Beckman scintillation counter equipped with a single photon monitor was used to detect the chemiluminescence produced by the reaction of superoxide and luminol.

Registry No. 2, 123027-68-9; 3, 123027-69-0; 4, 123027-70-3; 5, 123027-71-4; 6, 707-94-8; 7, 37687-26-6; 8, 14215-97-5; 9, 123027-72-5; 10, 123027-73-6; 11, 70042-31-8; 12, 123027-74-7; 13, 123027-75-8; 14, 123027-76-9; 15, 670-54-2; 16, 55781-00-5; 17, 123027-77-0; 18, 123027-78-1; 19, 123027-79-2; 20, 123027-80-5; 21, 123027-81-6; 22, 41969-71-5; 23, 102690-94-8; 24, 123027-82-7; 25, 123027-83-8.

Supplementary Material Available: Hydrogen bonding in 2 and 3 as determined by X-ray crystallographic studies (1 page). Ordering information is given on any current masthead page.

Orally Effective Acid Prodrugs of the β-Lactamase Inhibitor Sulbactam

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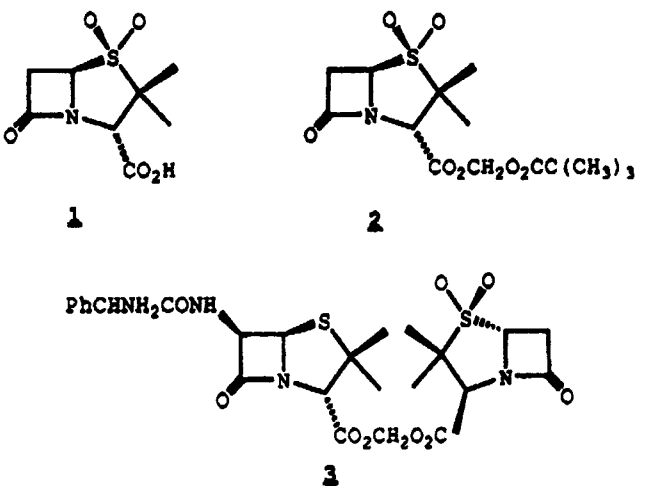
Sulbactam (1) is a β-lactamase inhibitor with limited oral bioavailability. Lipophilic double-ester prodrug sulbactam pivoxil (2) significantly improves the oral absorption of sulbactam, as does the mutual prodrug double ester sultamicillin (3). We have found that double-ester prodrugs of sulbactam terminating in a carboxyl group (8) also were effective oral-delivery vehicles in rats. Carboxyl-terminated double esters have several potential advantages over their nonionizable lipophilic counterparts, including water solubility, crystallinity, choice of salts for dosage forms, and formation of innocuous byproducts on hydrolysis.

The penicillins remain among the safest and most effective β-lactam antibiotics available for the treatment of bacterial infections. Their effectiveness has, however, been eroded over time through extensive use and natural selection for resistant strains. A majority of these strains inactivate penicillins through the action of β-lactamase enzymes. Effective inhibitors of these defensive enzymes have been developed and proved clinically useful in restoring and expanding the antibacterial spectrum of semisynthetic penicillins.[1] Sulbactam (1) is a β-lactamase inhibitor derived from 6-aminopenicillanic acid,[2] and like other penicillins, it has limited bioavailability after oral administration because of poor absorption from the gastrointestinal tract. This problem was alleviated by the synthesis of double-ester prodrugs,[3] such as sulbactam pivoxil (2), in analogy to the ampicillin prodrug esters,[4] and culminated in the discovery of the mutual prodrug 3, sultamicillin[5] (Chart I).

Double-ester prodrugs of these β-lactam antibiotics are very well absorbed and biolabile, effectively delivering the desired drugs to serum upon rapid enzymatic hydrolysis.[3-5] There are, however, limiting aspects of the double ester prodrug concept in its current embodiment. Bundgaard and Nielsen have recently enumerated these limitations as poor water solubility, limited stability in vitro, and the propensity of many of these lipophilic esters to exist as oils, creating formulation problems.[6] We report here the results of our efforts to address these limitations through synthesis and evaluation of a series of double-ester prodrugs of sulbactam terminating in a free carboxylic acid moiety. While we presumed that a carboxylic acid terminus could provide greatly improved water solubility at neutral pH and crystalline salts with good formulation characteristics, it was not obvious to us that intestinal absorption would equal that observed with lipophilic esters 2 or 3.

