A NEW PARENTERAL CEPHALOSPORIN. SK&F 59962: 7-TRIFLUOROMETHYLTHIOACETAMIDO-3-(1-METHYL-1H-TETRAZOL-5-YLTHIOMETHYL)-3-CEPHEM-4-CARBOXYLIC ACID. CHEMISTRY AND STRUCTURE ACTIVITY RELATIONSHIPS

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The synthesis, microbiological profile and *in vivo* effectiveness in laboratory animals of a series of cephalosporins having 7-acyl substituents derived from methylthioacetic acid are described. Structure-activity relationships examined include the effect of oxidation of the side-chain sulfur atom, replacement of the (side-chain) methyl hydrogens by fluorine and replacement of the 3-acetoxy substituent by thioheterocycles. One derivative, 7-trifluoromethylthioacetamido-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid (SK&F 59962), was found to have outstanding antibacterial activity *in vitro* and *in vivo*.

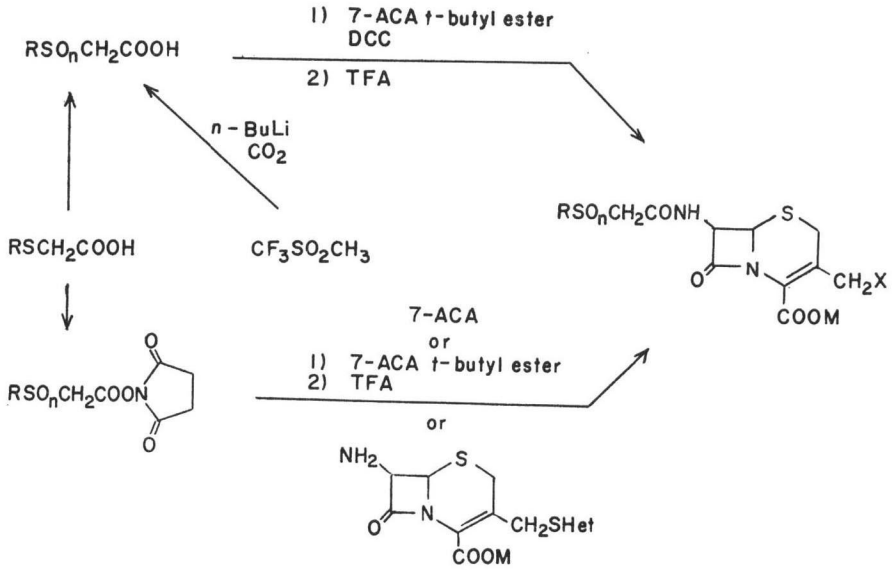
Studies on the structure-activity relationships for cephalosporin antibiotics have tended toward the attachment of relatively large substituents on the 7-position of the cephalosporin nucleus. The β-lactam antibiotics that have attained a role in medicine have reinforced this tendency. Most carry on the amino group of the nucleus an acetic acid moiety to which is attached, either directly or by a hetero atom linkage, a ring system such as phenyl, thiophene, pyridine or tetrazole. Thus, reviews on structure-activity relationships among the penicillins and cephalosporins are dominated by such derivatives.[1] An exception to this compound type is cephacetrile which has a 7-substituent derived from cyanoacetic acid. This paper describes additional examples of cephalosporins with relatively simple 7-acyl side chains that possess broad-spectrum antibacterial activities. One derivative in particular, 7-trifluoromethylthioacetamido-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid (**11**, SK&F 59962), has proved to be one of the most active cephalosporins evaluated in our biological screen and it provides a sufficiently effective combination of antimicrobial and pharmacokinetic properties[2] to make it a candidate for clinical evaluation in humans.

The cephalosporins described here have acyl groupings derived from methylthioacetic acid. This report deals primarily with the effects on biological activity of varying the oxidation state of the sulfur atom (sulfide, sulfoxide, sulfone) and of replacing the methyl group hydrogen atoms by fluorine. Additionally, the influence of 3-substituent variation on the activity of cephalosporin structures having the 7-trifluoromethylthioacetamido grouping is examined.

