structure on ionization of the phenols.

Homohydrogen Bonding. From our measured equilibrium constants for homohydrogen bonding (Table II) it is clear that this interaction is strong and remarkably constant for these eight phenols. Since the "free" phenol in eq 1 is actually hydrogen bonded to the solvent, a more realistic equilibrium is eq 4. Expressed this way, $\Delta G°$ =

$$PhO^- + PhOH\cdots OSMe_2 \rightleftharpoons PhO^-\cdots HOPh + Me_2SO \quad (4)$$

6.1 kcal/mol, or the hydrogen bond between phenol and its conjugate base is favored by 6.1 kcal/mol over the hydrogen bond between phenol and Me_2SO. The latter bond strength has been measured: $\Delta H°$ = 6.9, 7.21 kcal/mol.[27] Although we cannot quantitatively combine these values because of the unknown entropy of reaction 4, it is clear that the phenol–phenoxide bond is quite strong.

The values of the homohydrogen-bonding constants for substituted phenols are functions of bond-donating and -accepting ability. As the acidities of the phenols increase, the hydrogen bond donating ability increases, but the accepting ability of the conjugate base decreases.[6,13] For the eight phenols of this study these two factors compensate for each other so that the equilibrium constants are the same for all of them.

Experimental Section

The phenols were all commercially available and were purified by distillation and/or crystallization until they were pure by VPC or TLC. The preparation and purification of the indicators have been previously described. Spectrophotometric grade Me_2SO, a gift from Crown Zellerbach, Camas WA, was purified by distillation from sodium amide,[9] and potassium dimsyl was prepared by using potassium hydride.[20] The experimental details of the indicator method have been described.[9,20] For the present compounds 5–10 titration points were used to calculate the pK_a and K_{hb} by a general least-squares curve-fitting procedure (see supplementary material).

Acknowledgment. Some of the acidity measurements were made by Mark E. Stark. This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation. We thank Professors E. M. Arnett and R. W. Taft for helpful comments.

Registry No. Me_2SO, 67-68-5; PhOH, 108-95-2; *p*-methylphenol, 106-44-5; *m*-methylphenol, 108-39-4; *p*-chlorophenol, 106-48-9; *m*-fluorophenol, 372-20-3; *m*-chlorophenol, 108-43-0; *m*-cyanophenol, 873-62-1; *m*-nitrophenol, 554-84-7.

Supplementary Material Available: Equations for and a fuller description of the two procedures used to work up the data from the overlapping indicator method of measuring pK_a and K_{hb} and Table V, a numerical comparison of the two methods for phenol (9 pages). Ordering information is given on any current masthead page.

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Notes

Sulfazecin Analogues. Preparation of 4-(Fluoromethyl)-1-sulfo-2-azetidinone Derivatives

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The recent discoveries of sulfazecins[1] and monobactams[2] from bacteria have stimulated considerable interest in the synthesis of 1-sulfo-2-azetidinones.[3] In the course of our studies on the synthesis of sulfazecin analogues, we planned to introduce a fluorine atom into the methyl group at the 4β-position, because the 4β-methyl-1-sulfo-2-azetidinone derivative was reported to have a potent antibacterial activity especially against Gram-negative strains[4] and the electron-withdrawing property of the fluorine atom would increase the chemical reactivity of the β-lactam ring that might be correlated with the biological activity.[5]

In this paper, we describe a facile synthesis of the 4-(fluoromethyl)-1-sulfo-2-azetidinone derivatives[6] starting with commercially available 2-fluoroethanol. 2-Fluoroethanol was converted, without isolation of intermediates, in a one-pot procedure into β-lactam 1 (see Scheme I). Thus, Swern oxidation[7] of 2-fluoroethanol with oxalyl chloride and dimethyl sulfoxide followed by treatment with 2,4-dimethoxybenzylamine gave an imine. The resulting methylene chloride solution of the imine was used for the cycloaddition reaction with phthalimidoacetyl chloride in the presence of triethylamine to give β-lactam 1 (31.6% yield from 2-fluoroethanol). The IR spectrum of 1 showed an absorption band at 1760 cm^{-1} attributable to a β-lactam,

† Deceased.

