(NH_2OH extinguishable). MS: 379 (M − K + glycerol matrix).

Potassium (5*R*,6*S*)-2-(4′-hydroxyphenyl)-6-[(1*R*)-1-hydroxyethyl]-carbapen-2-em-3-carboxylate (32) was obtained from the allyl ester **31** in 30% yield. IR: 1735 (β-lactam C=O). NMR (D_2O): 1.16 (CH_3, d, J = 8 Hz), 2.9 and 3.26 (H2), 3.34 (H6, dd, J = 2, 4 Hz), 4.04–4.22 (H5 and H8, m), 6.74 and 7.17 (phenyl H, dd, J = 4, 43 Hz). UV: λ_{max} (H_2O) 300 nm (NH_2OH extinguishable).

Potassium (1*R*,5*R*,6*S*)-2-[4′-(azidomethyl)phenyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (49) was prepared from allyl ester **45** in 39% yield. NMR (D_2O): 0.9 (CH_3, d, J = 8 Hz), 1.14 (CH_3, d, J = 6 Hz), 3.30 (H6, dd, J = 1.5, 3 Hz), 3.22–3.40 (H1, m), 4.14 (H5, dd, J = 1.5, 5 Hz), 4.04–4.20 (H8, m), 4.27 (CH_2N_3, s, 2 H), 7.29 (aromatic H, 2 d, J = 4 Hz). UV: λ_{max} (H_2O) 286 nm (NH_2OH extinguishable).

Potassium (1*R*,5*R*,6*S*)-2-[2′-(azidomethyl)-5′-pyridyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (50) was obtained from allyl ester **46** in 32% yield. NMR (D_2O): 0.94 (CH_3, d, J = 8 Hz), 1.16 (CH_3, d, J = 8 Hz), 3.39 (H6, dd, J = 1.5, 3 Hz, 1 H), 3.30–3.46 (H1, m), 4.21 (H5, dd, J = 1.5, 5 Hz), 4.16 (H8, m), 4.42 (CH_2N_3, s), 7.3–8.5 (pyridyl H, m). UV: λ_{max} (H_2O) 290 nm (NH_2OH extinguishable).

Potassium (1*R*,5*R*,6*S*)-2-[4′-(hydroxymethyl)phenyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (53) was prepared from allyl ester **48** in 68% yield. NMR (D_2O): 1.36 (CH_3, d, J = 8 Hz), 1.60 (CH_3, d, J = 6 Hz, 3 H), 3.78 (H6 and H1, m, 2 H), 4.59 (H5 and H8, m, 2 H), 4.92 (CH_2O, s, 2 H), 7.70 (phenyl H, 2 d, J = 4 Hz, 4 H). UV: λ_{max} (H_2O) 288 nm (NH_2OH extinguishable).

(1*R*,5*R*,6*S*)-2-[4′-(Aminoethyl)phenyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic Acid (51). The carbapenem azide **49** (37 mg, 0.0974 mmol) was dissolved in 3 mL of water. Ten milligrams of 10% Pd/C and 0.39 mL (0.195 mmol) of 0.5 M pH 7 4-morpholinepropanesulfonic acid buffer were added. The mixture was hydrogenated at 45 psi on a Parr shaker apparatus for 15 min at room temperature. The solids were filtered and washed with 2 × 2 mL of water. The filtrate was concentrated to 0.5 mL, applied on reverse-phase silica gel plates, and worked up as described for **25d** to give 72% of the carbapenem amino acid **51**. UV: λ_{max} (H_2O) 287 nm (NH_2OH extinguishable). MS: FAB positive ion, 319 (M + H); FAB negative ion, 317 (M − H).

(1*R*,5*R*,6*S*)-2-[2′-(Aminomethyl)-5′-pyridyl]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid (52) was similarly obtained from the azide **50** as described above for **51** in 80% yield. NMR: 0.95 (CH_3, d, J = 6 Hz), 1.16 (CH_3, d, J = 6 Hz), 3.25–3.45 (H6 and H1), 4.0–4.30 (H5 and H8), 7.20–8.50 (pyridyl H). UV: λ_{max} (H_O) 290 nm (NH_2OH extinguishable).

Acknowledgment. We thank Dr. C. Shunk for the preparation of starting material, J. Smith , H. Flynn, and Dr. B. Arison for mass spectral and 200-MHz NMR measurements, and J. Kahan, H. Kropp, and J. Sundelof for the antimicrobial and DHP susceptibility assays.

Anticonvulsant *O*-Alkyl Sulfamates. 2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose Sulfamate and Related Compounds†

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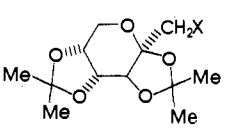
Novel sugar sulfamate 1 (McN-4853, topiramate) has been found to exhibit potent anticonvulsant activity analogous to that of phenytoin. In the maximal electroshock seizure test, orally at 2 h in mice, 1 had an ED_{50} of 39 mg/kg. Orally, 1 had a duration of action in excess of 8 h. Other aspects of the pharmacology of 1, as well as neurochemistry and carbonic anhydrase inhibition, are discussed. The conformational behavior of 1 in solution and in the solid state is discussed. A series of analogues of 1 were synthesized and examined for anticonvulsant properties.

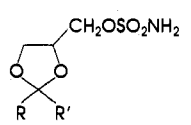
Anticonvulsants are the primary drugs used for the treatment of epileptic disorders.[1] However, despite the availability of several drugs, only about 75% of the epileptic population significantly benefits from current pharmacotherapy, and many of these patients experience adverse side effects, such as drowsiness, ataxia, or gingival hyperplasia.[1] Thus, the search for less toxic, more efficacious agents for the treatment of seizure disorders has been a continuing endeavor.