Chemistry

The cephalosporins having an acetoxymethyl substituent on the 3-position were prepared by coupling the side-chain acid to 7-ACA or its *t*-butyl ester,[3] either directly using DCC (*t*-butyl ester) or *via* the activated ester derived from the side-chain acid and N-hydroxysuccinimide (acid

Scheme 1



n = 0, 1, 2; R = CH_3, CF_3; Het = see text;
X = $OCOCH_3$, SHet; M = H^+, Na^+

Table 1. Empirical formulas for compounds reported

Compound	Formula [a]	Compound	Formula [a]
1	$C_7H_9NO_4S$	**11**	$C_{13}H_{12}F_3N_6O_4S_3Na$
2	$C_7H_9NO_5S$	**12**	$C_{14}H_{12}F_3N_4O_4S_4Na$
3	$C_7H_9NO_6S$ [b]	**13**	$C_{14}H_{12}F_3N_4O_5S_3Na \cdot 1.25H_2O$ [g]
4	$C_7H_6F_3NO_4S$	**14**	$C_{14}H_{13}F_3N_5O_4S_3Na \cdot CH_3OH$
5	$C_{13}H_{16}N_2O_6S_2$ [c]	**15**	$C_{14}H_{13}F_3N_5O_4S_3Na \cdot H_2O, 0.5\ CH_3OH$
6	$C_{13}H_{16}N_2O_7S_2 \cdot 0.5\ H_2O$	**16**	$C_{15}H_{15}F_3N_5O_4S_3Na \cdot 1.5\ H_2O$
7	$C_{13}H_{15}N_2O_5S_2Na \cdot H_2O$ [d]	**17**	$C_{14}H_{14}F_3N_5O_4S_3$
8	$C_{13}H_{13}F_3N_2O_6S_2 \cdot DMF$	**18**	$C_{13}H_{12}F_3N_5O_4S_3$ [h]
9	$C_{13}H_{12}F_3N_2O_7S_2Na$ [e]	**19**	$C_{12}H_{10}F_3N_6O_4S_3Na \cdot H_2O$
10	$C_{13}H_{13}F_3N_2O_8S_2$ [f]	**20**	$C_{13}H_{12}F_3N_5O_5S_3$ [i]

a All compounds were analyzed for C, H and N. Except where indicated, analytical results were within ±0.4 % of theoretical values.
b C: Calcd., 35.74; Found, 36.28.
c N: Calcd., 7.77; Found, 7.31.
d H: Calcd., 3.96; Found, 4.42.
e Contains 1 mol sodium trifluoroacetate; S: Calcd., 10.89; Found, 11.21.
f Contains 5 % dicyclohexylurea.
g N: Calcd., 10.88; Found, 10.19.
h Contains 0.1 mol EtOAc; C: Calcd., 34.70; Found, 35.15.
i N: Calcd., 14.85: Found, 14.12.

or *t*-butyl ester) as shown in Scheme 1. When the cephalosporin *t*-butyl esters were obtained as intermediates, the protecting *t*-butyl group was subsequently removed by treatment with neat TFA at room temperature. The cephalosporin analogs with a heterocyclicthiomethyl substituent at the 3-position were prepared by reacting the activated N-hydroxysuccinimide ester of the side-chain acid with the triethylamine salt of the appropriate heterocyclicthiomethyl nucleus in dry

Scheme 2

$$AgF + CS_2 \longrightarrow AgSCF_3 \xrightarrow{ICH_2COOH} CF_3SCH_2COOH$$

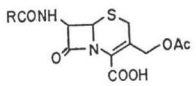
DMF according to the general procedure listed in the Experimental Section. The 3-heterocyclic-thiomethyl nuclei were prepared by reacting 7-ACA with the corresponding heterocyclic thiol by the widely used, general procedure[4] also outlined in the Experimental Section.

Methylthioacetic acid[5] was coupled to N-hydroxysuccinimide to give the activated ester using DCC in THF. This ester was oxidized to its sulfoxide and sulfone by using one and two equivalents of *m*-chloroperbenzoic acid, respectively. Trifluoromethylthioacetic acid was activated for coupling in the same way. However, conversion of this ester to its sulfoxide or sulfone by direct oxidation proved to be unfeasible. Trifluoromethylsulfinylacetic acid was prepared from the sulfide by oxidation with hot peracetic acid. The corresponding sulfone was synthesized by carbonation of the anion of methyl trifluoromethyl sulfone[6] (Scheme 1). Coupling of the trifluoromethylsulfinylacetic and trifluoromethylsulfonylacetic acids to 7-ACA was accomplished by reacting the nucleus *t*-butyl ester with the respective acid in the presence of DCC.