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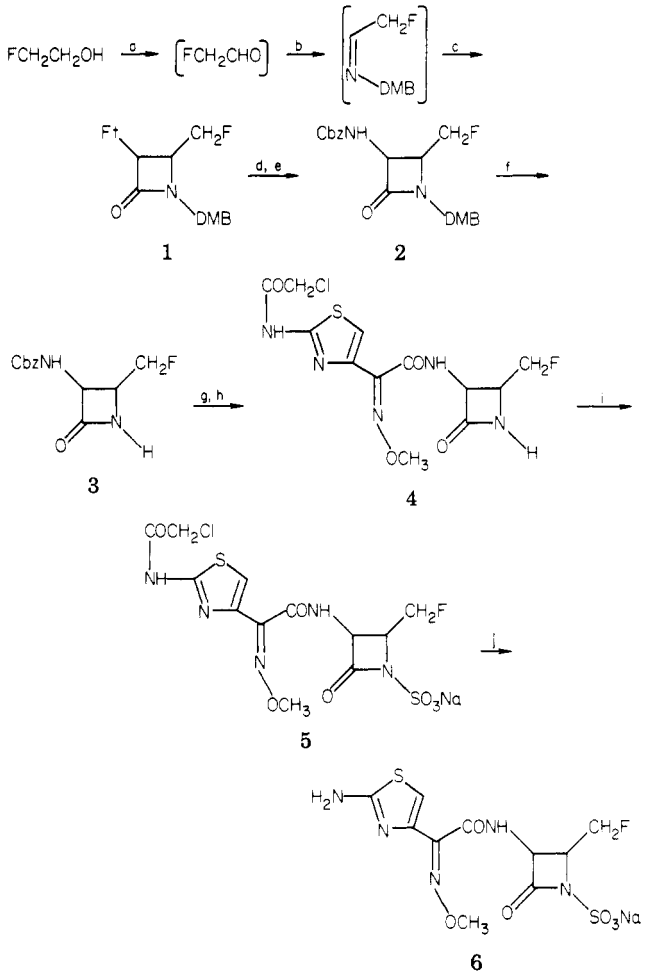
0022-3263/84/1949-1427$01.50/0

Scheme I[a]

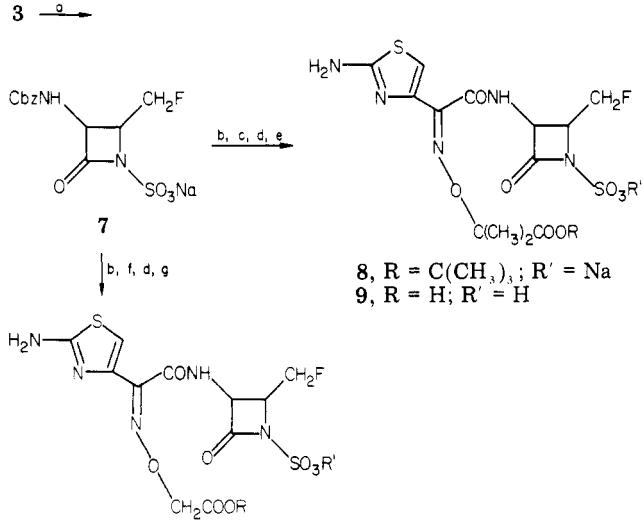


[a] (a) $(COCl)_2$, Me_2SO, CH_2Cl_2; (b) DMB-NH_2, $MgSO_4$; (c) $FtCH_2COCl$, Et_3N; (d) CH_3NHNH_2, $(CH_3OCH_3)_2$; (e) Cbz-Cl, propylene oxide, CH_2Cl_2; (f) $K_2S_2O_8$, K_2HPO_4, CH_3CN-H_2O; (g) 10% Pd/C, H_2, MeOH; (h) 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-(methoxyimino)acetyl chloride, Et_3N, THF; (i) SO_3-DMF followed by Dowex 50W (Na^+); (j) CH_3NHCS_2Na, H_2O. [b] DMB, 2,4-dimethoxybenzyl; Ft, phthalimide, Cbz, benzyloxycarbonyl.