Chart I



1 2 3

Table I. Physical Constants, Synthetic Data

compd	X	% yield	mp,[a] °C	formula	anal.
8a	CH_2	88		$C_{12}H_{14}NO_9SNa$	C,H,N
8b	$C(CH_3)_2$	90	120-122	$C_{14}H_{18}NO_9SNa$	C,H,N
8c	$(CH_2)_3$	85	71-72	$C_{14}H_{18}NO_9SNa$	C,H,N,Na
8d	$(CH_2)_4$	84	100-102	$C_{15}H_{21}NO_9S \cdot H_2O$	C,H,N

[a] Melting points are of crystalline free carboxylic acids.

Synthesis

Synthesis of the desired novel double esters started from the benzyl half-ester of selected diacids 4. Formation of

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(4) Daehne, W. v.; Frederiksen, E.; Gundersen, E.; Lund, F.; Morch, P.; Petersen, H. J.; Roholt, K.; Tybring, L.; Godtfredsen, W. O. *J. Med. Chem.* **1970**, *13*, 607-612.
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(6) Bundgaard, H.; Nielsen, N. M. *J. Med. Chem.* **1987**, *30*, 451-454.

0022-2623/90/1833-0344$02.50/0

Scheme I

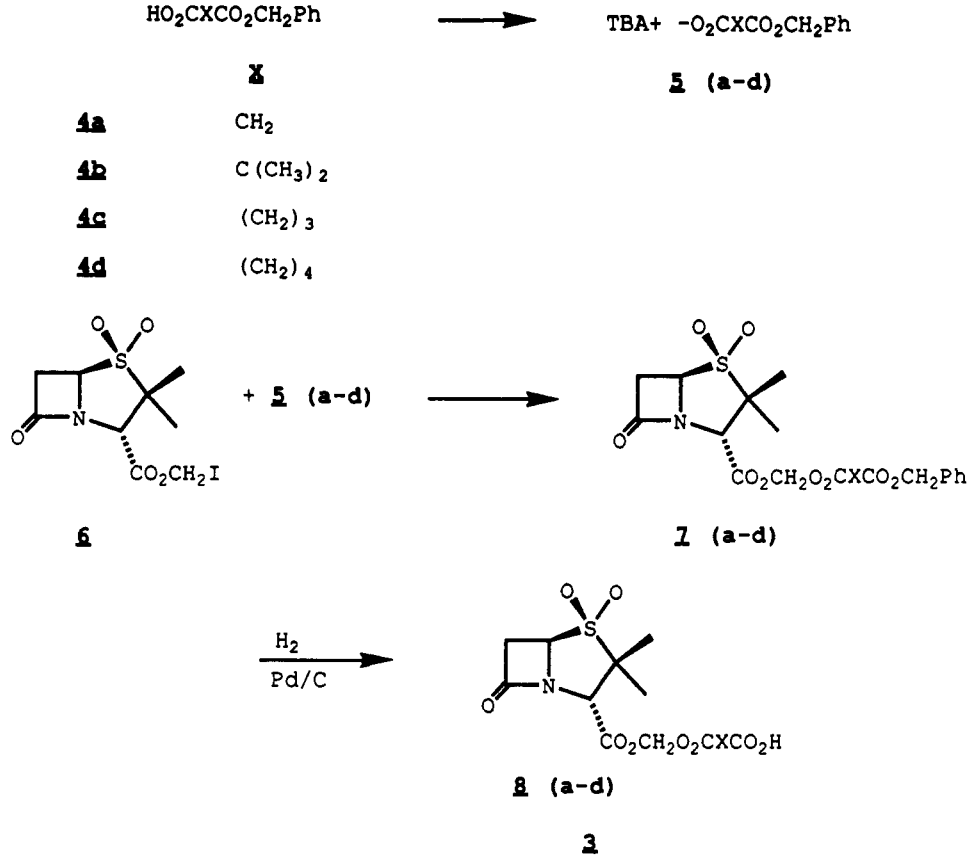

Table II. Oral Pharmacokinetics[a] of Sulbactam Double-Ester Prodrugs in Fasted Rats (10 mg/kg, sulbactam equivalents)

compd	X	$t_{1/2}$,[b] h	C_{max}, sulbactam equivalents, μg/mL	AUC, μg/mL h	ratio[c]
1		1.2	0.7	1.4	0.2, $p < 0.001$*
2		1.5	6.2	8.5	1.0
8a	CH_2	0.8	2.0	3.5	0.8, $p < 0.001$*
8b	$C(CH_3)_2$	1.0	3.9	6.2	1.0, $p = 0.007$*
8c	$(CH_2)_3$	1.1	8.2	10.0	1.2, $p = 0.06$*
8d	$(CH_2)_4$	1.0	5.2	7.5	1.0, $p = 0.18$*
7d	$(CH_2)_4$	1.0	1.6	2.3	0.4, $p < 0.001$*

