 45.56. [c] Calcd: H, 4.28; found: 4.76. [d] Calcd: N, 7.00; found: 6.37. [e] Calcd: H, 4.23; found: 5.11. [f] Calcd: N, 6.92; found: 7.87. [g] Calcd: C, 55.24; found: 52.61. [h] Calcd: N, 10.74; found: 10.09.

+ DCl. Paper chromatograms from bioautographs were run in MEK–H_2O (92:8) for acids or *n*-BuOH–AcOH–H_2O (3:1:1) for amino acids. All cryst compds were characterized by ir, uv, nmr, and elemental anal. (C, H, N). Unless stated otherwise these analyses were within ±0.4% of the theoretical value.

***p*-Methoxybenzyl 3-Methoxymethyl-7-phenoxyacetamido-2-cephem-4-carboxylate (5a).**—A soln of 1.17 g (2.5 mmoles) of *p*-methoxybenzyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate (**3a**) in 250 ml of CCl_4 was thoroughly purged with N_2; 445 mg (2.5 mmoles) of NBS and 61.5 mg (0.375 mmole) of azobisisobutyronitrile (AIBN) were added, and the mixture was heated in an oil bath at 84°. Reaction was complete in 4 hr. Cooling, filtering to remove succinimide, and evapg provided the crude allylic bromide as an oil. This was dissolved in 100 ml of abs MeOH containing 725 mg (5 mmoles) of $PhNMe_2$. After 24 hr, work-up provided 970 mg of crude **5a**, which was purified by column chromatography on silica gel–15% H_2O to give a 40% yield of **5a**, mp 116–118°, as well as 15% recovered **3a**.

***p*-Methoxybenzyl 3-Methoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide (6a).**—A soln of 100 mg of **5a** in *i*-PrOH was oxidized with 37 mg of 85% *m*-$ClC_6H_4CO_3H$ to give 63 mg (61%) of **6a**, mp 183–185°, which crystd directly from the reaction mixture. Addl material was recovered from the mother liquors.

***p*-Methoxybenzyl 3-Methoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate (7a).**—A soln of 1.028 g (2 mmoles) of **6a** in 75 ml of DMF was reduced with 15 ml of AcCl and 6 g of $Na_2S_2O_4$. After 4 hr, work-up provided 1.32 g of a dark brown semisolid which was purified by column chromatography on silica gel–15% H_2O to give 300 mg of **7a**, which crystd from Et_2O, mp 116–117.5°.

***p*-Methoxybenzyl 3-Methoxymethyl-7-amino-3-cephem-4-carboxylate Tosylate (8a).**—To a soln of 498 mg (1 mmole) of **7a** in 50 ml of dry C_6H_6 was added 99 mg of pyridine (1.25 mmoles) and 260 mg of PCl_5 (1.25 mmoles). The mixture was heated in an oil bath at 55° for 2 hr. After evapn to dryness, ice-cold MeOH was added; the resultant soln was allowed to stand overnight at room temp. MeOH was removed under reduced pressure, and the residue was dissolved in 60 ml of THF–H_2O (1:1). A slightly exothermic reaction ensued. After 20 min at room temp, most of the THF was removed under reduced pressure, EtOAc was added, and the pH was adjusted to 6.5. The organic layer was removed, washed with NaCl soln, dried ($MgSO_4$), and evapd to a small vol. A soln of 190 mg of TsOH·H_2O in EtOAc was added, and the desired tosylate soon crystd. There was obtained 307 mg (57%) of **8a**, mp 160–164°.

***tert*-Butyl 3-Methoxymethyl-7-amino-3-cephem-4-carboxylate Tosylate (8b).**—A soln of 8.08 g (0.02 mole) of *tert*-butyl 7-phenoxyacetamido-3-methyl-2-cephem-4-carboxylate (**3b**) in 400 ml of CCl_4 was brominated with 4.98 g (1.4 equiv) of NBS and 164 mg (0.05 equiv) of AIBN. The crude bromide was methanolyzed using 100 ml of abs MeOH and 2.0 g of $CaCO_3$ as an HBr scavenger.