and the coupling constant (J = 5 Hz) of **1** observed in its NMR spectrum supported the 3,4-cis configuration. The trans isomer was not detected in this reaction. Treatment of **1** with methylhydrazine followed by acylation with benzyloxycarbonyl chloride gave **2** in 27.5% yield. Oxidative cleavage of the 2,4-dimethoxybenzyl group was successfully effected by treating **2** with potassium persulfate[8] in the presence of dipotassium phosphate to afford **3** in 60.5% yield. Deprotection of **3** by hydrogenolysis using 10% palladium–charcoal, followed by acylation with 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-(methoxyimino)acetyl chloride[9] in the presence of triethylamine gave **4** in 81.0% yield. Sulfonation of **4** with sulfur trioxide–dimethylformamide complex[3c] gave **5** in 70.7% yield. Finally, cleavage of the chloroacetyl group was effected by treating **5** with methyldithiocarbamate[9] to give the desired compound (**6**) in 59.0% yield.

Next, we prepared carboxyalkoxyimine derivatives (**9** and **11**) (see Scheme II). N-Unsubstituted β-lactam **3** was

Scheme II[a]



8, R = $C(CH_3)_3$; R′ = Na
9, R = H; R′ = H

10, R = PNB; R′ = Na
11, R = H; R′ = H

[a] (a) SO_3-DMF followed by Dowex 50W (Na^+); (b) 10% Pd/C, H_2, DMF; (c) 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-[[1-methyl-1-(*tert*-butyloxycarbonyl)ethoxy]imino]acetic acid, NHBT, DCC, DMF; (d) CH_3NHCS_2Na, H_2O; (e) CF_3COOH followed by Dowex 50W (H^+); (f) 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-[[(*p*-nitrobenzyloxycarbonyl)methoxy]imino]-acetic acid, NHBT, DCC, DMF; (g) 10% Pd/C, H_2, H_2O followed by Dowex 50W (H^+). [b] Cbz, benzyloxycarbonyl; PNB, *p*-nitrobenzyl.

sulfonated in a manner similar to that employed for the preparation of **5** to give **7** in 71.8% yield. Deprotection of **7** by hydrogenolysis followed by acylation with 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-[[1-methyl-1-(*tert*-butyloxycarbonyl)ethoxy]imino]acetic acid[10] in the presence of *N*-hydroxybenzotriazole and *N*,*N*′-dicyclohexylcarbodiimide gave, after removal of the chloroacetyl group, **8** in 36.0% yield. Treatment of **8** with trifluoroacetic acid gave **9** in 60.3% yield. On the other hand, **7** was converted into **10** in 43.5% yield by a similar sequence. The *p*-nitrobenzyl group of **10** was removed by hydrogenolysis to afford **11** in 48.7% yield.

The 4-(fluoromethyl)-1-sulfo-2-azetidinone compounds (**6**, **9**, and **11**) thus obtained showed, as expected, potent in vitro antibacterial activity against Gram-negative bacteria. These compounds were almost comparable or slightly superior to the *dl*-4β-methyl compound[11] in their activities against the bacterial strains tested.

Experimental Section

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured with a Hitachi 215 spectrophotometer. ^1H NMR spectra were taken on a Varian EM-390 (90 MHz) spectrometer or on a JEOL GK-400 (400 MHz) FT NMR spectrometer (compounds **2**, **6**, **9**, and **11**)

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(9) Ochiai, M.; Morimoto, A.; Miyawaki, T.; Matsushita, Y.; Okada, T.; Natsugari, H.; Kida, M. *J. Antibiot.* **1981**, *34*, 171.

(10) This compound was prepared according to the procedure[12] reported for the synthesis of 2-[2-(tritylamino)thiazol-4-yl]-(*Z*)-2-[[1-methyl-1-(*tert*-butyloxycarbonyl)ethoxy]imino]acetic acid. The amino protecting group was changed from trityl to chloroacetyl.
(11) The 3*S* cis-compound was reported in the literature.[4] The *dl* compound was prepared by a multistep procedure (carbobenzoxylation, $NaBH_4$ reduction, mesylation, iodination, $NaBH_3CN$ reduction, $K_2S_2O_8$ oxidation, hydrogenolysis, acylation, and dechloroacetylation) starting from *cis*-3-amino-(2,4-dimethoxybenzyl)-4-(methoxycarbonyl)-2-azetidinone.[8]
(12) Roussel-Uclaf. U.S. Pat. 4 288 434.

with $SiMe_4$ as internal standard. Extracted solutions were dried over sodium sulfate. All the β-lactams prepared are racemic.