[a] Values presented are best values obtained in series of five rats, **2** was run as a standard control in each study. [b] Half-life for disappearance of sulbactam from rat. [c] The ratio is AUC of compd/AUC of **2** determined in the same study. An asterisk indicates that differences from the control **2** are statistically significant using the Student's *t* test with significance at $p = 0.05$.

tetrabutylammonium salts **5**, and alkylation with iodomethyl penicillanate sulfone (**6**)[5a] gave the mixed benzyl esters **7**. Cleavage of the benzyl ester was effected by hydrogenolysis to give carboxylic acids **8**, and sodium salts (Table I) were obtained through exchange with sodium 2-ethylhexanoate (Scheme I).

Oral Bioavailability

Pharmacokinetic parameters were measured after oral administration to rats and compared to that of prodrug **2**, the standard. Serum levels of sulbactam were determined by bioassay at several time points and the serum half-life ($t_{1/2}$), maximum concentration (C_{max}), and area under the curve (AUC) derived from a plot of serum concentration vs time were calculated. The AUC is a measure of the bioavailability of the drug, and a ratio of the AUC for the novel compound to that of **2** as standard provides a measure of relative bioavailability in the animal being investigated.

Surprisingly, all the double-ester acids were effective as oral delivery forms for sulbactam, being more effective than the corresponding lipophilic benzyl esters **7** and more or less equivalent to the more lipophilic and less water soluble (pivaloyloxy)methyl ester **2**. Furthermore, the free-acid forms were generally crystalline solids, which could be converted to sodium salts with improved water solubility. The salts were indistinguishable from the free acids in oral pharmacokinetic studies (Table II).

Conclusions

The in vivo performance of carboxyl-terminated prodrugs of sulbactam is interesting in that transient masking[4] of a carboxyl group is accomplished with a double-ester moiety terminating in the same group. The literature[3,4] teaches that lipophilic esters are most effective in facilitating oral delivery of ampicillin. In contrast, we have now shown that polar hydrophilic esters of sulbactam can also improve its oral bioavailability. It is tempting to speculate that the carboxyl-terminated double esters of sulbactam are absorbed in the intestinal tract as if they were fatty acids[7] and that the absence of a hydrophilic substituent

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at the sulbactam terminus opposite the carboxyl facilitates transport as a "pseudo-fatty acid".

There are several advantages inherent to carboxyl-terminated double-ester prodrugs for oral delivery of pharmaceutical agents. The carboxyl moiety imparts improved water solubility, especially as the pH rises, as in transit from the stomach to the small intestine. It also provides improved prospects for isolation of crystalline solids as free acids or as sodium salts, thus creating options to improve formulation of oral delivery forms. Another advantage is the formation of potentially innocuous organic diacids as by products after hydrolysis to the parent drug in vivo. Clinically, these advantages can be translated to drugs that are more efficacious, safe, and convenient to use.

In summary, the acid-termination concept of ester-prodrug design has provided novel and effective delivery forms for the β-lactamase inhibitor sulbactam. Similar application to other drugs in order to improve oral bioavailability, formulation, water solubility, and simultaneous byproduct formation is suggested.

Experimental Section

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian VT-300 spectrometer operating at 300 MHz using $CDCl_3$ and D_2O. Chemical shifts are reported in ppm (δ) and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br s (broad singlet). Mass spectra were obtained from an A.E.I. MS-30. IR spectra were obtained on a Perkin-Elmer 283 B instrument. Reagents and solvents were purchased from common commercial suppliers and were used as received. Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen. Reaction products were purified, when necessary, by chromatography on silica gel (63-200) using the systems indicated. Thin-layer chromatography was performed on silica gel 60 F254 precoated 5 × 20 cm plates. Yields were not optimized. Elemental analyses were performed by the Analytical Department at Pfizer Central Research.

