Both equations indicate that in this series activity decreases with increasing bulk at the 9α position and increases as the 9α-substituent becomes more electron withdrawing. While these conclusions are in agreement with those of Hansch and Wolff,[7] they bring into question the significance of the π term. These authors concluded that a π containing term was required for a good correlation and suggested that its importance might relate either to the effect of lipophilicity on transport or might reflect a hydrophobic interaction at the active site. An alternative interpretation is that the role of their π term is to lower the predicted activity of compounds containing strongly hydrated 9α-substituents. In an aqueous environment such substituents would have a larger effective bulk and hence a lower than predicted activity. (Calculations by eq 2c of the effective van der Waals volume required to account for the observed activity give a volume comparable to a monohydrated hydroxyl group.) Such an explanation seems to be in accord with the correlation between molecular shape and glucocorticoid activity reported by Weeks et al.[24]

In conclusion, we believe that these studies clearly establish the importance of steric factors in QSAR involving steroid hormones. The nature of the substituents in both studies was such as to permit a clear differentiation between steric parameters and π.[22] Moreover, the studies illustrate the importance of investigating a variety of steric parameters and they suggest the possible importance of difference or squared steric terms. Further studies will be required to establish the generality of the latter effect.

Acknowledgment. The authors are grateful to the SUNY/Buffalo Computing Center for their donation of computing services of a CDC 6400 computer.

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Semisynthetic Cephalosporins. Synthesis and Structure–Activity Relationships of 7-Sulfonylacetamido-3-cephem-4-carboxylic Acids

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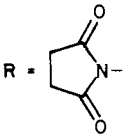
The synthesis and in vitro and in vivo activities of a series of 7-sulfonylacetamido-3-cephem-4-carboxylic acids with acetoxymethyl or heterocyclic thiomethyl substituents at the 3 position are described. Lengthening the alkyl chain attached to the sulfonyl group increased gram-positive activity but the effect on gram-negative activity was variable. Other structural changes on the 7-acyl side chain resulted in only minor changes in in vitro activity. The protective effectiveness in infected mice generally paralleled the in vitro activity, except that the butylsulfonyl derivatives were less protective than predicted by in vitro activity. Replacement of the 3-acetoxymethyl by a 3-heterocyclic thiomethyl group resulted in an overall improvement of activity both in vitro and in vivo.

A majority of cephalosporins that possess significant antibacterial activity have on the 7 position an acetamido group to which is attached a heterocyclic or benzene ring. This ring may be attached directly or linked through a heteroatom. These substituents are relatively large and complex by virtue of the attached aromatic ring. An exception to this is cephacetrile which has a simple cyanoacetamido grouping at the 7 position. It seemed reasonable that other simple side chains might impart broad-spectrum antibacterial activity and this led us to investigate derivatives of mercaptoacetic acid. Previously, we reported the broad-spectrum activities of 7-trifluoromethylthioacetamido-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid (SK&F 59962) and its closely related analogues.[1,2] This article presents some of the structure–activity studies that led to this compound. It extends the previous work to additional derivatives of mercaptoacetic acid in which the sulfur atom is oxidized to the sulfonyl state. It also describes the structure–activity relationships observed by altering the length of the alkyl group on the sulfur atom, by substituting for the alkyl group strongly electron-donating or -withdrawing substituents such as amino or trifluoromethyl, and by altering the 7-substituent size through substitution of phenyl for the alkyl group and through alkylation of the α-methylene. Additionally, the effect on activity of varying the 3-substitutent is presented; for each alteration at the 7 position, the 3-acetoxymethyl analogue was compared with one or more 3-heterocyclic thiomethyl analogues.

Chemistry. The cephalosporins were prepared by acylation of 7-aminocephalosporanic acid (7-ACA) or its 3-heterocyclic thiomethyl analogues. The latter were made