***cis,rac*-2-[1-[(2,4-Dimethoxyphenyl)methyl]-2-(fluoromethyl)-4-oxo-3-azetidinyl]-1*H*-isoindole-1,3(2*H*)-dione (1).** To a stirred, cooled (−60 °C) solution of oxalyl chloride (4.0 mL, 0.046 mol) and dimethyl sulfoxide (6.8 mL, 0.095 mol) in methylene chloride (80 mL) was added 2-fluoroethanol (2.4 mL, 0.041 mol) in methylene chloride (6 mL) under nitrogen. The mixture was stirred at −60 °C for 45 min and then triethylamine (28 mL) was added. After stirring for an additional hour at room temperature 2,4-dimethoxybenzylamine (3.34 g, 0.020 mol) and anhydrous magnesium sulfate (40 g) were added, and the mixture was stirred at room temperature for 4 h. After filtration of the magnesium sulfate, triethylamine (3 mL) was added to the stirred, cooled (0 °C) filtrate, and then phthalimidoacetyl chloride (4.6 g, 0.201 mol) in methylene chloride (30 mL) was added dropwise. The mixture was allowed to stand overnight at room temperature. The reaction solution was washed successively with water, dilute hydrochloric acid, and saturated aqueous sodium chloride and dried. After evaporation of the solvent, the residue was chromatographed on silica gel. Elution with benzene/ethyl acetate (3:1, v/v) gave 1 (2.52 g, 31.6% from 2-fluoroethanol) as a colorless powder: IR (KBr) 1760, 1720, 1610, 1420, 1390, 1200 cm^{-1}; NMR ($CDCl_3$) δ 3.80 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 3.9–4.9 (5 H, m, NCH_2, CH_2F, C_2-H), 5.40 (1 H, d, J = 5 Hz, C_3-H), 6.46 (2 H, m, Ar H), 7.25 (1 H, m, Ar H), 7.80 (4 H, m, Ar H).

Phenylmethyl *cis,rac*-[1-[(2,4-Dimethoxyphenyl)methyl]-2-(fluoromethyl)-4-oxo-3-azetidinyl]carbamate (2). To a stirred, cooled (0 °C) solution of 1 (2.52 g, 0.0063 mol) in ethylene glycol dimethyl ether (20 mL) was added methylhydrazine (1.4 mL, 0.026 mol). After being stirred at room temperature for 1.5 h, the solvent was evaporated off, and the residue was dissolved in methylene chloride (20 mL). The mixture was allowed to stand overnight at room temperature. The insoluble materials were filtered off and the filtrate was concentrated. To the concentrate was added ethyl acetate (100 mL), and insoluble materials were filtered off. The filtrate was extracted with dilute hydrochloric acid (three times), and the aqueous layer was adjusted to pH 8 with aqueous sodium bicarbonate. The solution was extracted with chloroform (three times), and the combined organic extracts were washed with saturated aqueous sodium chloride and dried. Evaporation of the solvent gave 3-amino-4-(fluoromethyl)-1-(2,4-dimethoxybenzyl)-2-azetidinone as an oil (0.96 g), which was used without further purification.

To a stirred, cooled (0 °C) solution of the 3-aminoazetidinone (0.96 g) in methylene chloride (6 mL) were added propylene oxide (3 mL) and benzyloxycarbonyl chloride (1.1 mL, 7.7 mmol), and the mixture was stirred at room temperature for 2.5 h. After evaporation of the solvent the residue was chromatographed on silica gel. Elution with chloroform/ethyl acetate (9:1, v/v) gave 2 (0.7 g, 27.5%) as colorless crystals: mp 114–115 °C; IR(KBr) 3300, 1765, 1690, 1540, 1260 cm^{-1}; NMR ($CDCl_3$) δ 3.737 (1 H, dm, J = 27.1 Hz, C_2-H), 3.805 (6 H, s, 2 OCH_3), 4.373 (2 H, AB q, J_{AB} 14.6 Hz, $\delta_{AB}\nu_0$ = 0.410, N-CH_2), 4.474 (1 H, ddd, J = 45.9, 10.7, and 2.4 Hz, CH_AF), 4.597 (1 H, ddd, J = 47.6, 10.7, and 2.4 Hz, CH_BF), 5.107 (2 H, AB q, J_{AB} = 12.0 Hz, $\delta_{AB}\nu_0$ = 0.018, CH_2O), 5.159 (1 H, dd, J = 9.6, 5.0 Hz, C_3-H), 5.406 (1 H, d, J = 9.3 Hz, NH), 6.453 (2 H, m, Ar H), 7.142 (1 H, m, Ar H), 7.342 (5 H, m, Ar H).