For these studies trifluoromethylthioacetic acid was synthesized from iodoacetic acid and trifluoromethylthiosilver by the method of ORDA *et al.*[7] The silver mercaptide was prepared from silver fluoride and carbon disulfide by the procedure of EMELEUS and MACDUFFIE[8] (Scheme 2).

The final cephalosporins were characterized and tested as free acids or as their sodium salts (Table 1).

Table 2. *In vitro* and *in vivo* activities of alkylthioacetamidocephalosporanic acids



Compound	R	Minimum inhibitory concentration (mcg/ml)[a]								Mouse PD_{50}[b] (mg/kg, sc) *E. coli* 12140
		S.a.(R)	*S.a.*(S)	*S.f.*	*E.c.*	*K.p.*	*Sal.p.*	*Sh.p.*	*E.a.*	
5	CH_3SCH_2	0.4	0.4	25	6	3	1.6	6	NT	>200
6	CH_3SOCH_2	6	6	>200	25	25	25	50	NT	>200
7	$CH_3SO_2CH_2$	3	1.6	200	13	13	13	13	NT	62
8	CF_3SCH_2	0.4	0.2	25	3	1.6	0.8	3	50	46
9	CF_3SOCH_2	1.6	1.6	100	6	3	3	6	NT	29
10	$CF_3SO_2CH_2$	6	3	200	6	6	13	13	25	>50
	Cephalothin	0.2	0.2	25	3	3	1.6	1.6	50	50

a The *in vitro* antibacterial activities are reported as minimum inhibitory concentrations (MIC) in mcg/ml. The MIC's were determined in twofold dilution by the agar dilution method (reference 2). Organisms selected for inclusion in this Table are: *S.a.* (R), *Staphylococcus aureus* HH 127 (penicillin G resistant); *S.a.*(S), *Staphylococcus aureus* 23390 (Smith); *S.f.*, *Streptococcus faecalis* HH 34358; *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.

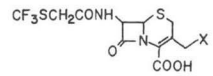
b The PD_{50} values are expressed as the total dose of compound which afforded protection to 50% of the mice challenged (ip) with *E. coli* 12140 or *K. pneumoniae* 4200 (Table 3). The doses were administered subcutaneously in equally divided portions at 1 and 5 hours post-infection. Values were calculated by the method of LICHTFIELD, J. T., Jr. & F. WILCOXON: J. Pharmacol. Exp. Ther. 96: 99~113, 1949.
NT. Not tested.

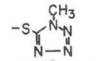
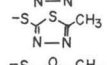
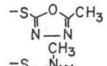
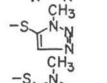
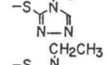
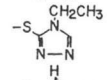
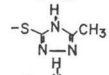
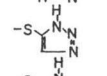
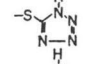
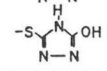
Biological Activities

The *in vitro* activities of the cephalosporins derived from 7-ACA against three gram-positive and five gram-negative bacteria are shown in Table 2. The data for these organisms are representative of those obtained from a larger group of bacteria used in our initial screen for evaluating β-lactam antibiotics. Curiously, in the unfluorinated series (**5**, **6** and **7**) the sulfoxide (**6**) is less active than either the sulfone or the sulfide.* The sulfide (a previously reported compound[9]) has an *in vitro* activity profile essentially the same as that of cephalothin against this group of organisms. Although the sulfone is less active *in vitro* than its unoxidized analog, it protects mice infected with *Escherichia coli* whereas the latter does not at the highest level tested, *viz.*, 200 mg/kg (Table 2).