A wide diversity of chemical structure types exhibit anticonvulsant antivity. These compounds, many of which are cyclic amides (e.g., imides, carboxamides, sulfonamides, carbamates, hydantoins, and ureas),[1a-c] can be classified into two groups. There are agents (e.g., phenytoin and carbamazepine) effective for tonic-clonic seizures and

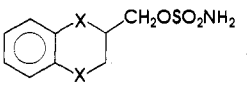
Chart I



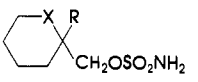
1 X = OSO_2NH_2
2 X = OSO_2NHMe
3 X = OSO_2NMe_2
4 X = OH
5 X = $OC(O)NH_2$
6 X = OSO_2N_3
7 X = OSO_2NHPh
8 X = OC(O)NHPh



9 R = R′ = Me
10 R/R′ = $(CH_2)_5$
11 R = Me; R′ = $(CH_2)_8CH_3$



14 X = CH_2
15 X = O



12 X = O; R = H
13 X = CH_2; R = CH_3

agents (e.g., ethosuximide and nitrazepam) effective for petit mal seizures, which can be characterized pharmaco-

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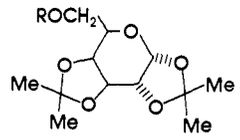
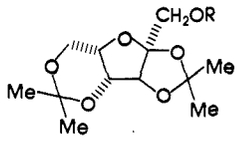
§ University of Pennsylvania.

0022-2623/87/1830-0880$01.50/0

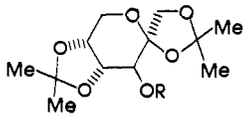
Chart II



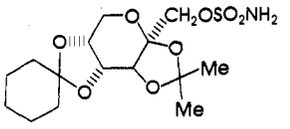
16a R = H
16b R = SO_2NH_2



17a R = H
17b R = SO_2NH_2



18a R = H
18b R = SO_2N_3
18c R = SO_2NH_2



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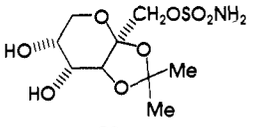

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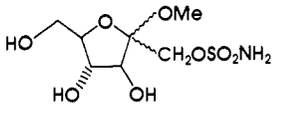
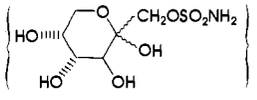


22

Chart III



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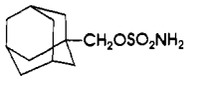

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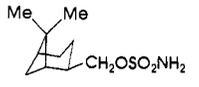

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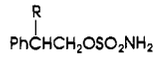
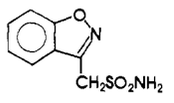


25 R = H
26 R = Ph



27

logically by the ability to prevent maximal electroshock seizures (MES) or pentylenetetrazole-induced seizures, respectively.[1] We discovered that 2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate (**1**, McN-4853, topiramate) exerts a potent anticonvulsant effect in the MES assay. Since this compound is structurally distinct from known agents, in the sense that it is a monosaccharide derivative and contains a sulfamate functionality, we synthesized and studied some analogues to ascertain those features associated with biological activity. This paper describes some structure–activity work and the biological evaluation of **1**.

Results and Discussion

Chemistry. Most of the sulfamate derivatives (**1–3, 7, 9–18, 23–26**; Charts I–III) were synthesized from the corresponding alcohols, many of which were obtained commercially or in one step from reduction of a commercially available ester, or from ketalization of glycerol. Three different procedures were employed to make these sulfamate compounds: (1) the alcohol was reacted with the appropriate sulfamoyl chloride[2,3] in the presence of NaH (for **1–3, 7, 9–17b, 23–26**),[3,4] (2) the alcohol was reacted with sulfuryl chloride in the presence of pyridine to give a chlorosulfate intermediate,[5] which was then treated with an appropriate amine (for **1** and **2**),[3,4] or (3) the alcohol-derived chlorosulfate was converted with sodium azide to an azidosulfate (**6** and **18b**), which was reduced by copper in methanol or by catalytic hydrogenation with palladium on carbon (for **1** and **18c**).[3,5a–c]

Sulfamate **22** (mixture of isomers enriched in furanosides) was prepared by acid-catalyzed methanolysis of **1**, and **19** was obtained by reaction of **1** with 1-(trimethylsiloxy)cyclohexene and HCl.[6] NMR spectroscopic data for **19** allowed us to assign the 4,5-cyclohexylidene substitution. The hydrolysis products of **1**, i.e., **20** and **21**, were prepared under acid catalysis. The nature of **21** is a mixture of furanose (ca. 30%) and pyranose (ca. 70%) forms with the SO_2NH_2 group linked to the anomeric center (anhydro compounds).

Carbamate **5** was obtained by reacting alcohol **4** with chlorosulfonyl isocyanate followed by hydrolysis,[7] or with trichloromethyl chloroformate (phosgene equivalent[8]) followed by ammonolysis; **8** was produced from **4** and phenyl isocyanate.

Anticonvulsant Testing. Anticonvulsant activity was generally determined by using a standard MES test.[9] In this test, activity is indicated by a block of the hind-limb tonic-extensor seizure caused by application of an electric shock to mice via corneal electrodes. Data for the compounds of interest are presented in Tables I and II. A number of the compounds were evaluated for anticonvulsant activity, in a preliminary fashion, by using a maximal electroshock seizure threshold (MEST) test,[10] a modification of the CS_{50} method of Chen et al.[11] The MEST method is related to the maximal electroshock seizure (MES) test, but it employs a much smaller current (8 vs. 50 mA). It follows that compounds inactive in the MEST assay could not exhibit activity in the MES assay, because the latter has a much higher seizure-inducing current. Compounds inactive in the MEST test, which were not subsequently tested in the MES test, are so noted in Table I. A listing of 95% confidence limits for the MES ED_{50} data is furnished in Table III.[12]

Considering the *data in Table I* (30–60 min after dosing), sulfamates **1, 2, 9, 14, 15, 17b, 25**, and **26** showed significant activity ($ED_{50} \leq 150$ mg/kg) in the MES test, with **14, 25**, and prototype **1** having the greatest potency.

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(10) Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F. *J. Med. Chem.* **1984**, *27*, 1067.

(11) Chen, G.; Ensor, C. R.; Bohner, B. *Life Sci.* **1968**, *7*, 1063.

(12) Ninety-five percent confidence limits were calculated according to a published method: Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.