Table I. Side-Chain Acids and Activated Esters



Compd	Structure	Formula	Analyses
1	$CH_3SCH_2CO_2H$	$C_3H_6O_2S$[a]	
2	$C_2H_5SCH_2CO_2H$	$C_4H_8O_2S$[b]	
3	n-$C_3H_7SCH_2CO_2H$	$C_5H_{10}O_2S$[c]	
4	n-$C_4H_9SCH_2CO_2H$	$C_6H_{12}O_2S$[c]	
5	$C_6H_5SCH_2CO_2H$	$C_8H_8O_2S$[b]	
6	$CH_3SCH(CH_3)CO_2H$	$C_4H_8O_2S$[d]	
7	$H_2NSO_2CH_2CO_2H$	$C_2H_5NO_4S$[e]	
8	$CF_3SO_2CH_2CO_2H$	$C_3H_3F_3O_4S$[f]	
9	$CH_3SO_2CH_2CO_2R$	$C_7H_9NO_6S$	H, N; C[g]
10	$C_2H_5SO_2CH_2CO_2R$	$C_8H_{11}NO_6S$	C, H, N
11	n-$C_3H_7SO_2CH_2CO_2R$	$C_9H_{13}NO_6S$	C, H, N
12	n-$C_4H_9SO_2CH_2CO_2R$	$C_{10}H_{15}NO_6S$	C, H, N
13	$CH_3SO_2CH(CH_3)CO_2R$	$C_8H_{11}NO_6S$	h
14	$C_6H_5SO_2CH_2CO_2R$	$C_{12}H_{11}NO_6S$	C, H, N

[a] I. Schmolka and R. E. Spoerri, *J. Org. Chem.*, 22, 1721 (1957). [b] W. J. Kenney, J. A. Walsh, and D. A. Davenport, *J. Am. Chem. Soc.*, 83, 4019 (1961). [c] E. Larsson, *Ber.*, 6313, 1347 (1930). [d] M. Protiva et al., *Cesk. Farm.*, 6, 425 (1957); *Chem. Abstr.*, 52, 9944*h* (1958). [e] R. L. Hinman and L. Locatell, Jr., *J. Am. Chem. Soc.*, 81, 5653 (1959). [f] L. M. Yagupol'skii, A. G. Panteleimonov, and V. V. Orda, *Zh. Obshch. Khim.*, 34, 3456 (1964). [g] C: calcd, 35.74; found, 36.28. [h] Characterized by ir and NMR.

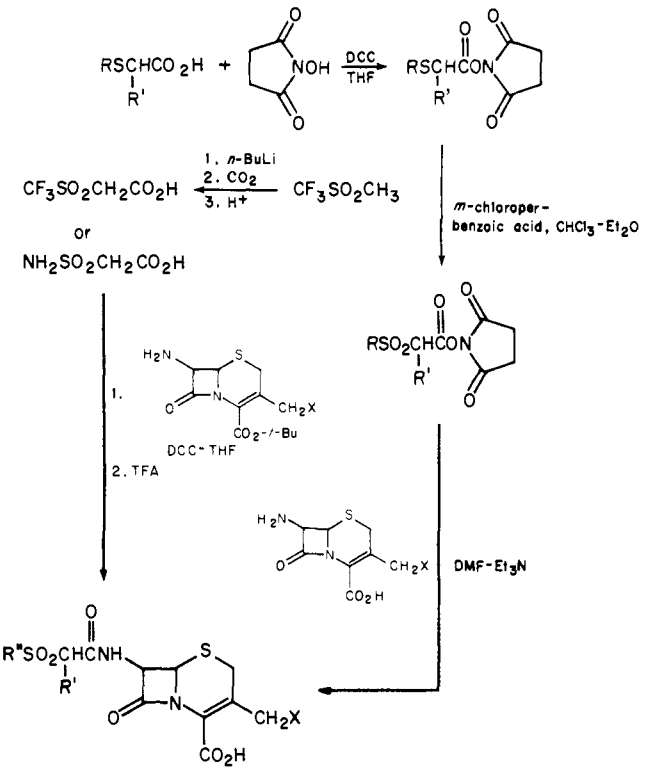
by displacement of the acetate of 7-ACA with an appropriate thiol by the widely used general procedure[3] described in the Experimental Section. Alternatively, several derivatives (**31**, **32**, **35**, and **36**) were synthesized by direct coupling of the side-chain acid to a 7-amino-3-cephem-4-carboxylic acid in which the carboxyl group was protected with a *tert*-butyl group which was subsequently removed with trifluoroacetic acid.