In the fluorinated series (**8**, **9** and **10**) the trifluoromethylthioacetyl derivative also has *in vitro* activity essentially equal to that of the unfluorinated analog and cephalothin. The fluorinated sulfoxide and sulfone, as with the unfluorinated analogs, have significantly less gram-positive activity than the corresponding sulfide. Here there is a progressive drop in gram-negative activity on oxidation of the sulfur atom, but the MIC values against gram-negative

Table 3. *In vitro* and *in vivo* activities of 3-heterocyclicthiomethyl-7-trifluoromethylthioacetamido-3-cephem-4-carboxylic acids



	X	Minimum inhibitory concentration(mcg/ml) [a]								Mouse PD_{50} [b] (mg/kg, sc)	
		S.a. (R)	*S.a.*(S)	*S.f.*	*E.c.*	*K.p.*	*Sal.p.*	*Sh.p.*	*E.a.*	*E. coli* 12140	*K. pneumoniae* 4200
8	OAc	0.4	0.2	25	3	1.6	0.8	3	50	46	200
11		0.4	0.2	13	0.4	0.8	0.4	0.2	1.6	2	14.5
12		0.4	0.2	13	1.6	1.6	0.8	0.8	6	14	55
13		0.4	0.2	6	3	3	1.6	1.6	6	17	35
14		0.4	0.2	25	6	0.8	3	3	13	>50	>50
15		0.8	0.4	25	0.8	0.8	0.4	0.8	3	16	32
16		0.8	0.4	13	1.6	1.6	0.8	0.4	6	32	NT
17		0.8	0.8	50	3	3	3	1.6	13	9	35
18		0.8	0.4	50	3	3	1.6	1.6	6	24	30
19		1.6	1.6	100	3	1.6	3	3	50	17	NT
20		0.4	0.4	50	6	3	3	3	25	>50	>50
	Cephalothin	0.2	0.2	25	3	3	1.6	6	50	50	73

a See footnote a, Table 2.
b See footnote b, Table 2.

*This could reflect a probable equimixture of diastereomeric sulfoxides.

organisms for these compounds are still comparable with those of cephalothin. However, the most significant observation in comparing the biological activities of these compounds, which led to additional analogs, was that the trifluoromethylthioacetyl derivative (**8**) also protects mice infected with *E. coli* while, as mentioned above, the parent methylthioacetyl analog (**5**) does not (Table 2).

The advantages of replacing the acetoxy grouping on the 3-position of the cephalosporin molecule by certain heterocyclic thiols in terms of improved antimicrobial activity are well documented.[4] The data in Table 3 illustrate the effects of this type of variation on *in vitro* activity and protective effectiveness in mice for 7-trifluoromethylthioacetamido cephalosporins using compound **8** as reference. In this series, introduction of the heterocyclicthiomethyl group at the 3-position has a relatively insignificant effect on the gram-positive activity. In general, the MIC values against the staphylococci are unchanged, or have doubled. An exception is compound **19** where the MIC values against the staphylococci exceed one mcg/ml (four to eightfold increase). This cephalosporin carries a polar, unsubstituted tetrazole ring. The variation in activity against *Streptococcus faecalis* is also within one tube dilution from that of the acetoxymethyl analog (**8**) with the exception of compounds **13** (four times more active) and **19** (four times less active).

Eight of the ten analogs having a thioheterocycle in place of acetoxy display significantly greater activity against *Enterobacter aerogenes*. This structural change does not result in a significant improvement of *in vitro* activity for most of these analogs agaist the other four gram-negative organisms listed in Table 3. In spite of this, these derivatives are generally more effective than compound **8** in protecting mice infected with either *E. coli* or *Klebsiella pneumoniae* (Table 3; exceptions: compounds **14** and **20**). Two analogs (**11** and **15**) have *in vitro* activities consistently better than compound **8** against the gram-negative organisms. The improvement in the *in vitro* activity (MIC) of compound **15** does not result in better mouse infection-protection effectiveness (PD_{50} values). While the MIC values against *E. coli* and *K. pneumoniae* are generally lower than for the other analogs, except compound **11**, the PD_{50} values are essentially the same. A striking improvement in activity, both *in vitro* and *in vivo*, occurs when the 3-acetoxy group is displaced by 1-methyltetrazolethiol to give compound **11** (SK&F 59962). Against most gram-negative organisms this cephalosporin has generally displayed a fourfold or better improvement in MIC's over cephalothin's.[2] The improvement in activity against enterobacter is 25-fold. The superiority of SK&F 59962 over cephalothin in *in vivo* effectiveness is reflected in the 25- and 5-fold differences in the subcutaneous PD_{50} values in *E. coli* and *K. pneumoniae* infected mice, respectively (Table 3).