Table I. Chemical and Biological Data

compound	formula[a]	mp, °C (solv)[b]	$[\alpha]_D$ (*c*, solv)[c]	MES (ip/po) ED_{50}, mg/kg[d]
1	$C_{12}H_{21}NO_8S$[e]	125–126 (EA/H)	−34.0 (0.40, M)	64/61
2	$C_{13}H_{23}NO_8S$	lt yel syrup (LC)	−30.0 (0.29, M)	50–100/∼200
3	$C_{14}H_{25}NO_8S$[f]	57–58 (E/W)	−31.3 (0.31, M)	>100/>200
4[g]	$C_{12}H_{20}O_6$	97–97.5 (EE/P)	−35.0 (0.50, W)[h]	I_{200}/I_{400}[i]
5	$C_{13}H_{21}NO_7$	122–125 (E/PE)	−34.2 (0.40, M)[j]	*i*
6	$C_{12}H_{19}N_3O_8S$	105–107 (I)	−27.0 (0.20, M)	>100/∼200[k]
7	$C_{18}H_{25}NO_8S$	115–116 (C/H)	−36.3 (0.30, M)	I_{100}/I_{200}
8	$C_{19}H_{25}NO_7$	165.5–167.5 (EA/H)	−44.7 (0.30, M)	I_{200}/I_{400}[i]
9	$C_6H_{13}NO_5S$	lt yel syrup (LC)		∼100/∼75
10	$C_9H_{17}NO_5S$[l]	soft wax (HPLC)		169/∼150
11[m]	$C_{14}H_{29}NO_5S$[n]	49–51 (HPLC)		319/>200
12	$C_6H_{13}NO_4S$	colorless syrup (LC)		195/154
13	$C_8H_{17}NO_3S$	40–42 (C/H)		270/∼400
14	$C_{11}H_{15}NO_3S$	108–109 (C/H)		56/82
15	$C_9H_{11}NO_5S$	94–96 (C)		∼100/118
16b[o]	$C_{12}H_{21}NO_8S$[p]	48–50 (LC)	−53.6 (0.32, C)[h]	∼175/>200
17b	$C_{12}H_{21}NO_8S$	133–135 (HPLC)	−5.5 (0.93, M)	∼100/∼150
18c	$C_{12}H_{21}NO_8S$	white foam (LC)		*i*
19	$C_{15}H_{25}NO_8S$	179–180 (EA/H)	−29.9 (0.50, M)	I_{100}/>400
20	$C_9H_{17}NO_8S$	130–132 (EA/H)	+25.7 (0.82, M)[i]	I_{100}/I_{200}
21[m]	$C_6H_{11}NO_7S$[q]	lt yel syrup[r]	−28.4 (0.10, M)	*i*
22[m]	$C_7H_{15}NO_8S$[s]	lt yel syrup[r]	−14.8 (0.50, W)	*i*
23	$C_{11}H_{19}NO_3S$	140–141 (E/W)		>100/∼200
24[t]	$C_{10}H_{19}NO_3S$	51–53 (E/W)	−14.7 (0.12, M)	I_{100}/I_{200}
25	$C_8H_{11}NO_3S$	lt yel syrup[r,u]		∼50/∼100
26	$C_{14}H_{15}NO_3S$	116–118 (C/H)		I_{100}/147
phenytoin[v]				10/10
acetazolamide[v]				--/45

[a] All new compounds were analyzed within ±0.4% for C, H, and N, unless otherwise noted; some compounds also were analyzed for S or water (within ±0.4%). Water composition was confirmed by Karl-Fischer analysis, and solvent additives were confirmed by ^1H NMR integration (90- or 360-MHz spectra, as required). [b] The recrystallization solvent is given in parentheses: EA = ethyl acetate, H = hexane, W = water, E = ethanol, EE = ethyl ether, P = pentane, PE = petroleum ether (30–60 °C), I = 2-propanol, C = chloroform. Other materials were purified by column chromatography (LC) or preparative HPLC and isolated by evaporation of solvent from the appropriate fractions. [c] Optical rotations (units of degrees) were measured at 23–24 °C, unless otherwise indicated. Concentration (*c*) in g/100 mL and solvent (M = methanol, W = water, C = chloroform) are given in parentheses. [d] Maximal electroshock seizure test in mice; ip and/or po data are given. Activity was measured at 30–60 min following administration of drug. I = inactive, 0–10% block at the subscripted maximum dose (mg/kg). See Table II for time-course data. Results in the MEST assay (see text) are indicated for a few compounds. [e] C, H analysis. [f] C, H, S analysis. [g] Lit.[26] mp 97 °C. [h] Rotation was measured at 25 °C. [i] Inactive in the MEST assay at 100 mg/kg (ip). [j] Rotation was measured at 26 °C. [k] ED_{50} in the MEST assay (ip) was 402 mg/kg (262–616). [l] Contains 0.05 mol of cyclohexanone and 0.2 mol of water. [m] Mixture of diastereomers. The carbamate analogue of **11** (1:1 mixture of two diastereomers; mp 59–62 °C (PE))[13] was found to have an ED_{50} of 85 mg/kg (74.3–98.3), ip. [n] Contains 0.1 mol of 2-undecanone and 0.2 mol of water. [o] Reported as a syrup in the literature: Kochetkov, N. K.; Usov, A. I.; Deryabin, V. V. *J. Gen. Chem. USSR* **1972**, *42*, 2755; lit. $[\alpha]_D$ −58° (*c* 0.58, $CHCl_3$). [p] Contains 0.2 mol of water. A different sample, purified by HPLC and containing 0.02 mol of water, had mp 91–93 °C. [q] Contains 0.8 mol of water. [r] Not subjected to chromatography. [s] Contains 0.5 mol of water; C, H, and water analysis. [t] From (−)-*cis*-myrantol. [u] Distilled by Kugelrohr at 80 °C (pot temperature) (0.07 torr). [v] Reference compound.

Table II. Anticonvulsant Testing. Time-Course Data[a]

	% block in MES test (mice) at specific time in min									
compd	po dose, mg/kg	30	60	120	240	ip dose, mg/kg	30	60	120	240
1	100	40	80	80	100	50	20	60	70	50
2	200	20	70	100	100	100	30	90	80	30
3	200	30	40	80	80	100	30	30	50	30
4	400	0	0	0	0	200	0	0	0	0
6	200	30	50	70	100	100	20	40	50	30
7	200	0	0	0	0	100	0	0	0	0
8	400	0	0	0	0	200	0	0	0	0
9	200	70	90	100	100	100	50	70	90	70
10	200	70	30	20	10	100	30	10	0	0
13	400	50	40	80	30	200	30	30	20	20
14	100	80	80	80	30	50	30	50	0	0
15	200	100	100	80	80	100	30	60	30	0
16b	400	50	80	90	80	200	20	40	50	30
17b	200	70	80	70	50	100	30	50	20	0
19	200	10	0	20	20	100	0	0	0	0
20	200	0	0	0	0	100	0	0	10	0
23	200	40	90	50	200	100	40	20	0	0
24	200	10	10	10	0	100	10	10	0	0
25	200	70	100	100	80	100	90	100	70	20
26	200	80	70	80	100	100	0	0	0	0
phenytoin	15	50	80	70	30	10	60	60	80	70
zonisamide	40	20	40	40	50					

[a] See Experimental Section. Ten mice were used for each time point.