Anal. Calcd for $C_{21}H_{23}F_1N_2O_5$: C, 62.67; H, 5.76; N, 6.96. Found: C, 62.65; H, 5.98; N, 6.93.

Phenylmethyl *cis,rac*-[2-(Fluoromethyl)-4-oxo-3-azetidinyl]carbamate (3). A suspension of 2 (0.483 g, 1.2 mmol), potassium persulfate (0.486 g, 1.8 mmol) and dipotassium phosphate (0.426 g, 2.5 mmol) in a mixed solution of acetonitrile (24 mL) and water (36 mL) was stirred at 95 °C for 1.5 h under nitrogen. The acetonitrile was distilled under reduced pressure, and then saturated aqueous sodium chloride (10 mL) was added to the residue. The solution was extracted with ethyl acetate, and the extract was washed with saturated aqueous sodium chloride and dried. After evaporation of the solvent the residue was chromatographed on silica gel. Elution with ethyl acetate gave 3 (183 mg, 60.5%) as colorless crystals: mp 172–173 °C; IR (KBr) 3350, 1785, 1745, 1680, 1550 cm^{-1}; NMR (Me_2SO-d_6) δ 3.85 (1 H, m, C_2-H), 4.42 (2 H, dd, J = 6, 47 Hz, CH_2F), 4.92 (1 H, dd, J = 5, 9 Hz, C_3-H), 4.95 (2 H, s, CH_2O), 7.26 (5 H, s, Ar H), 7.90 (1 H, d, J = 9 Hz, C_3-NH), 8.35 (1 H, s, N_1-H).

Anal. Calcd for $C_{12}H_{13}F_1N_2O_3$: C, 57.14; H, 5.19; N, 11.08. Found: C, 57.12; H, 5.57; N, 11.30.

***cis,rac,(Z)*-2-[(Chloroacetyl)amino]-α-(methoxyimino)-*N*-[2-(fluoromethyl)-4-oxo-3-azetidinyl]-4-thiazoleacetamide (4).** A mixture of 3 (0.202 g, 0.8 mmol) and 10% palladium/charcoal (200 mg) in methanol (15 mL) was stirred under hydrogen at room temperatue for 70 min. The catalyst was filtered off and washed with methanol. The filtrate and washings were combined and concentrated under reduced pressure. After the concentrate had been dissolved in tetrahydrofuran (15 mL), triethylamine (0.3 mL, 2.2 mmol) and 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-(methoxyimino)acetyl chloride hydrochloride[9] (0.266 g, 0.8 mmol) were added to the solution, and the mixture was stirred at room temperature for 2 h. The solvent was evaporated, and then the residue was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride, dried, and evaporated to dryness. The residue was treated with ether to give 4 (245 mg, 81.0%) as a colorless powder: IR (KBr) 3270, 1760, 1670, 1560, 1060 cm^{-1}. This material was used without purification in subsequent reactions.

Sodium *cis,rac,(Z)*-3-[[[2-[(Chloroacetyl)amino]-4-thiazolyl](methoxyimino)acetyl]amino]-2-(fluoromethyl)-4-oxo-1-azetidinesulfonate (5). Sulfur trioxide–dimethylformamide complex (1.25 mL of 1.58 M solution, 2 mmol) was added to 4 (0.245 g, 0.65 mmol) at −50 °C, and the mixture was kept at 5 °C for 67 h. After the addition of pyridine (0.24 mL, 3 mmol) and water (10 mL), the mixture was stirred with Dowex 50W (Na form, 5 g, wet) at room temperature for an hour. The resin was filtered off, and the filtrate was subjected to chromatography on Amberlite XAD-2. Elution with water, followed by lyophilization, gave 5 (220 mg, 70.7%) as a colorless powder: IR (KBr) 1770, 1670, 1550, 1270, 1050 cm^{-1}; NMR (D_2O) δ 4.00 (3 H, s, OCH_3), 4.37 (2 H, s, $ClCH_2$), 5.60 (1 H, d, J = 5 Hz, C_3-H), 7.36 (1 H, s, proton at position 5 of the thiazole ring).