The exceptionally good antibacterial activities of SK&F 59962 seen in the preliminary studies reported here are retained in additional mouse infection protection studies and expanded *in vitro* spectra. These data together with the advantageous pharmacokinetic profile of SK&F 59962 will be described in subsequent publications.[2]

Experimental Section

Melting points were determined in open capillary tubes, using a Thomas-Hoover Uni-Melt apparatus (A.H. Thomas Co., Philadelphia, Pa.) Infrared spectra were obtained in Nujol mull using a Perkin-Elmer Infracord. Nmr spectra were obtained (unless indicated otherwise) in

DMSO-d_6 or DMSO-d_6-D_2O on a Varian T-60 spectrometer using TMS as internal standard. The ir and nmr data of all cephalosporins were consistent with structure. When elemental analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ± 0.4 % of 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.

N-Hydroxysuccinimidoyl Methylthioacetate (**1**)

A mixture of 5.30 g (50 mmol) of methylthioacetic acid, 5.76 g (50 mmol) of N-hydroxysuccinimide and 10.3 g (50 mmol) of dicyclohexylcarbodiimide (DCC) in 40 ml of dry THF was stirred at room temperature overnight. The precipitated urea was removed and the filtrate was evaporated to give a crystalline residue. The product was recrystallized from carbon tetrachloride to give 8.0 g (80 %) of white plates: mp 86~88°C, ir 1820, 1780, 1725 cm^{-1}; nmr ($CDCl_3$) δ 2.34 (s, 3), 2.85 (s, 4), 3.45 ppm (s, 2).

N-Hydroxysuccinimidoyl Methylsulfinylacetate (**2**)

A solution of 4.1 g (25 mmol) of 85 % *m*-chloroperbenzoic acid in 40 ml of ether was added dropwise to a stirred solution of 4.06 g (20 mmol) of **1** in 25 ml of ether immersed in an ice bath. The reaction was stirred for 1 hour at 0°C and for an additional 1.5 hours at room temperature. The precipitated sulfoxide was collected, stirred with 50 ml of ether and filtered giving 4.1 g of white powder. The product was recrystallized from EtOAc to give 2.9 g (66 %) of white needles: mp 133~140°C; ir 1815, 1775, 1725 cm^{-1}; nmr δ 2.82 (s, 1½), 2.90 (s, 4), 3.30 (s, 1½), 4.40 ppm (a, b, 2, J=15 Hz).

N-Hydroxysuccinimidoyl Methylsulfonylacetate (**3**)

To 4.06 g (20 mmol) of **1** in 40 ml of $CHCl_3$ was added 8.1 g (50 mmol) of 85 % *m*-chloroperbenzoic acid in 40 ml of ether. The reaction was stirred at room temperature for 3 days. The precipitate was collected and washed with ether to give a white powder which was crystallized from acetone to give 3.2 g (68 %) of white prisms: mp 148°C dec.; ir 1810, 1770, 1725, 1250 cm^{-1}; nmr δ 2.85 (s, 4), 3.22 (s, 3), 5.0 ppm (s, 2).

N-Hydroxysuccinimidoyl Trifluoromethylthioacetate (**4**)

This compound was prepared by the same procedure used for compound **1**. Yield, 85 % (yellow crystals). An analytical sample was obtained by recrystallization from *n*-butanol to give off-white plates: mp 77~79°C, ir ($CHCl_3$) 1825, 1780, 1730, 1175, 1125, 1065 cm^{-1}; nmr ($CDCl_3$) δ 2.85 (s, 4), 3.95 ppm (s, 2).

7-Methylthioacetamidocephalosporanic Acid (**5**)

This compound was prepared by acylation of 7-ACA with activated ester **1** according to the general procedure outlined for compounds **8**, **11**~**20**.