Table III. 95% Confidence Limits for the MES ED_{50} Data

compd	time, min	MES ED_{50}, ip	MES ED_{50}, po
1	30	64 (50–93)	61 (50–87)
9	30	105 (75–160)	
10	30	169 (140–223)	
11	30	319 (290–349)	
12	60	195 (138–274)	154 (126–188)
13	60	270 (206–354)	
14	60	56 (50–62)	82 (66–102)
15	45		118 (92–158)
26	45		147 (127–171)

However, **26** showed only oral activity. Compounds **10–13**, **16b**, and **23** possessed modest activity, and compounds **4–6**, **18c**, **19–22**, and **24** were virtually inactive. Considering the time-course *data in Table II*, it is clear that several compounds show substantial activity, including some compounds not recognized above. On the basis of *oral dosing*, sulfamates **1–3**, **6**, **9**, **14**, **15**, **17b**, **25**, and **26** exhibit notable potency and duration of action (≥80% block at 200 mg/kg at >120 min). Of these compounds, **1**, **9**, and **25** exhibit high potency on ip administration. In the case of structure **1**, from an SAR point of view, activity is reduced slightly with monomethyl substitution on nitrogen and greatly with dimethyl substitution. The azidosulfate analogue of **1** (i.e., **6**) is moderately active, but phenyl sulfamate **7** is inactive. The carbamate analogue **5** also lacks anticonvulsant activity, which underscores the importance of the sulfamate group (also alcohol **4** is inactive). However, a comparison of **11** with its carbamate analogue contradicts this arrangement.[13] Removal of the acetonide units from **1**, as with methanolysis product **22** or hydrolysis products **20** and **21**,[14] resulted in loss of activity. The isomeric C-3 fructopyranose sulfamate **18c**, galactopyranose sulfamate **16b**, and the monocyclohexylidene analogue **19** showed relatively poor activity. The weak activity for **19** is particularly striking, as it is modified only slightly from **1** and assumes the same conformation that **1** does in solution (vide infra).

Because of the structural complexity of the sugar sulfamates, we sought to find anticonvulsant activity in simpler sulfamate derivatives. On the basis of our early SAR with some sugar derivatives, the SO_2NH_2 unit on a primary alcohol was retained, along with suitable lipophilicity. Monocycles **12** and **13** were found to possess modest activity, being around 4–5 times less potent than **1**. Benzo-fused derivatives **14** and **15** exhibited quite respectable anticonvulsant activity. Bicyclic sulfamate **24** and adamantane derivative **23** were hardly active. Diphenylethyl sulfamate, **26**, showed moderate oral activity, whereas monophenyl compound **25** showed reasonable activity by both routes of administration.

Glycidol derivatives **9–11** were particularly interesting as "half-structures" of prototype **1**. Sulfamate acetonide **9** showed significant activity even though it is very water soluble. The more lipophilic congeners **10** and **11** also were active, but less so than **9**.

The majority of compounds were examined over a 4-h time course, both po and ip, in the MES test. Data, reported as percent block of seizures, are collected in Table II. Compounds that showed significant oral activity at 100–200 mg/kg are **1–3**, **6**, **9**, **14**, **15**, **17b**, **23**, **25**, and **26**; and those that showed significant intraperitoneal activity at 50–100 mg/kg are **1**, **2**, **9**, **14**, **17b**, and **25**. Moderate activity was exhibited by **10**, **13** and **16b**, po, and by **3**, **13**, **15**, **16b**, and **23**, ip. Good duration of action on oral administration was demonstrated by **1–3**, **6**, **9**, **15**, **16b**, **17b**, **25**, and **26**; good duration ip was demonstrated by **1** and **9**.

Considering this limited data set, an unsubstituted sulfamate group and a certain type of lipophilic attachment are preferred for anticonvulsant activity.

Carbonic Anhydrase Inhibition. Since the sulfamate functionality appears to be important for anticonvulsant activity (cf. **1** and **5**), and since there are anticonvulsant sulfonamides, such as acetazolamide, which inhibit the enzyme carbonic anhydrase,[15] we tested **1** for its ability to inhibit carbonic anhydrase in mouse and human erythrocytes.[16] The K_i values for **1** were 2.0 μM in lysed mouse erythrocytes and ca. 200 μM in intact human erythrocytes. This is much weaker than the activity of acetazolamide, with a K_i value of 0.017 μM in lysed mouse erythrocytes. In lysed human erythrocytes, the K_i values for acetazolamide and **1** were 0.005 and 120 μM, respectively. Our results demonstrate that **1** is a relatively weak inhibitor of erythrocyte carbonic anhydrase.

In preliminary experiments, we evaluated six congeners of **1** for their inhibition of carbonic anhydrase. In lysed mouse erythrocytes, **9**, **14**, and **24** were moderately potent inhibitors (K_i values of 0.20, 0.16, and <0.5 μM, respectively), **16b** was weak (K_i = 7.3 μM), and **5** and **6** were inactive (0% inhibition at 83 and 2 μM, respectively). From these results, there appears to be a lack of correlation between inhibition of erythrocyte carbonic anhydrase and anticonvulsant activity.

Additional Testing of 1.[17a] Compound **1** was particularly interesting because of its potency and duration of activity. In mice, **1** was active beyond 8 h after dosing. Its ED_{50} values in mice at 2 h were 38 mg/kg (27.2–49.5) ip and 39 mg/kg (27.5–52.5) po. The ED_{50} value, po, in rats was 17.5 mg/kg (at 2 h) vs. 40 mg/kg for phenytoin and 18.5 mg/kg for acetazolamide. Oral activity of **1** at 4 h was essentially the same as that at 2 h (ED_{50} of 36 mg/kg in mice, 18 mg/kg in rats).