The alkyl- and arylthioacetic acids (Table I) were reported previously. They were prepared by direct displacement of the appropriate thiol on chloroacetic (compounds **1**–**5**) or α-chloropropionic acid (compound **6**). These acids were coupled to *N*-hydroxysuccinimide with DCC in THF to give the activated esters in excellent yield. The latter were often oils or very low melting solids which were oxidized with 2 equiv of *m*-chloroperbenzoic acid (MCPBA) in chloroform–ether to give the crystalline sulfones **9**–**14**. These activated esters were stable, highly active acylating agents that reacted with the triethylamine salts of the 7-amino-3-cephem-4-carboxylic acids in dry DMF to give cephalosporins **15**–**30**, **33**, **34**, **37**, and **38**, as outlined in Scheme I.

This general method was not successful when applied to the synthesis of compounds **31** and **35**. In this case, trifluoromethylthioacetic acid[4] could be coupled to *N*-hydroxysuccinimide to give the intermediate activated ester, but this could not be oxidized to the corresponding sulfone. Instead, trifluoromethylsulfonylacetic acid (**8**) was obtained by carbonation of the lithium salt of methyl trifluoromethyl sulfone[5] and coupled to the 7-amino-3-cephem-4-carboxylic acid *tert*-butyl ester[6,7] using DCC. The *tert*-butyl protecting group was removed by treatment with TFA at room temperature to give **31** and **35** (Scheme I).

Cephalosporins **32** and **36** were made by the same coupling method using sulfamoylacetic acid (**7**). The TFA cleavage was carried out in the presence of *m*-dimethoxybenzene to trap the *tert*-butyl cation and minimize its

Scheme I



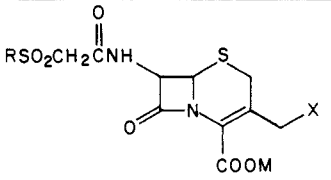
R = C_1–C_4 *n*-alkyl, phenyl
R' = H or CH_3
R'' = R, CF_3, NH_2
X = see Table II

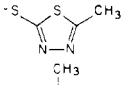
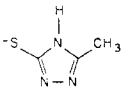
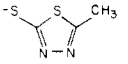
reaction with other positions on the cephalosporin.

All cephalosporins were characterized and tested as free acids or as their sodium salts (Table II).

Biology. The cephalosporins presented here show antibacterial activity against a variety of gram-positive and gram-negative organisms. The in vitro activities of the cephalosporins having a 7-methylsulfonylacetic acid side chain are shown in Table III. The data for these organisms are representative of those obtained from a larger group of four gram-positive and eleven gram-negative bacteria used in our initial screen for evaluating β-lactam antibiotics. These data illustrate the effect of 3-position variation on the antibiotic activity for a series in which the 7 position remains constant. Displacement of the acetate by various heterocyclic thiols does not produce a significant change in the gram-positive activity as exemplified by the MIC values against a penicillin G resistant strain of *Staphylococcus aureus* [*S.a.*(*R*)]. For all compounds, the activity remains within one tube dilution of the parent 3-acetoxymethyl analogue **15**; and all are relatively less active than the controls (cefazolin, cephalothin, and SK&F 59962). On the other hand, this structural change has a variable effect on the activity against gram-negative bacteria. While in a few cases the activity is lowered, the general trend is toward improvement of the antibacterial activity. In line with a frequent observation in our laboratory, the methyltetrazole analogue **17** is the most active of the group tested. This is illustrated further in the analogue sequences (acetoxymethyl, methylthiadiazolethiomethyl, methyltetrazolethiomethyl) listed in Table IV. The relatively poor gram-negative activity of **20** (also a tetrazole) might be due to the highly polar nature of the 3-heterocyclic thiomethyl substituent. This compound is also anomalous in its other properties. For example, its mouse infection protection activity (PD_{50}) value) against