7-Methylsulfinylacetamidocephalosporanic Acid (**6**)

A solution of 7-ACA *t*-butyl ester (1.64 g, 5 mmol) and **2** (1.10 g, 5 mmol) in 20 ml of dry DMF was stirred at room temperature for 36 hours. An additional 0.5 g of **2** was added and stirring continued for another 36 hours. The solution was poured into 100 ml of water and extracted with 3×75 ml of EtOAc. The combined extracts were washed with water, dried and evaporated *in vacuo* to give a yellow gum. Chromatography on silica gel (25 g) and elution with benzene - acetone (8 : 1) and then acetone gave 1.4 g (65 %) of pure compound. This was dissolved in 6 ml of TFA. After standing at room temperature for 30 minutes the solution was added dropwise to 200 ml of ether. The precipitate was collected to give 780 mg (74 %) of **6**.

7-Methylsulfonylacetamidocephalosporanic Acid (**7**)

A slight excess of triethylamine was added dropwise to a suspension of 1.64 g (6 mmol) of 7-ACA in 20 ml of dry DMF. To this was added 1.42 g (6.0 mmol) of **3**. After 1.5 hours at room temperature the reaction was poured into 100 ml of ice-water and extracted with 75 ml of EtOAc which was discarded. The aqueous phase was acidified to pH 2.0 and extracted with three 75-ml portions of EtOAc. The combined extracts were washed with water, dried and evaporated to about 25 ml. To this was added 10 mmol of 30 % sodium 2-ethylhexanoate in

isopropanol. The solution was stirred while 150 ml of ether was added dropwise. The sodium salt was collected and dried to yield 905 mg (37 %) of off-white **7**.

7-Trifluoromethylthioacetamidocephalosporins (**8**, **11**~**20**)

Triethylamine was added dropwise to a stirred suspension of 10 mmol of the appropriate nucleus in 50 ml of dry DMF* until solution was complete. Ten mmol of the activated ester was added in one portion. Stirring was continued for 1.5 hours after which the reaction mixture was poured into 200 ml of ice-water. This 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 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 isopropanol) was added. Ether was added dropwise with rapid stirring to precipitate the sodium salt of the cephalosporin which was collected and dried under vacuum.

3-S-Heterocyclicthiomethyl Nuclei

To a suspension of 0.1 mol of 7-ACA in 200 ml of water and 100 ml of acetone was added 0.225 mol of $NaHCO_3$ in 200 ml of water, and the resultant solution was heated to 40~50°C. The appropriate thiol (0.125 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 a small aliquot of the reaction mixture to 3.5. The reaction was judged to be complete when the ir spectrum showed no acetoxy remaining (~4 hr). 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 filtered, 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 minutes to 5 hours depending on the presence of residual 7-ACA (nmr) in the crude product. After filtering through Celite the filtrate was cooled and adjusted to pH 3.5 with 20 % NaOH. The precipitate was washed with water and acetone and dried. The nuclei were used without further purification.

7-Trifluoromethylsulfinylacetamidocephalosporanic Acid (**9**)

DCC (309 mg, 1.5 mmol) was added to 7-ACA *t*-butyl ester (592 mg, 1.5 mmol) and trifluoromethylsulfinylacetic acid (264 mg, 1.5 mmol) in 10 ml of dry THF. After stirring at room temperature overnight, the precipitated urea was removed and washed with a small portion of solvent. The filtrate was evaporated to leave a gum which was dissolved in 10 ml of TFA and allowed to stand at room temperature for 30 minutes. The TFA was removed under vacuum and the residue dissolved in EtOAc. This was filtered and treated with 1.5 mmol of sodium 2-ethylhexanoate in isopropanol. The solution was added dropwise to 200 ml of petroleum ether and the salt was collected, washed with ether and dried to give 515 mg (73 %) of the sodium salt of **9**.

7-Trifluoromethylsulfonylacetamidocephalosporanic Acid (**10**)

This cephalosporin was prepared by the same procedure used to make compound **9**. In this case the gum obtained from evaporating the THF was triturated with ether giving a 47 % yield of crystalline product. This was dissolved in TFA and allowed to stand at room temperature for 30 minutes. The TFA was evaporated and the resulting gum was dissolved in EtOAc, washed with water, dried and evaporated. The residue was triturated with ether-petroleum ether to give, after drying, 63 % of **10** as an off-white solid.

* For compound **20** formamide was substituted for DMF.

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