Consequently, we assessed the neurotoxicity of **1** in the rotoreel test.[17b] In mice, **1** had TD_{50} values (po in mice; TD_{50} = neurotoxic dose ED_{50}) of 1095 mg/kg at 4 h (approximate peak time for MES ED_{50}) and 407 mg/kg at 1 h (peak for TD_{50}) vs. 48.5 mg/kg at 2 h (peak for TD_{50}) for phenytoin. The LD_{50} (ip) for **1** was >1000 mg/kg (after 24 h). Compound **1** showed marginal activity at 100 mg/kg against PTZ-induced seizures, like phenytoin but unlike acetazolamide. It was also virtually inactive against seizures caused by bicuculline, picrotoxin, and strychnine, in analogy to phenytoin and carbamazepine. The loss of

(13) The carbamate analogue of **11**, dioxamate, is reported to have anticonvulsant properties: *Merck Index*, 10th ed.; 1983; p 440, No. 3303.

(14) The hydrolysis product of **1**, obtained by treating **1** with 90% aqueous trifluoroacetic acid at 25 °C, had lost both isopropylidene units. Characterization of the syrup was complicated by the presence of both furanoid and pyranoid structures, each a mixture of two diastereomers (^{13}C NMR).

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(16) The method used for determining carbonic anhydrase activity has been described previously: (a) Itada, N.; Forster, R. E., II *J. Biol. Chem.* **1977**, *252*, 3881. (b) Dodgson, S. J.; Forster, R. E., II; Storey, B. T.; Mela, L. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 5562. (c) Dodgson, S. J.; Forster, R. E., II; Storey, B. T. *J. Biol. Chem.* **1982**, *257*, 1705.

(17) (a) Information on the methods employed in this subsection is given in the Experimental Section. (b) Dunham, N. W.; Miya, T. S. *J. Am. Pharm. Assoc., Sci. Ed.* **1957**, *46*, 208.

Figure 1. Stereoview of the energy-minimized twist-boat structure for 1, showing the van der Waals dot surface.

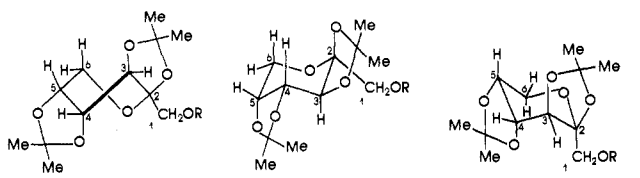
anticonvulsant activity in reserpinized mice suggests a similarity in mode of action between 1 and acetazolamide;[18] however, the mild decrease in anticonvulsant activity of 1 in tetrabenazine-treated mice is similar to observations with phenytoin, not to those with acetazolamide (which shows a total loss of activity).

We have evaluated 1 in a variety of CNS receptor assays. At a concentration of 1.0 μM, it slightly increased the binding of ^{3}H-WB-4101 to the α-1 adrenergic receptor in rat brain membrane preparations but had no effect on the affinity of tritiated norepinephrine. Compound 1 showed no effect on the binding of tritiated diazepam to the benzodiazepine receptor (neither inhibition nor enhancement), or on synaptosomal uptake of tritiated GABA or norepinephrine. It does not bind to GABA-A, muscarinic, or dopamine D_2 receptors.

Compound 1 was sent to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS, epilepsy branch) for independent assessment.[19] They found an ED_{50} in the MES test (ip in mice at 2 h) of 33 mg/kg for 1 vs. 9.5 mg/kg for phenytoin and a rotorod TD_{50} (ip in mice) of 401 mg/kg (at 30 min) for 1 vs. 65.5 mg/kg (at 2 h) for phenytoin. In oral testing in mice, the NINCDS obtained an ED_{50} (at 2 h) of 18.5 mg/kg for 1 vs. 9.0 mg/kg for phenytoin and a TD_{50} of 389 mg/kg (at 1 h) for 1 vs. 86.7 mg/kg (at 2 h) for phenytoin. The LD_{50} values (ip) for 1 and phenytoin were 1482 and 229 mg/kg, respectively. The ED_{50} for 1 in antagonism of pentylenetetrazole-induced seizures (sc in mice) was found to be >800 mg/kg (ip or po, at 2 h). In oral administration to rats, 1 showed greater potency than phenytoin in the MES test: 11.4 mg/kg (at 6 h) vs. 29.8 mg/kg (at 4 h).

Anticonvulsants Containing the SO_2N Unit. Substituted benzene and heterocyclic sulfonamides have been reported to display anticonvulsant properties.[20] Many of these agents are potent inhibitors of carbonic anhydrase, leading to the suggestion that this may be the source of their anticonvulsant characteristics.[15a,15c,20b,20e] There have also been a few reports of aliphatic sulfonamide derivatives with anticonvulsant activity.[21] One of these, zonisamide (27), has received considerable recent attention.[21a,22] This agent is only a weak inhibitor of carbonic anhydrase,[22a] in analogy with 1. As far as we are aware, this paper represents the first disclosure of sulfamate derivatives with anticonvulsant activity.

Conformational Properties of 1 and 20. Cyclic diacetals of pyranoses with a "cis–anti–cis" arrangement tend to adopt a twist-boat ($^6S_4$) conformation, viz., **28**.[23] ^{1}H NMR data for 4 and its 1-acetate indicated this conformation.[23b] We examined 1 in solution ($CDCl_3$) by ^{1}H NMR (360 MHz) and derived a complete set of spectral data by using 2-D COSY and ^{13}C–^{1}H heterocorrelation techniques.



28 **29** **30**

The critical parameters are the coupling constants for protons on the pyranose ring: J_{34} = 2.6 Hz, J_{45} = 7.9 Hz, J_{56} = 0.8 Hz, and $J_{56'}$ = 1.9 Hz. For chair conformation **29**, one would expect J_{34} to be a large coupling of ca. 10 Hz (anti coupling) and J_{45} to be a small coupling of 2–3 Hz (gauche coupling), which is not the case for 1. Alternative chair **30** would exhibit a large coupling for one of the J_{56} values and a small coupling for J_{45}. Neither situation is observed in the data for 1. A conformational averaging for 1 is probably excluded by the large J_{45} value (for a dihedral angle of ca. 0°) and the very small values for J_{56} and $J_{56'}$. Thus, 1 appears to assume a twist structure predominantly in $CDCl_3$ solution.