The crude Δ^2-3-methoxymethyl cephalosporin **5b** (8.8 g) was oxidized in *i*-PrOH with 4.06 g (0.02 mole, 85%) of *m*-$ClC_6H_4CO_3H$. The isolated crude **6b** weighed 9.1 g. This material was reduced in 15 ml of DMF–135 ml of MeCN (cooled) with 9.1 g of $SnCl_2$ and 9.1 ml of AcCl. After cooling 20 min and standing 1 hr at room temp, the mixture was worked up to give 7.7 g of crude Δ^3-3-methoxymethyl cephalosporin (**7b**).

The **7b** in 350 ml of dry C_6H_6 was treated with 2.1 g (1.5 equiv) of pyridine and 5.55 g (1.5 equiv) of PCl_5 for 2 hr at 55–60°. Usual work-up provided a concd EtOAc soln of amine which was treated with 3.05 g of TsOH·H_2O in EtOAc to give 1.7 g of crude **8b**, mp 158° dec. Recrystn from *i*-PrOH provided excellent material (18% yield from Δ^2-deacetoxy ester **3b**).

Compounds prepared analogously included: ***p*-methoxybenzyl 7-phenoxyacetamido-3-ethoxymethyl-3-cephem-4-carboxylate 1-oxide,** mp 188–189° dec, from EtOAc–Et_2O, prepd as for **6a**; ***p*-methoxybenzyl 7-phenoxyacetamido-3-ethoxymethyl-3-cephem-4-carboxylate,** mp 123–124.5° (from EtOAc–Et_2O), prepd as for **7a**; ***p*-methoxybenzyl 3-ethoxymethyl-7-amino-3-cephem-4-carboxylate tosylate,** mp 143–144.5° (from EtOAc), prepd as for **8a**.

3-Methoxymethyl 7-Phenoxyacetamido-3-cephem-4-carboxylic Acid (9a).—To a soln of 174 mg of **7a** and 119 mg of anisole in 25 ml of dry C_6H_6 was added 1.25 ml of F_3CCO_2H. After stirring for 2 hr at room temp, the reaction mixture was evapd, taken up in EtOAc, and extd 3 times with aq $NaHCO_3$. The extracts were cooled, layered with EtOAc, and acidified to pH 2.8. From the EtOAc layer was obtained 140 mg of a foam, which gave 86 mg of Δ^3-acid **9a**, mp 135–137°, after crystn from Et_2O.

7-Phenoxyacetamido-3-alkoxymethyl-3-cephem-4-carboxylic Acids.—These substances were prepared in a manner analogous to that used in the preparation of 3-methoxymethyl cephalosporin, but purification was modified because of consistent lack of crystallinity throughout the series.

The Δ^2-3-alkoxymethyl *t*-Bu esters were purified by column chromatography, and the structures were confirmed by nmr.

Oxidation and reduction at the S atom provided the crude Δ^3-3-alkoxymethyl *t*-Bu esters which were purified by column chromatography; the structures were confirmed by nmr.

Ester cleavage in 98–100% HCO_2H provided the desired cephalosporanic acids.

Acylations of 7-Amino-3-methoxymethyl-3-cephem-4-carboxylate Esters.—A mixture of the tosylate salt of the 7-amino-3-methoxymethyl-3-cephem-4-carboxylate ester and $NaHCO_3$ (4 equiv) in Me_2CO was cooled, and the desired acid chloride was added. After 1 hr in the cold and 2 hr at room temp, diln with H_2O pptd the acylated cephalosporin esters. Structures were confirmed by nmr and elemental anal.

After acid-catalyzed ester cleavage (F_3CCO_2H for *p*-methoxybenzyl, HCO_2H for *t*-Bu), the isolated cephalosporanic acids were converted into their Na salts by treatment with NaOAc in a MeOH–EtOH mixture.

7-Amino-3-alkoxymethyl-3-cephem-4-carboxylic Acids.—The tosylate salt of the appropriate nucleus ester was converted into the free amine, and the ester group was cleaved by acid treatment (F_3CCO_2H for *p*-methoxybenzyl, HCO_2H for *t*-Bu). The crude amino acids were dissolved in a mixture of EtOAc and H_2O, and the pH was adjusted to 3.6 with Et_3N. Refrigeration of the sepd aq layer pptd the solid amino acid.

Phenylglycyl Derivatives of 7-Amino-3-alkoxymethyl-3-cephem-4-carboxylic Acids.—These compounds were prepared in a manner similar to that already described, using F_3CCO_2H cleavage of the *t*-BOC group.

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