Table II. Structures of Cephalosporin Analogues



Compd	R	X	M	Formula	Analyses
15	CH_3	OAc	Na	$C_{13}H_{15}N_2O_8S_2Na\cdot H_2O$	C, H, N
16	CH_3		Na	$C_{14}H_{15}N_4O_6S_4Na\cdot H_2O$	C, H, N
17	CH_3		Na	$C_{13}H_{15}N_6O_6S_3Na\cdot 0.5H_2O$	C, H, N[a]
18	CH_3		Na	$C_{14}H_{16}N_5O_6S_3Na\cdot H_2O\cdot 0.25EtOAc$	C, H, N[b]
19	CH_3		Na	$C_{14}H_{16}N_5O_6S_3Na\cdot 0.25H_2O$	C, H, N
20	CH_3		Na	$C_{12}H_{13}N_6O_6S_3Na\cdot H_2O$	C, H, N[c]
21	CH_3		Na	$C_{13}H_{14}N_5O_6S_3Na\cdot 0.25Et_2O\cdot 1.25H_2O$	C, H, N
22	C_2H_5	OAc	Na	$C_{14}H_{17}N_2O_8S_2Na$	C, H, N
23	n-C_3H_7	OAc	H	$C_{15}H_{20}N_2O_8S_2$	C, H, N
24	n-C_4H_9	OAc	H	$C_{16}H_{22}N_2O_8S_2$	C, H, N
25	C_2H_5		H	$C_{15}H_{18}N_4O_6S_4$	C, H, N
26	n-C_3H_7		Na	$C_{16}H_{19}N_4O_6S_4Na\cdot H_2O$	C, H, N
27	n-C_4H_9		Na	$C_{17}H_{21}N_4O_6S_4Na\cdot H_2O$	C, H, N
28	C_2H_5		Na	$C_{14}H_{17}N_6O_6S_3Na\cdot 0.5H_2O$	C, H, N
29	n-C_3H_7		Na	$C_{15}H_{19}N_6O_6S_3Na\cdot 0.75H_2O$	C, H, N
30	n-C_4H_9		Na	$C_{16}H_{21}N_6O_6S_3Na\cdot H_2O$	C, H, N[d]
31	CF_3	OAc	H	$C_{13}H_{13}F_3N_2O_8S_2$[e]	C, H, N
32	NH_2	OAc	Na	$C_{12}H_{15}N_3O_8S_2Na\cdot 0.5H_2O$	C, H, N
33	C_6H_5	OAc	Na	$C_{18}H_{17}N_2O_8S_2Na\cdot H_2O$	C, H, N
34	f	OAc	Na	$C_{14}H_{17}N_2O_8S_2Na\cdot 0.5H_2O$	C, H, N
35	CF_3		Na	$C_{13}H_{12}F_3N_6O_6S_3Na\cdot 1.5H_2O\cdot 0.25EtOAc$	C, H, N
36	NH_2		Na	$C_{12}H_{14}N_7O_6S_3Na\cdot 1.5H_2O\cdot 0.1Et_2O$	C, H, N
37	C_6H_5		H	$C_{18}H_{18}N_6O_6S_3$	[g]
38	f		Na	$C_{14}H_{17}N_6O_6S_3Na\cdot 0.5H_2O$	C, H, N[h]

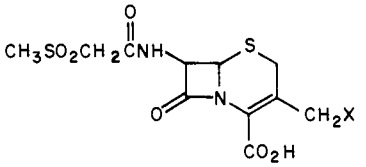
[a] N: calcd, 17.53; found, 16.78. [b] N: calcd, 14.37; found, 13.50. [c] N: calcd, 17.71; found, 16.72. [d] N: calcd, 15.74; found, 15.03. [e] Contains 5% dicyclohexylurea. [f] Entire side chain is $CH_3SO_2CH(CH_3)C(=O)$. [g] We are grateful to Dr. Pierre Crooy, Recherche et Industrie Thérapeutiques, Genval, Belgium, for this sample. [h] N: calcd, 17.03; found, 16.48.

E. coli, 45 mg/kg, is significantly better than would be expected from its MIC value (*E. coli*, 50 μg/ml), Table III.

The data in Table IV illustrate the effect of altering the length of the alkyl group attached to sulfur in three analogous series: where the 3-substituent is acetoxymethyl, methylthiadiazolethiomethyl, and methyltetrazolethiomethyl. As already indicated, the methyltetrazolethiomethyl analogues tend to be the most active, the acetoxymethyl analogues the least. In each series, lengthening the alkyl group attached to sulfur results in a progressive increase in in vitro gram-positive activity (4- to 16-fold overall). Against gram-negative bacteria there is also a trend toward greater activity, but the trend is more variable and less pronounced. The gram-negative activity appears to be more sensitive to variation of the 3-position substitutent than to changes at the 7 position.