The twist form of 1 was energy-minimized with the SYBYL molecular modeling program (Tripos Associates, Inc., St. Louis, MO) to generate the structure displayed in Figure 1, accompanied by a van der Waals dot surface (see Experimental Section). A single-crystal X-ray analysis of

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(19) (a) We express our thanks to Dr. Harvey Kupferberg and Gill Gladding for supplying us with data on 1 and for permitting us to publish some of that data herein. (b) For a review of the NINCDS program, see: Kupferberg, H. J.; Swinyard, E. A.; Gladding, G. D. *Adv. Epileptol.* **1980** (pub. 1981), *12*, 13; *Chem. Abstr.* **1981**, *95*, 1969.

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1 shows a similar twist structure in the solid state.[24] It is apparent from this model (Figure 1) that the molecule is a combination of a large, globular hydrophobic region and a small hydrophilic SO_2NH_2 unit. We suggest that the nature and disposition of these two segments are important for the biological activity. Indeed, the anticonvulsant activity can be exquisitely sensitive to the shape of the lipophilic portion: cf. **1** vs. **19**, **1** vs. **16b**, and **1** vs. **24**.

We also analyzed the 360-MHz ^1H NMR spectrum of monoacetonide **20**. The ring coupling constants indicated that **20** largely adopts a chair conformation of the type in **30** (J_{34} = 3.3 Hz, J_{45} = 3.3 Hz, J_{56e} = 5.2 Hz, J_{56a} = 9.3 Hz, and J_{46e} = 0.7 Hz). This result is consistent with information already in the literature.[23] In this context, it is interesting to note the vast difference between $[\alpha]_D$ values for **1** and **20**, which may be associated with the conformational distinction.

Conclusion

We have found *O*-alkyl sulfamates with anticonvulsant properties analogous to those of phenytoin. Especially notable compounds with regard to potency and duration of action are **1** (McN-4853), **9** (McN-5762), **14** (McN-5456), **17b** (McN-6623), and **25** (McN-6044). On the basis of its overall profile of activity and its minimal neurotoxicity, **1** (topiramate) was selected for clinical development as an anticonvulsant drug.

Experimental Section

General Methods and Materials. IR spectra (Perkin-Elmer 521 spectrophotometer) and ^1H NMR spectra (Perkin-Elmer R-32 or Varian EM-390 (90 MHz) spectrometer) were recorded on all target compounds (Table I) and were consistent with the assigned structures. ^1H NMR spectra had Me_4Si as an internal reference (abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, br = broadened). High-field ^1H NMR spectra were obtained in certain instances at 360 MHz on a Bruker AM-360WB spectrometer. ^{13}C NMR spectra were recorded on a JEOL FX60Q spectrometer at 15.1 MHz. ^{13}C NMR integrations were performed under pulsing conditions suitable for that purpose. GLC analysis was conducted on a Perkin-Elmer 3920B instrument with a flame-ionization detector, equipped with a Hewlett-Packard 3352B data system and 18652 A/D converter, with a 3% SE-30 on Chromosorb Q (100/120 mesh) column (6 ft × $^1/_8$ in.). TLC analysis was performed on Whatman MK1F silica gel (80 Å) plates (1 × 3 in.), which were generally visualized by sulfuric acid charring, and by UV when applicable. Melting points are corrected. Mass spectra (electron impact) were determined on a Hitachi Perkin-Elmer RMU-6E instrument at 70 eV. Preparative HPLC separations were performed with a Waters Prep 500 instrument, on silica gel columns.

Sulfamoyl chloride was prepared from chlorosulfonyl isocyanate (Aldrich Chemical Co.) and formic acid.[25] Phenylsulfamoyl chloride was obtained by reacting sodium *N*-phenylsulfamate with PCl_5 in refluxing benzene for 21 h; *N*-methylsulfamoyl chloride was prepared from *N*-methylsulfamic acid and PCl_5.[26] L-Sorbofuranose diacetonide **17a** was a gift from Hoffmann-La Roche (see Acknowledgment).

2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose Sulfamate (1), from 4 and Sulfamoyl Chloride. To a cold solution (−4 °C) of diisopropylidenefructopyranose **4**[27] (75 g, 0.29 mol) in dry DMF (725 mL) was added 50% oily sodium hydride (16.34 g, 0.34 mol as NaH). After the mixture was stirred for 90 min, sulfamoyl chloride (54.9 g, 0.48 mol) was added and the stirring was continued for an additional 3.5 h at 0 °C. The reaction mixture was poured into cold water and extracted with toluene. The organic solution was dried (Na_2SO_4), and the solvent was removed under vacuum to give a syrup, which crystallized immediately. Recrystallization from ethyl acetate/hexane yielded pure **1**, 45.1 g (46%): mp 125–126 °C; IR (KBr) ν_{max} 3389 (NH_2), 1381, 1186 (SO_2) cm^{-1}; 90-MHz ^1H NMR ($CDCl_3$) δ 1.35, 1.40, 1.45, 1.55 (4 s, 12, CH_3), 3.8 (m, 2, H_6), 4.1–4.4 (m, 4), 4.5–4.7 (dd, 1, H_4), 5.2 (br s, 2, NH_2); 360-MHz ^1H NMR ($CDCl_3$) δ 1.32, 1.47 (2 s, 6, 4,5-CH_3), 1.40, 1.54 (2 s, 6, 2,3-CH_3), 3.80 (dd, 1, J = 0.8, 13.0 Hz, H_6), 3.90 (dd, 1, J = 1.9, 13.0 Hz, H_6), 4.20 (d, 1, J = 11.0 Hz, H_1), 4.24 (ddd, 1, J = 7.9, 0.7, 1.9 Hz, H_5), 4.28 (d, 1, J = 2.4 Hz, H_3), 4.30 (d, 1, J = 11.0 Hz, H_1), 4.60 (dd, 1, J = 7.9, 2.6 Hz, H_4), 5.00 (br s, 2, NH_2).