Sodium *cis,rac,(Z)*-3-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-2-(fluoromethyl)-4-oxo-1-azetidinesulfonate (6). To a stirred solution of 5 (0.19 g, 0.4 mmol) in water (5 mL) was added sodium methyldithiocarbamate (0.10 g, 0.78 mmol). After being stirred at room temperature for an hour, the mixture was subjected to chromatography on Amberlite XAD-2. Elution with water, followed by lyophilization, gave 6 (100.5 mg, 59.0%) as a colorless powder: IR (KBr) 3440, 1770, 1670, 1620, 1535, 1280, 1250, 1055 cm^{-1}; NMR (D_2O) δ 4.000 (3 H, s, OCH_3), 4.606 (1 H, dddd, J = 23.9, 5.6, 3.4, 2.7 Hz, C_2-H), 4.783 (1 H, ddd, J = 45.4, 11.0, 2.7 Hz, CH_AF), 4.948 (1 H, ddd, J = 46.9, 11.0, 3.4 Hz, CH_BF), 5.603 (1 H, d, J = 5.6 Hz, C_3-H), 6.990 (1 H, s, proton at position 5 of the thiazole ring).

Anal. Calcd for $C_{10}H_{11}FN_5NaO_6S_2 \cdot 1.5H_2O$: C, 27.91; H, 3.28; N, 16.27. Found: C, 27.98; H, 3.45; N, 16.33.

Sodium *cis,rac*-2-(Fluoromethyl)-4-oxo-3-[[(phenylmethoxy)carbonyl]amino]-1-azetidinesulfonate (7). Sulfur trioxide–dimethylformamide complex (1.9 mL of 1.58 M solution, 3.0 mmol) was added to 3 (0.252 g, 1 mmol) at −50 °C. The mixture was kept at 5 °C for 87 h. After the addition of pyridine (0.4 mL, 5 mmol) and water (15 mL), the mixture was stirred with Dowex 50W (Na form, 7 g, wet) at room temperature for an hour. Filtration, followed by concentration of the filtrate to about 20 mL gave 7 (45 mg) as colorless crystals. The filtrate was concentrated and the residue was subjected to chromatography on XAD-2. Elution with water and then with 10% ethanol, followed by lyophylization of the eluate, gave an additional crop of 7 (229 mg, 71.8%) as a colorless powder: IR (KBr) 3425, 3300, 1770, 1700, 1540, 1280, 1260, 1235, 1065 cm^{-1}; NMR (Me_2SO-d_6 + D_2O) δ 4.94 (1 H, d, J = 5 Hz, C_3-H), 5.03 (2 H, s, CH_2O), 7.32 (5 H, s, Ar H).

***cis,rac,(Z)*-α-[[[1-(2-Amino-4-thiazolyl)-2-[[2-(fluoromethyl)-4-oxo-1-sulfo-3-azetidinyl]amino]-2-oxoethylidene]amino]oxy]-α,α-dimethylacetic Acid 1,1-Dimethylethyl Ester Monosodium Salt (8).** A mixture of 7 (0.256 g, 0.7 mmol) and 10% palladium/charcoal (250 mg) in dimethylformamide (7 mL) was stirred under hydrogen at room temperature for 30 min. The catalyst was filtered off and washed with dimethylformamide (6 mL). To the combined filtrate and washings were added 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-[[1-methyl-1-(*tert*-butyloxycarbonyl)ethoxy]imino]acetic

acid[10] (0.248 g, 0.61 mmol), *N*-hydroxybenzotriazole (0.107 g, 7 mmol) and *N,N'*-dicyclohexylcarbodiimide (0.144 g, 7 mmol) under ice-cooling. The mixture was stirred at 0 °C for 30 min and then at room temperature for 15 h. After the addition of water (20 mL) and sodium methyldithiocarbamate (0.182 g, 1.4 mmol) under ice-cooling, the mixture was stirred at room temperature for 2 h. Insoluble materials were removed by filtration and the filtrate was subjected to chromatography on Amberlite XAD-2. Elution with 5% ethanol, followed by lyophilization, gave **8** (135 mg, 36.0%) as a colorless powder: IR (KBr) 3430, 1770, 1730, 1670, 1630, 1530, 1250, 1150, 1080 cm^{-1}; NMR (D_2O) δ 1.45 (9 H, s, $C(CH_3)_3$), 1.53 (6 H, s, $C(CH_3)_2$), 5.58 (1 H, d, J = 5 Hz, C_3-H), 6.98 (1 H, s, proton at position 5 of the thiazole ring).