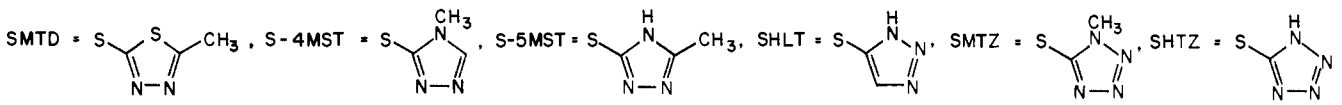
Table V lists analogues with more pronounced structural changes on the 7-substituent. Compounds **31** and **35** have a very strongly electron-withdrawing trifluoromethyl substituent on the sulfonyl group while **32** and **36** have an electron-donating amino group attached. Compound **31** is slightly more active than the corresponding methyl analogue **15**; the differences between compounds **35** and **17** are insignificant. Compounds **32** and **36** are less active

Table III. In Vitro and in Vivo Activities of 7-Methylsulfonylacetamido-3-cephem-4-carboxylic Acids



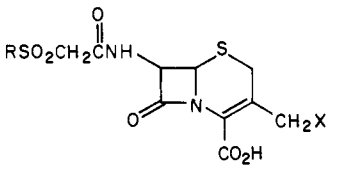
Compd	X[d]	Minimum inhibitory concentrations, μg/ml[a,b]						Mouse PD_{50} vs. *E. coli*, mg/kg sc[c]
		S.a.(R)[e]	*E.c.*	*K.p.*	*Sal.p.*	*Sh.p.*	*E.a.*	
15	OAc	3.1	13	13	13	13	>200	62
16	SMTD	1.6	13	3.1	3.1	13	>200	NT
17	SMTZ	1.6	1.6	1.6	0.8	1.6	25	7
18	S-4MST	3.1	6.2	6.2	3.1		>200	22
19	S-5MST	1.6	6.2	3.1	1.6	13	200	10
20	SHTZ	6.2	50	3.1	3.1	25	>200	45
21	SHLT	1.6	13	6.2	6.2	13	>200	NT
Cefazolin		0.4	0.8	0.8	0.8	0.4	1.6	6
Cephalothin		0.2	3.1	3.1	1.6	6.2	50	50
SK&F 59962		0.4	0.4	0.8	0.4	0.2	1.6	2

[a] The in vitro antibacterial activities are reported as minimum inhibitory concentrations (MIC) in μg/ml. The MIC's were determined by the twofold agar dilution method on trypticase soy agar. Organisms selected for inclusion in this table are *S.a.(R)*, *Staphylococcus aureus* HH 127 (penicillin G resistant); *E.c.*, *Escherichia coli* 12140; *K.p.*, *Klebsiella pneumoniae* 4200; *Sal.p.*, *Salmonella paratyphi* ATCC 12176; *Sh.p.*, *Shigella paradysenteriae* HH 117; *E.a.*, *Enterobacter aerogenes* ATCC 13048. [b] All compounds reported in this table showed activity against *Streptococcus faecalis* from 13 to >200 μg/ml; therefore, these data are not included. None of the compounds demonstrated significant activity against *Pseudomonas aeruginosa*. [c] The PD_{50} values are expressed as the total dose of compound in mg/kg required to protect 50% of the mice challenged intraperitoneally with *E. coli* 12140. The compounds were injected subcutaneously in equally divided portions at 1 and 5 h postinfection. Values were calculated by the method of Lichtfield and Wilcoxon [*J. Pharmacol. Exp. Ther.*, **96**, 99-113 (1949)]. NT, not tested. [d] X is from Table II where



[e] MIC's were also determined vs. *S. aureus* 23390 (Smith) and in all cases the MIC values were within one tube dilution of those reported for *S. aureus* HH 127.

Table IV. In Vitro and in Vivo Activities of 7-Alkylsulfonylacetamido-3-cephem-4-carboxylic Acids