2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose Methylsulfamate (2). A. From 4 and Sulfuryl Chloride. A solution of sulfuryl chloride (93 mL, 1.15 mol) in methylene chloride (100 mL) was added dropwise to a cold solution (−35 °C) of **4** (150 g, 0.58 mol) in methylene chloride (400 mL) and pyridine (150 mL). The reaction mixture was stirred and allowed to warm to room temperature; it was stirred for an additional 2 h. Solvents were removed under vacuum. Part of the resulting semisolid (35 g, 0.10 mol) was dissolved in anhydrous acetonitrile (150 mL), and methylamine was introduced. The reaction mixture was tightly stoppered for 3 days, and then the solvent was removed under vacuum. The resulting syrup was subjected to liquid chromatography (dry column of silica gel, ethyl acetate/hexane, 4:1) to yield a light yellow syrup, **2** (4.1 g, 12%), which was homogeneous by TLC and ^1H NMR: IR ($CHCl_3$) ν_{max} 3320 (NH_2), 1360, 1190 (OSO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4–1.6 (4 s, 12, CH_3), 2.8 (d, 3, NMe), 4.8 (m, 1, NH).

B. From 4 and *N*-Methylsulfamoyl Chloride. A solution of diisopropylidenefructopyranose **4** (15 g, 0.06 mol) in DMF (120 mL) at 0 °C was treated with sodium hydride (3.49 g, 0.09 mol as NaH, 60% oil dispersion). After the mixture was stirred for 30 min, *N*-methylsulfamoyl chloride (8.8 g, 0.07 mol) was added and stirring was continued for 60 min. The reaction mixture was poured into cold water and extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The pale yellow syrup was chromatographed (prep HPLC, hexane/ethyl acetate, 2:1) to afford **2** (14.77 g, 73%) as a colorless syrup: ^1H NMR ($CDCl_3$) δ 4.8 (m, 2, NH included), 4.4 (m, 2), 4.2 (m, 2), 3.9 (m, 2), 2.8 (d, 3, CH_3), 1.4 (m, 12); CI-MS (CH_4), m/e 354 (M + H).

2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose Dimethylsulfamate (3). By the method described for the preparation of **1**, 20 g (0.08 mol) of **4**, 6.1 g (0.13 mol) of sodium hydride, and 17.6 (0.12 mol) of dimethylsulfamoyl chloride in 200 mL of dimethylformamide gave 25.6 g (85%) of **3**. Two recrystallizations from ethanol/water furnished pure **3** (25.1 g, 83%): mp 57–58 °C; IR (KBr) ν_{max} 1375, 1130 (OSO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40, 1.45, 1.50, 1.60 (4 s, 12, methyls), 2.9 (s, 3, *N*-methyl), 3.9 (m, 2, H_6), 4.2 (s, 2, CH_2OSO_2), 4.4 (m, 2, H_3 and H_5), 4.7 (dd, 1, H_4).

2,3:4,5-Bis-*O*-(methylethylidene)-β-D-fructopyranose Carbamate (5). Attempted preparation of **5** from **4** and HNCO, according to a published procedure,[28] resulted in decomposition, presumably because of ketal hydrolysis. A procedure employing chlorosulfonyl isocyanate (CSI)[7] was successful, as was one employing a phosgene equivalent.[8]

A solution of **4** (10.4 g, 0.04 mol) in 25 mL of dry methylene chloride was added slowly to a stirred solution of 5.7 g (0.04 mol) of CSI in 25 mL of methylene chloride with ice-bath cooling. After the reaction mixture was allowed to stand overnight, it was diluted with methylene chloride to a volume of 75 mL. One-half of this solution (20 mmol) was combined with 25 mL of water with rapid stirring. The reaction mixture was heated at 35 °C for 1 h. The organic solution was separated, rinsed with water, dried (Na_2SO_4), and evaporated to provide 1.5 g of brown resin, which was mainly

(24) We thank Prof. Penelope Codding for performing the X-ray analysis of **1**. In the solid-state structure, the torsional angles of the 1,3-dioxolane rings differ from those of the structure in Figure 1; the shape of the tetrahydropyran ring is virtually the same. Details of the X-ray work will be published separately. (The interested reader may obtain further information by contacting Prof. Codding, The Univeristy of Calgary, 2500 University Drive, N.W., Calgary, Alberta, Canada T2N 1N4.)

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one substance by TLC. Recrystallization from ethyl acetate/hexane (1:2) to −20 °C deposited 0.77 g (13%) of light tan solid. Repetition of this reaction at room temperature for 2 h, on twice the scale, gave 3.7 g of crude product. Recrystallization afforded two crops of 1.85 and 0.60 g. The three batches were combined and recrystallized from ether/petroleum ether (3:1) to obtain 1.80 g (10%) of **5** as off-white crystals: mp 118–122 °C; IR (KBr) ν_{max} 3485 and 3370/3340 (NH), 1752 (CO), 1071 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34, 1.39, 1.49, 1.54 (4 s, 12, 4 methyls), 3.4–5.0 (m, 9, br s for NH at δ 4.82).

2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose Azidosulfate (6). A solution of sulfuryl chloride (5.13 g, 0.038 mol) in methylene chloride (10 mL) was added dropwise to a cold solution (−15 °C) of **4** (5 g, 0.02 mol) in a mixture of pyridine (10 mL) and methylene chloride (10 mL). The reaction mixture was stirred for 8 h and let warm to 23 °C under nitrogen. After 2 h, the solvent was removed under vacuum. The resulting semisolid was dissolved in dry acetonitrile (50 mL), and sodium azide (2.47 g, 0.04 mol) was added. After 18 h at 23 °C, the mixture was filtered and the solvent was removed under vacuum to give a solid (6.24 g, 90%). Recrystallization from 2-propanol afforded white crystalline **6** (4.0 g, 58%): mp 105–107 °C; IR (KBr) ν_{max} 2150 (N_3), 1408, 1255 (OSO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40, 1.45, 1.50, 1.60 (4 s, 12, methyls), 3.8 (m, 2 H_6), 4.4 (m, 4, including CH_2OSO_2), 4.65 (dd, 1, H_4).