(Pivaloyloxy)methyl Penicillanate Sulfone (2). Under a N_2 atmosphere were combined the sodium salt of **1** (2.55 g, 10 mmol), 50 mL of acetone, TBA-Br (0.97 g, 3 mmol), and chloromethyl pivalate (1.44 mL, 10 mmol). The resulting suspension was heated at a gentle reflux for 18 h and then concentrated and chromatographed (50% ethyl acetate/hexane) to yield **2**: ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 9 H), 1.40 (s, 3 H), 1.56 (s, 3 H), 3.45 (m, 2 H), 4.38 (s, H), 4.59 (q, H) 5.68 (d, H), 5.92 (d, H); IR (KBr) 1805, 1785, 1773, 1754 cm^{-1}. Anal. ($C_{14}H_{21}NO_7S$) C, H, N, S.

Benzyl Malonate Half-Ester (4a). Under a N_2 atmosphere a solution of potassium hydroxide (6.5 g, 0.1 mol) in 125 mL of benzyl alcohol was added dropwise to a solution of dibenzyl malonate (28.4 g, 0.1 mol) in 250 mL benzyl alcohol. The resulting suspension was stirred for 3 h and then was diluted with 1.5 L of ether; the solids were filtered, washed well with ether, and air dried to yield the desired benzyl malonate half-ester (20.5 g, 88%): ^{1}H NMR (D_2O) δ 3.35 (s, 2 H), 5.20 (s, 2 H), 7.45 (s, 5 H).

Benzyl 2,2-Dimethylmalonate Half-Ester (4b). (a). To a 0 °C solution of sodium hydroxide (4.0 g, 0.1 mol) in 75 mL of H_2O was added tetra-*n*-butylammonium hydrogen sulfate (TBA-HSO_4, 17 g, 0.05 mol), the resulting solution was stirred for 15 min, the cooling was removed, and a 100-mL solution of $CHCl_3$ containing dibenzyl malonate (14.2 g, 0.05 mol) and methyl iodide (6.6 mL, 0.1 mol) was added in one portion. The reaction was allowed to stir for 40 min during which time the above sequence was repeated to prepare a new solution of NaOH/TBA-HSO_4/H_2O. Upon completion of the 40-min stir, the $CHCl_3$ layer was separated, methyl iodide (6.6 mL, 0.1 mol) was added, and this $CHCl_3$ solution was combined with the second NaOH/TBA-HSO_4/H_2O solution and stirred for 40 min. The $CHCl_3$ layer was separated, dried (Na_2SO_4), and concentrated, and the resulting oil was triturated with diethyl ether to precipitate out TBA iodide, which was removed by filtration, and the filtrates were concentrated to yield dibenzyl 2,2-dimethylmalonate as an oil (15.0 g, 96%): ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 6 H), 5.1 (s, 4 H), 7.27 (m, 5 H).

(b). A solution of potassium hydroxide (3.12 g, 48 mmol) in 75 mL of benzyl alcohol was added to dibenzyl 2,2-dimethylmalonate (15.0 g, 48 mmol) in 75 mL of benzyl alcohol, and the resulting solution was stirred for 72 h. Upon completion of the stirring, the reaction was diluted with 1.5 L of ether and extracted with H_2O (2 × 100 mL). The aqueous extracts were combined and washed with ether (2 × 100 mL) and then overlayed with 200 mL of fresh ether and acidified to pH 2.5 with 6 N HCl. The ether layer was separated, dried (Na_2SO_4), and concentrated to yield benzyl 2,2-dimethylmalonate half-ester (8.6 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 6 H), 5.16 (s, 2 H), 7.31 (m, 5 H).

Benzyl Glutarate Half-Ester (4c). Under a N_2 atmosphere, glutaric acid anhydride (22.8 g, 0.2 mol), 400 mL of toluene, and benzyl alcohol (108 g, 1.0 mol) were combined and heated at reflux for 18 h. The solvent was removed and the residue was partitioned in 400 mL of ethyl acetate and 200 mL of H_2O. The pH was then adjusted to 8.0 with 6 N NaOH; the aqueous layer was separated, washed with ether (2 × 300 mL), overlayed with 300 mL of fresh ether, and acidified. The ether layer was separated, dried (Na_2SO_4), and concentrated to yield 25.2 g (57%) of **4c** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.96 (m, 2 H), 2.42 (q, 4 H), 5.1 (s, 2 H), 7.33 (m, 5 H).