***cis,rac*,(*Z*)-α-[[[1-(2-Amino-4-thiazolyl)-2-[[2-(fluoromethyl)-4-oxo-1-sulfo-3-azetidinyl]amino]-2-oxoethylidene]amino]oxy]-α,α-dimethylacetic Acid (9).** To **8** (0.131 g, 0.25 mmol) was added trifluoroacetic acid (5 mL) under ice-cooling, and the mixture was stirred for 2.5 h. The mixture was evaporated to dryness under reduced pressure, and the residue was subjected to chromatography on Dowex 50W (H^+ form, 20 mL). Elution with water gave the fractions containing **9**, which were combined and concentrated to 20 mL. The concentrate was rechromatographed on Amberlite XAD-2. Elution with 5% ethanol, followed by lyophilization, gave **9** (68 mg, 60.3%) as a colorless powder: IR (KBr) 3400, 1770, 1680, 1640, 1270, 1240, 1180, 1050 cm^{-1}; NMR (D_2O) δ 1.551 (3 H, s, CH_3), 1.559 (3 H, s, CH_3), 4.606 (1 H, ddt, J = 24.4, 5.6, 2.9 Hz, C_2-H), 4.71–5.35 (2 H, m, CH_AH_BF, not clearly assigned), 5.606 (1 H, d, J = 5.9 Hz, C_3-H), 7.160 (1 H, s, proton at position 5 of the thiazole ring).

Anal. Calcd for $C_{13}H_{16}F_1N_5O_8S_2 \cdot 1.5H_2O$: C, 32.50; H, 3.99; N, 14.58. Found: C, 32.46; H, 3.98; N, 14.83.

***cis,rac*,(*Z*)-α-[[[1-(2-Amino-4-thiazolyl)-2-[[2-(fluoromethyl)-4-oxo-1-sulfo-3-azetidinyl]amino]-2-oxoethylidene]amino]oxy]acetic Acid 4-Nitrophenylmethyl Ester Monosodium Salt (10).** A mixture of **7** (0.296 g, 0.84 mmol) and 10% palladium/charcoal (300 mg) in dimethylformamide (7 mL) was stirred under hydrogen at room temperature for 45 min. The catalyst was filtered off and washed with dimethylformamide (6 mL). To the combined filtrate and washings were added 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-[[(*p*-nitrobenzyloxycarbonyl)methoxy]imino]acetic acid[13] (0.365 g, 0.8 mmol), *N*-hydroxybenzotriazole (0.123 g, 0.8 mmol), and *N,N'*-dicyclohexylcarbodiimide (0.165 g, 0.8 mmol) under ice-cooling. The mixture was stirred at 0 °C for 30 min and than allowed to stand overnight at room temperature. After being cooled to 0 °C, the mixture was diluted with water (20 mL) and, then sodium methyldithiocarbamate (0.210 g, 1.6 mmol) was added. After being stirred at room temperature for 2 h, the mixture was subjected to chromatography on Amberlite XAD-2. Elution with 5% ethanol, followed by lyophilization, gave **10** (206 mg, 43.5%) as a colorless powder: IR (KBr) 3430, 1760, 1670, 1270, 1250, 1050 cm^{-1}; NMR (D_2O) δ 4.85 (2 H, s, OCH_2CO), 5.20 (2 H, s, OCH_2Ph), 6.84 (1 H, s, proton at position 5 of the thiazole ring).