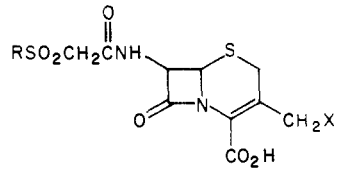


Compd	R[d]	X[d]	Minimum inhibitory concentration, μg/ml[a,b]						Mouse PD_{50} vs. *E. coli*, mg/kg sc[c]
			S.a.(R)[e]	*E.c.*	*K.p.*	*Sal.p.*	*Sh.p.*	*E.a.*	
15	Me	OAc	3.1	13	13	13	13	>200	62
22	Et	OAc	0.8	25	6.2	3.1	25	>200	70
23	Pr	OAc	0.8	13	6.2	3.1	13	200	56
24	Bu	OAc	0.2	13	13	3.1	6.2	50	180
16	Me	SMTD	1.6	13	3.1	3.1	13	>200	12
25	Et	SMTD	0.4	3.1	1.6	1.6	6.2	100	8
26	Pr	SMTD	0.4	6.2	3.1	1.6	6.2	50	25
27	Bu	SMTD	0.1	6.2	6.2	1.6	6.2	25	>50
17	Me	SMTZ	1.6	1.6	1.6	0.8	1.6	25	7
28	Et	SMTZ	0.8	1.6	1.6	0.8	1.6	100	7
29	Pr	SMTZ	0.4	1.6	0.8	0.4	1.6	6.2	10
30	Bu	SMTZ	0.4	3.1	3.1	1.6	3.1	13	21
Cephalothin			0.2	3.1	3.1	1.6	6.2	50	50

[a-e] See corresponding footnotes to Table III.

than **15** or **17** but again the differences are slight. In contrast to the experience with the unoxidized thio analogues, fluorination of the methyl group when attached to the oxidized sulfur atom does not result in the significant improvement in both in vitro and in vivo activities seen with 7-trifluoromethylthioacetamido-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid (SK&F 59962).[1] The derivatives with phenyl attached to sulfur (**33** and **37**) were slightly less active overall than the corresponding methyl analogues. Compounds **34** and **38** have the α-methylene group (adjacent to sulfonyl) substituted by methyl. This results in pairs of diastereomeric sulfones of which one isomer of the pair might be expected to be more active than the other. Surprisingly, this change had less of an activity-lowering effect than would be expected from experience with other penicillins and ceph-

Table V. In Vitro and in Vivo Activities of Substituted Sulfonylacetamido-3-cephem-4-carboxylic Acids



Compd	R[d]	X[d]	Minimum inhibitory concentration, μg/ml[a,b] S.a.(R)[e]	E.c.	K.p.	Sal.p.	Sh.p.	E.a.	Mouse PD_{50} vs. E. coli, mg/kg sc[c]
31	CF_3	OAc	6.2	6.2	6.2	6.2	13	25	>50
32	NH_2	OAc	1.6	50	25	13	25	200	NT
33	Ph	OAc	1.6	50	13	13	25	>200	NT
34	*f*	OAc	3.1	25	3.1	13	25	50	NT
35	CF_3	SMTZ	1.6	1.6	3.1	1.6	0.8	3.1	17
36	NH_2	SMTZ	1.6	3.1	13	1.6	3.1	13	38
37	Ph	SMTZ	0.4	3.1	3.1	6.2	1.6	13	25
38	*f*	SMTZ	3.1	6.2	6.2	6.2	3.1	13	50
Cephalothin			0.2	3.1	3.1	1.6	6.2	50	50

[a-e] See corresponding footnotes to Table III. [f] For this compound, the entire side chain is $CH_3SO_2CH(CH_3)C(=O)$.

alosporins disubstituted on the α position of the 7-acyl group.

The PD_{50} values generally parallel the trends in in vitro activity. In Tables III–V the derivatives having a 3-acetoxymethyl group generally display poor PD_{50} values. This is not surprising since they have relatively poor in vitro activities against the *E. coli* strain (12140) used in the in vivo test. Although there is some lack of consistency in the PD_{50} values for the various series of analogues, the values presented in the three tables suggest that for this cephalosporin type, replacement of acetoxymethyl by heterocyclic thiomethyl improved the in vivo effectiveness. For example, the PD_{50} values for the heterocyclic thiomethyl analogues in Table III are consistently better than those for the 3-acetoxymethyl derivative. Trends in the in vivo activity as the alkyl group on the 7-substituent is increased in length can also be discerned (Table IV). While the in vitro activity against the indicator organism (*E. coli*) remains relatively constant in each series, the in vivo activity tends to fall off with the *S*-butyl derivatives.

Of the cephalosporins described in this article the 3-methyltetrazolethiomethyl analogues having smaller alkyl groups at the 7 position (**17**, **28**, and **29**) display the best overall in vitro and in vivo activities. While these cephalosporins display good broad-spectrum antimicrobial activities in vitro and they afford protection in vivo at relatively low dosage levels, 7-trifluoromethylthioacetamido-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid remains the cephalosporin of choice in this series.

Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover Uni-Melt apparatus. Unless indicated otherwise, infrared spectra were obtained in Nujol mull using a Perkin-Elmer Infracord; NMR spectra were obtained in Me_2SO-d_6 or Me_2SO-d_6–D_2O on a Varian T-60 spectrometer using Me_4Si as an internal standard. The ir and NMR data of all compounds were consistent with structure. Where elemental analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. $MgSO_4$ was used as drying agent for organic extracts. The heterocyclic thiols used in this work were prepared by procedures described in the literature. The side-chain acids used are listed in Table I.

***N*-Hydroxysuccinimide Esters of Thioacetic Acids.** An ice-bath cooled solution of 10 mmol of the alkyl- or arylthioacetic acid and 10 mmol of *N*-hydroxysuccinimide in 300 ml of THF was treated dropwise with 10 mmol of DCC in 75 ml of THF. When addition was complete the ice bath was removed, the mixture was stirred at room temperature overnight and filtered, and the filtrate was evaporated to give the product. These compounds were often viscous oils and were used without further purification.

***N*-Hydroxysuccinimide Esters of Sulfonylacetic Acids** (**9**–**14**). To 20 mmol of the appropriate thioacetic acid ester in 40 ml of $CHCl_3$ was added 50 mmol of 85% *m*-chloroperbenzoic acid in 150 ml of Et_2O. The mixture was stirred at room temperature overnight (for **9** it was stirred 3 days). The precipitate was removed and stirred with 100 ml of Et_2O and the solid product was collected and dried. Additional quantities of **11** and **12** were obtained by evaporating the filtrates to dryness and extracting the residue with one 100-ml portion of ether. The residual sulfones were all purified by recrystallization.

7-Amino-3-heterocyclic Thiomethyl-3-cephem-4-carboxylic Acids. To a suspension of 0.1 mol of 7-ACA in 200 ml of water and 100 ml of acetone was added 0.23 mol of $NaHCO_3$ in 200 ml of water, and the resultant solution was heated to 40–50°. The appropriate thiol (0.13 mol) in 200 ml of acetone was added and the solution was stirred under reflux. Periodically a solid sample was isolated by adjusting the pH of an aliquot of the reaction mixture to 3.5. The reaction was judged to be complete when the ir spectrum of the solid showed no acetoxy remaining (~4 h). The pH was maintained between 7.4–7.8 by the addition of 5% $NaHCO_3$ or 3 N HCl if necessary. When the reaction was complete the solution was cooled in an ice bath and acidified with 3 N HCl to pH 3.5. The resulting precipitate was collected, washed with water and acetone, and dried. The crude products were purified by suspending in water and adding 6 N HCl until solution was effected. The acidic solution (Norit) was held at room temperature for 30 min to 5 h depending on the presence of residual 7-ACA (NMR) in the crude product. After filtering through Supercel the filtrate was cooled and adjusted to pH 3.5 with 20% NaOH. The precipitate was washed with water and acetone and dried. These intermediates were used without further purification.

7-Aryl- or Alkylsulfonylacetamido-3-cephem-4-carboxylic Acids (**15**–**30**, **33**, **34**, **37**, **38**). Triethylamine was added dropwise to a stirred suspension of 10 mmol of the appropriate 7-amino-3-cephem-4-carboxylic acid in 50 ml of dry DMF until solution was complete. The activated ester (10 mmol) was added in one portion. Stirring was continued for 1.5 h after which the reaction mixture was poured into 200 ml of ice water. For the more water-soluble compounds, the DMF solution was added dropwise to 300 ml of Et_2O to give a gummy precipitate from which the solvent was decanted and the residue taken up in 200 ml of H_2O. The aqueous solution was extracted with 200 ml of EtOAc which was discarded. The aqueous phase was layered with fresh EtOAc and acidified to pH 1.5 with 3 N HCl. An emulsion

usually formed which was filtered by suction through a pad of Celite. The filtrate layers were separated and the aqueous phase was extracted twice more with EtOAc. The combined extracts were washed with water, dried, and evaporated to give the cephalosporin. If the cephalosporin was not solid it was dissolved in a small volume of EtOAc and excess sodium 2-ethylhexanoate (30% solution in 2-propanol) was added. Et_2O was added dropwise with rapid stirring to precipitate the sodium salt of the cephalosporin which was collected and dried under vacuum.