Benzyl Adipate Half-Ester (4d). Adipic acid (73 g, 0.5 mol), benzyl alcohol (81 g, 0.75 mol), *p*-toluenesulfonic acid (0.95 g, 5 mmol), and 400 mL of toluene were combined in a flask equipped with Dean–Stark trap and heated at reflux until the theoretical amount of H_2O (13.5 mL, 0.75 mol) was obtained. The reaction was then cooled, 300 mL of H_2O added, and the pH adjusted to 8 with 6 N NaOH. The aqueous layer was separated and washed with ether (2 × 100 mL), 200 mL of fresh ether was added, and the pH was adjusted to 2.0 with 6 N HCl. The ether layer was separated, dried (Na_2SO_4), and concentrated to yield 47 g of **4d** (40%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.68 (m, 4 H), 2.36 (m, 4 H), 5.09 (s, 2 H), 7.32 (m, 5 H).

[[3-(Benzyloxy)malonyl]oxy]methyl Penicillanate Sulfone 7a. Under a N_2 atmosphere were combined potassium benzylmalonate (11.6 g, 50 mmol) and 100 mL of DMF. To the resulting suspension was added iodomethyl penicillanate 1,1-dioxide (**6**,[5a] 18.65 g, 50 mmol) and this mixture was allowed to stir for 1 h at which point the clear yellow solution was diluted with 500 mL of ethyl acetate, washed (4 × 100 mL of H_2O, 1× with brine), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography (50% ethyl acetate/hexane) to afford **7a** (10 g, 45%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.53 (s, 3 H), 1.53 (s, 3 H), 3.44 (m, 2 H), 3.47 (s, 2 H), 4.37 (s, H), 4.57 (q, H), 5.15 (s, 2 H), 5.73 (d, H), 5.91 (d, H), 7.33 (m, 5 H); IR ($CHCl_3$) 1805, 1779, 1743 cm^{-1}; exact mass calcd for $C_{19}H_{22}NO_9S$ (M + 1) 440.1016, found 440.0966.

Tetrabutylammonium Benzyladipate (5d). To a solution of TBA-HSO_4 (0.488 g, 1.44 mmol) in 10 mL of H_2O was added $NaHCO_3$ (0.242 g, 2.88 mmol). After the foaming had subsided, benzyl adipate half-ester (0.34 g, 1.44 mmol) and 15 mL of $CHCl_3$ were added, the mixture was stirred for 5 min, and the $CHCl_3$ layer was separated. The aqueous layer was extracted with 15 mL of fresh $CHCl_3$. The extracts were combined, dried (Na_2SO_4), and concentrated to yield **5d** (0.69 g, 100%) as a foam: ^{1}H NMR ($CDCl_3$) δ 0.947 (t, 12 H), 1.39 (m, 8 H), 1.61 (m, 12 H), 2.21 (m, 2 H), 2.32 (m, 2 H), 3.28 (m, 8 H), 5.045 (s, 2 H), 7.30 (s, 5 H).

Tetrabutylammonium Benzylglutarate (5c). The TBA salt of monobenzyl glutarate was prepared (97%) as described for **5d**: ^{1}H NMR ($CDCl_3$) δ 0.942 (t, 12 H), 1.38 (m, 8 H), 1.6 (m, 8 H), 1.92 (m, 2 H), 2.23 (t, 2 H), 2.39 (t, 2 H), 3.28 (m, 8 H), 5.04 (s, 2 H), 7.28 (m, 5 H).

Tetrabutylammonium Benzyl 2,2-Dimethylmalonate (5b). The TBA salt of monobenzyl 2,2-dimethylmalonate was prepared (98%) as described for **5d**: ^{1}H NMR ($CDCl_3$) δ 0.922 (t, 12 H), 1.38 (s, 6 H), 1.41 (m, 8 H), 1.56 (m, 8 H), 3.23 (m, 8 H), 5.08 (s, 2 H), 7.28 (m, 5 H).