***cis,rac*,(*Z*)-α-[[[1-(2-Amino-4-thiazolyl)-2-[[2-(fluoromethyl)-4-oxo-1-sulfo-3-azetidinyl]amino]-2-oxoethylidene]amino]oxy]acetic Acid (11).** A mixture of **10** (0.205 g, 3.5 mmol) and 10% palladium/charcoal (200 mg) in water (15 mL) was stirred under hydrogen at room temperature for 1.5 h. The catalyst was filtered off and washed with water. The combined filtrate and washings were adjusted to pH 8 with aqueous sodium bicarbonate. The solution was subjected to chromatography on Amberlite XAD-2. Elution with water gave the fractions containing **11**. After the pH was adjusted to 3 with dilute hydrochloric acid, the solution was concentrated to 30 mL. The concentrate was subjected to chromatography on Dowex 50W (H^+ form). Elution with water gave the fractions containing **11**. After concentration to 40 mL, the material was rechromatographed on Amberlite XAD-2. Elution with water, followed by lyophilization, gave **11** (75.5 mg, 48.7%) as a colorless powder: IR (KBr) 3400, 1770, 1675, 1640, 1240, 1050 cm^{-1}; NMR (D_2O) δ 4.589 (1 H, ddt, J = 24.2, 5.6, 2.9 Hz, C_2-H), 4.70–5.01 (2 H, m, CH_AH_BF, not clearly assigned), 4.861 (2 H, s, OCH_2), 5.615 (1 H, d, J = 5.6 Hz, C_3-H), 7.191 (1 H, s, proton at position 5 of the thiazole ring).

(13) Takeda. Jpn. Kokai Tokkyo Koho 57-131758, 1982.

Anal. Calcd for $C_{11}H_{12}FN_5O_8S_2 \cdot 2H_2O$: C, 28.64; H, 3.50, N, 15.18. Found: C, 28.84; H, 3.55; N, 15.10.

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Registry No. (±)-*cis*-**1**, 88946-30-9; (±)-*cis*-**1** (amine), 88946-38-7; (±)-*cis*-**2**, 88946-31-0; (±)-*cis*-**3**, 88124-54-3; (±)-*cis*-**4**, 88946-32-1; (±)-*cis*-**5**, 88946-33-2; (±)-*cis*-**6**, 89015-35-0; (±)-*cis*-**7**, 88946-34-3; (±)-*cis*-**8**, 88946-35-4; (±)-*cis*-**9**, 86455-21-2; (±)-*cis*-**10**, 88946-36-5; (±)-*cis*-**11**, 88946-37-6; OMB–NH_2, 20781-20-8; $FtCH_2COCl$, 6780-38-7; FCH_2CH_2OH, 371-62-0; 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-(methoxyimino)acetyl chloride hydrochloride, 65243-22-3; 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-[[1-methyl-1-[(*tert*-butyloxy)carbonyl]ethoxy]imino]-acetic acid, 79656-47-6; 2-[2-[(chloroacetyl)amino]-4-thiazolyl]-(*Z*)-2-[[[(*p*-nitrobenzyloxy)carbonyl]methoxy]imino]acetic acid, 84208-28-6.

Sulfazecin Analogues. Preparation of 4-(Trifluoromethyl)-1-sulfo-2-azetidinone Derivatives

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The recently discovered sulfazecin and monobactam antibiotics are monocyclic β-lactams activated by an N-1 sulfonate substituent.[1,2] Aztreonam, a member of this new group of compounds that contains a methyl substituent in the 4-position of the β-lactam ring, has excellent activity against Gram-negative bacteria and is currently being evaluated in the clinic.[3] It is suggested in the literature that an increase in the reactivity of the β-lactam ring correlates well with antibacterial activity.[4] We reasoned that replacing the hydrogens of the 4-methyl group with fluorine atoms, which are strongly electronegative, would cause the β-lactam to be even more susceptible to nucleophillic attack. Thus, we hoped that replacing the methyl group by trifluoromethyl would have a good effect on antibacterial activity. In the preceding note by Ochiai and collaborators, this hypothesis was successfully tested by the preparation of the very active antibacterials, 4-(fluoromethyl)-3-(acylamino)-1-sulfo-2-azetidinones.[5] In the present paper, we describe the preparation of 3-(acylamino)-1-sulfo-2-azetidinones with *cis*- and *trans*-4-trifluoromethyl substituents.

During the course of this work, an alternate procedure for the preparation of these compounds was reported by Kronenthal et al.[6]

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