7-Trifluoromethylsulfonylacetamidocephalosporanic Acid (31). To a solution of 492 mg (1.5 mmol) of 7-ACA *tert*-butyl ester[6] and 309 mg (1.5 mmol) of DCC in 20 ml of dry THF was added over 10 min 290 mg (1.5 mmol) of trifluoromethylsulfonylacetic acid (Table I) in 10 ml of THF. Evolution of CO_2 indicated some decarboxylation of the starting acid. After stirring for 2 h an additional 150 mg of DCC was added followed by 150 mg of the acid. Similar quantities of DCC and acid were again added at 4 h and the mixture was stirred overnight. TLC indicated complete reaction. The precipitated urea was removed and the filtrate evaporated to a yellow gum. Trituration with a small quantity of Et_2O produced crystals which were collected to yield 352 mg (47%) of product. This was dissolved in TFA and allowed to stand at room temperature for 30 min. The TFA was evaporated and the resulting gum dissolved in EtOAc, washed, dried, and evaporated. The residue was triturated with Et_2O–petroleum ether to give after drying 197 mg (63%) of **31** as an off-white solid.

7-Trifluoromethylsulfonylacetamido-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic Acid (35). To a solution of 1.15 g (3.0 mmol) of 7-amino-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid *tert*-butyl ester[7] and 618 mg (3.0 mmol) of DCC in 40 ml of dry benzene was added at three 15-min intervals 576 mg (3.0 mmol) of trifluoromethylsulfonylacetic acid divided into three equal portions. After stirring for 1 h an additional 100 mg of acid was added and the mixture stirred for 1 h further. The precipitate was removed and the filtrate evaporated to a gum which was dissolved in 15 ml of TFA and allowed to stand for 30 min. The TFA was evaporated in vacuo and the gummy residue chromatographed on 50 g of silica gel eluting with $CHCl_3$–MeOH–HCOOH (90:10:3) to yield 550 mg of pale yellow oil. The oil was dissolved in 20 ml of EtOAc and treated with 600 mg of a 30% solution of sodium 2-ethylhexanoate in 2-propanol. Dropwise addition of Et_2O precipitated the product which was collected and dried to give 470 mg (30%) of **35** as a tan powder.

7-Sulfamoylacetamidocephalosporanic Acid (32). A solution of 1.65 g (5.0 mmol) of 7-ACA *tert*-butyl ester, 0.70 g (5.0 mmol) of sulfamoylacetic acid (Table I), and 1.03 g of DCC in 25 ml of dry THF was stirred at room temperature overnight. The precipitated urea was removed and the filtrate evaporated to a gum which was dissolved in 15 ml of TFA. After standing for 15 min, the TFA solution was added dropwise to 150 ml of Et_2O. The resulting precipitate was collected and stirred with 100 ml of EtOAc for 30 min. The insoluble material was removed and the filtrate treated with 1.0 g of a 30% solution of sodium 2-ethylhexanoate in 2-propanol. Dropwise addition of Et_2O precipitated the product which was collected, washed with Et_2O and then CH_3CN, and dried to give 709 mg (35%) of **32** as a yellow powder.

7-Sulfamoylacetamido-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic Acid (36). A solution of 7.15 g (18.6 mmol) of 7-amino-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid *tert*-butyl ester, 2.59 g (18.6 mmol) of sulfamoylacetic acid, and 3.84 g (18.6 mmol) of DCC in 75 ml of DMF was stirred at room temperature overnight. The precipitated urea was removed and the solvent evaporated. The residue was taken up in EtOAc, extracted with 3 N HCl, 5% $NaHCO_3$ and water, dried, and evaporated to give 9.0 g of gum. A 6-g portion was chromatographed on 240 g of silica gel eluting with benzene–acetone (9:1) followed by benzene–acetone (1:1) to yield 4.7 g of pure product. This was dissolved in a mixture of 25 ml of TFA and 25 ml of *m*-dimethoxybenzene and stirred for 1.5 h and the product precipitated by the dropwise addition of 150 ml of Et_2O. The crude product (5.3 g, 62%) contained rearranged *tert*-butyl impurities. Reprecipitation from MeOH–Et_2O yielded 445 mg of pure **36** which was converted to its sodium salt with sodium 2-ethylhexanoate.

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