[[5-(Benzyloxy)glutaryl]oxy]methyl Penicillanate Sulfone 7c via TBA Salts. Under a N_2 atmosphere were combined **5c** (8.0 g, 17 mmol) and 40 mL of acetone. The solution was stirred and iodomethyl sulbactam (**6**, 5.59 g, 15 mmol) was added. The solution was stirred for 30 min and then concentrated. The residue was dissolved in 150 mL of ethyl acetate, the precipitated TBA-I was filtered off, and the filtrates were washed with saturated $NaHCO_3$ (2 × 25 mL), dried (Na_2SO_4), concentrated, and purified

by column chromatography (1:1 ethyl acetate/hexane) to yield **7c** (3.9 g, 56%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.97 (m, 2 H), 2.42 (m, 4 H), 3.44 (m, 2 H), 4.38 (s, H), 4.58 (q, H), 5.094 (s, 2 H), 5.71 (d, H), 5.86 (d, H), 7.33 (m, 5 H); IR ($CHCl_3$) 1805, 772, 1765, 1733 cm^{-1}; exact mass calcd for $C_{21}H_{26}NO_9S$ (M + 1) 468.1329, found 468.1298.

[[3-(Benzyloxy)-2,2-dimethylmalonyl]oxy]methyl Penicillanate Sulfone (7b). The coupling of **5b** and **6** was carried out (52%) as described for the preparation of **7c**: ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.46 (s, 6 H), 1.47 (s, 3 H), 3.43 (m, 2 H), 4.32 (s, H), 4.48 (q, H), 5.14 (d, 2 H), 5.63 (d, H), 5.89 (d, H), 7.33 (m, 5 H); IR ($CHCl_3$) 1805, 1778, 1739 cm^{-1}; exact mass calcd for $C_{21}H_{26}NO_9S$ (M + 1) 468.1329, found 468.1298.

[[6-(Benzyloxy)adipoyl]oxy]methyl Penicillanate Sulfone (7d). The coupling of **5d** and **6** was carried out (61%) as described for the preparation of **7c**. ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3 H), 1.56 (s, 3 H), 1.67 (m, 4 H), 2.36 (m, 4 H), 3.44 (m, 2 H), 4.39 (s, H), 4.59 (q, H), 5.09 (s, 2 H), 5.71 (d, H), 5.86 (d, H), 7.33 (m, 5 H); IR ($CHCl_3$) 1807, 1770, 1733 cm^{-1}; exact mass calcd for $C_{22}H_{28}NO_9S$ (M + 1) 482.1485, found 482.1451.

(Adipoyloxy)methyl Penicillanate Sulfone (8d). To a solution of **7d** (14.4 g, 30 mmol) in 200 mL of ethyl acetate was added 5 g of 10% Pd/C and this mixture was hydrogenated in a 500-mL Parr bottle at 50 psi for 45 min. The reaction was checked by TLC for disappearance of the starting material. If **7d** remained, more catalyst was added and reaction was hydrogenated further. When reaction was complete, the catalyst was filtered off with Supercel as a filter aid. Filtrates were concentrated to a viscous oil, which was dissolved in 30 mL of acetone and H_2O added until the product crystallized. Acetone was removed by rotary evaporation. The solid residue was filtered, washed with H_2O, and air-dried to yield **8d** as white crystals (10.3 g, 84%): mp 100–102 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.58 (s, 3 H), 1.66 (m, 4 H), 2.37 (m, 4 H), 3.46 (m, 2 H), 4.42 (s, H), 4.6 (q, H), 5.73 (d, H), 5.88 (d, H); IR (KBr) 1764, 1727; exact mass calcd for $C_{15}H_{21}NO_9S$ (M + 1) 392.1016, found 392.0988. Anal. ($C_{15}H_{21}NO_9S \cdot H_2O$) C, H, N.

(Glutaryloxy)methyl Penicillanate Sulfone (8c). Hydrogenation of **7c** as described for **7d** gave **8c** (85%): crystallized from 2-propanol; mp 74–76; ^{1}H NMR ($CDCl_3$) δ 1.395 (s, 3 H), 1.58 (s, 3 H), 1.96 (m, 2 H), 2.44 (m, 4 H), 3.46 (m, 2 H), 4.43 (s, H), 4.61 (q, H), 5.75 (d, H), 5.86 (d, H); IR (KBr) 1786, 1769, 1702 cm^{-1}; exact mass calcd for $C_{14}H_{19}NO_9S$ (M + 1) 378.0859, found 378.0843. Anal. ($C_{14}H_{18}NO_9SNa$) C, H, N, Na.

[(2,2-Dimethylmalonyl)oxy]methyl Penicillanate Sulfone (8b). Hydrogenation of **7b** as described for **7d** gave **8b** (90%): crystallized neat; mp 121–123 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3 H), 1.47 (s, 6 H), 1.57 (s, 3 H), 3.46 (m, 2 H), 4.37 (s, H), 4.62 (q, H), 5.76 (d, H), 5.96 (d, H), 9.0 (br s, H); IR ($CHCl_3$) 1802, 1776, 1740 cm^{-1}; exact mass calcd for $C_{14}H_{19}NO_9S$ (M + 1) 378.0859, found 378.0868.

(Malonyloxy)methyl Penicillanate Sulfone (8a). Hydrogenation of **7a** as described for **7d** gave **8a** (88%) as an unstable gum: ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.58 (s, 3 H), 3.43 (m, 2 H), 3.47 (s, 2 H), 4.40 (s, H), 4.63 (m, H), 5.78 (d, H), 5.93 (d, H), 6.74 (br s, H). Anal. Sodium salt ($C_{12}H_{14}NO_9SNa$) C, H, N.

Preparation of Sodium Salts. To **8b** (3.77 g, 10 mmol) in 200 mL of ethyl acetate was added a 10-mL ethyl acetate solution containing sodium 2-ethylhexanoate (1.66 g, 10 mmol) under a N_2 atmosphere, and the mixture was stirred. A precipitate formed immediately. The mixture was stirred for 30 min, the solids were filtered, washed with ethyl acetate (2 × 30 mL), and dried under a N_2 atmosphere to obtain **8b** sodium salt as a white solid (3.9 g, 98%): ^{1}H NMR (D_2O) δ 1.37 (s, 6 H), 1.47 (s, 3 H), 1.62 (s, 3 H), 3.6 (m, 2 H), 4.76 (s, H), 5.11 (q, H), 5.83 (d, H) and 6.01 (d, H); IR (KBr) 1790, 1748, 1735, 1605 cm^{-1}. Anal. ($C_{14}H_{18}O_9NSNa$) C, H, N.

Animal Studies. Male outbred CD rats (70–90 g) were purchased from Charles River Breeding Laboratories, Inc., Kingston, RI. The sulbactam prodrugs were administered orally to rats at a dose of 10 mg/kg in a 0.5-mL volume of a CMC diluent.[8] Plasma was obtained from blood samples taken in heparinized hematocrit tubes from the orbital venous plexus of rats. Samples were obtained from a group of five rats for each prodrug and collected over a 4-h period. The sulbactam rat plasma levels were determined by a synergistic bioassay. The assay uses a strain of *Pasteurella hemolytica* (ATCC 43823) as indicator organism, which is seeded into Mueller–Hinton agar and supplemented with ampicillin and triphenyltetrazolium chloride and poured into large bioassay plates.[9] A sulbactam standard curve was prepared over a concentration range of 10–0.1 μg/mL by fortifying normal rat plasma with sulbactam. Following the dispensation of 25 μL of each sample and standard into 6-mm agar wells, the plates are incubated for 18 h at 37 °C. The sulbactam concentrations are subsequently determined following regression analysis of the zone size–concentration curve.

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Registry No. **1**, 68373-14-8; **1** sodium salt, 69388-84-7; **2**, 69388-79-0; **4c**, 54322-10-0; **4d**, 40542-90-3; **5b**, 123963-80-4; **5c**, 87353-15-9; **5d**, 87353-23-9; **6**, 76247-39-7; **7a**, 87343-28-0; **7b**, 87343-27-9; **7c**, 87343-26-8; **7d**, 87343-31-5; **8a**, 123963-81-5; **8a** sodium salt, 87353-40-0; **8b**, 87353-21-7; **8b** sodium salt, 87353-39-7; **8c**, 87353-01-3; **8c** sodium salt, 87353-37-5; **8d**, 87343-33-7; monobenzyl malonate, 40204-26-0; dibenzyl malonate, 15014-25-2; monobenzyl 2,2-dimethylmalonate, 86507-74-6; dibenzyl 2,2-dimethylmalonate, 57772-82-4; glutaric acid anhydride, 108-55-4; adipic acid, 124-04-9; potassium benzyl malonate, 41087-88-1; chloromethyl pivalate, 18997-19-8.

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