2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose Phenylsulfamate (7). By the method described for the preparation of **1**, 25 g (0.10 mol) of **4**, 9.01 g (0.19 mol) of sodium hydride, and 23.42 g (0.12 mol) of phenylsulfamoyl) chloride in 225 mL of DMF produced 9.0 g (23%) of **7**. Two recrystallizations from chloroform/hexane furnished pure **7** (8.0 g, 20%): mp 115–116 °C; IR (KBr) ν_{max} 3230 (NH), 1348, 1170 (OSO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (3 s, 12, 4 CH_3), 3.8 (m, 2, H_6), 4.2 (m, 4, includes CH_2OSO_2), 4.6 (dd, 1, H_4), 5.9 (br s, 1, NH), 7.2 (m, 5, arom).

2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose Phenylcarbamate (8).[29] Alcohol **4** (5.2 g, 20 mmol) in 15 mL of dry methylene chloride and 1 mL of pyridine was treated with 2.4 g of phenyl isocyanate (20 mmol) in 5 mL of methylene chloride. After 5 h, the reaction was complete by TLC. The reaction mixture was filtered, diluted with 20 mL of hexane, and concentrated to half-volume. After cooling to 23 °C, the white solid was collected, giving 5.95 g (78%) of **8**. Recrystallization from 75 mL of ethyl acetate/hexane (1:1) afforded 4.15 g (55%) of colorless prismatic needles: mp 165.5–167.5 °C; UV (MeOH) λ_{max} (ϵ) 280 (470), 272 (810), 262 (1300), 256 (1505), 234 (17 070) nm; IR (KBr) ν_{max} 3356 (NH), 1747 (C=O), 1222, 1072 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33, 1.38, 1.49, 1.54 (4 s of equal height, 12, 4 methyls), 3.6–4.7 (m, 7), 6.69 (br s, 1, NH), 6.9–7.6 (m, 5).

(1,4-Dioxaspiro[4.5]dec-2-yl)methyl Sulfamate (10). A mixture of glycerol (50 g, 0.54 mol), *p*-toluenesulfonic acid (1.5 g), and cyclohexanone (52.92 g, 0.54 mol) in toluene (150 mL) was refluxed with removal of water by a Dean–Stark trap. After 2 h, the reaction mixture was cooled, washed with water, then saturated brine, dried (K_2CO_3), and filtered. After filtration, the solution was concentrated to yield 64.6 g (69%) of a light yellow syrup. A portion (20 g, 0.12 mol) of this syrup was added dropwise to a suspension of sodium hydride (7.24 g, 0.15 mol) in 150 mL of DMF at 0–5 °C. The reaction mixture was stirred for an additional 30 min under argon, after which sulfamoyl chloride (23 g, 0.2 mol) was added portionwise at 0–5 °C. The solution was stirred for 15 min, poured onto ice, and extracted with ethyl ether. The ether solution was washed with water, washed with saturated brine, dried ($MgSO_4$), and concentrated to a syrup. This material was purified by preparative HPLC, with hexane/ethyl acetate (4:1) as the eluent, to yield 11.5 g (38%) of pure **10**: IR ($CHCl_3$) ν_{max} 3356 (NH_2), 1370, 1186 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–1.6 (m, 10), 3.8–4.4 (m, 5), 5.2–5.3 (br s, 2, NH_2).

(2-Methyl-2-nonyl-1,3-dioxolan-4-yl)methyl Sulfamate (11). A solution of 2-methyl-2-nonyl-1,3-dioxolane-4-methanol[30] (25 g, 0.102 mol) in 50 mL of toluene was added dropwise to a suspension of sodium hydride (6.38 g, 50% in oil, 0.133 mol) in 150 mL of DMF at 0–5 °C. The suspension was stirred under argon for 30 min. Sulfamoyl chloride (15.3 g, 0.132 mol) was added portionwise at 0–5 °C, and the resultant solution was stirred for an additional 15 min, poured onto ice, and extracted with ethyl ether. The ether extract was washed once with water, washed with saturated brine, dried ($MgSO_4$), and concentrated to a thin syrup. This material was purified by preparative HPLC with hexane/ethyl (4:1) as the eluent, to give 12.48 g (39%) of **11**, a waxy solid: mp 49–51 °C; IR (KBr) ν_{max} 3391 (NH_2), 1381, 1187 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8 (distorted t, 3), 1.2–1.3 (m, 17), 1.5–1.6 (m, 2), 3.75 (m, 1), 4.1–4.3 (m, 3), 4.3–4.4 (m, 1), 5.0 (d, 2, NH_2).

(Tetrahydro-2*H*-pyran-2-yl)methyl Sulfamate (12). To a cold solution (−5 °C) of tetrahydropyran-2-methanol (2.33 g, 0.02 mol) in DMF (40 mL) was added 50% oily sodium hydride (1.17 g, 0.024 mol as NaH). After the mixture was stirred for 45 min, sulfamoyl chloride (3.42 g, 0.03 mol) was added and the stirring was continued for 45 min at −5 °C. The reaction mixture was poured into cold water and extracted with chloroform. The organic extract was dried (Na_2SO_4) and concentrated to a syrup, which was chromatographed on a dry column of silica gel (ethyl acetate/hexane, 4:1) to afford pure **12** (1.96 g, 50%) as a pale yellow syrup: IR ($CHCl_3$) ν_{max} 3350 and 3440 (NH_2), 1370, 1180 (OSO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6 (m, 6), 3.7 (m, 3), 4.2 (d, 2, CH_2OSO_2), 5.3 (br s, 2, NH_2).

1,2:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose Azidosulfate (18b). A solution of sulfuryl chloride (15.6 g, 0.116 mol) in methylene chloride (120 mL) was added dropwise to a cold solution (−35 °C) of **18a**[27] (15 g, 0.058 mol) in pyridine (40 mL). The reaction mixture was allowed to warm to 23 °C under nitrogen and then was stirred for 2 h. The reaction mixture was concentrated under vacuum, and the semisolid residue was dissolved in dry acetonitrile (140 mL). Sodium azide (10.45 g, 0.16 mol) was added, and the mixture was stirred at 0 °C for 18 h. The solution was concentrated to a syrup, which was redissolved in methylene chloride (100 mL). The solution was washed with water, 2% H_2SO_4, and brine, dried (Na_2SO_4), and evaporated to a syrup (19.50 g, 92%), which crystallized. Recrystallization from ethanol/water furnished **18b** as a white solid (3.3 g, 63%): mp 68–69 °C; IR (KBr) ν_{max} 2160 (N_3), 1390, 1180 (OSO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4, 1.45, 1.5, 1.6 (4 s, 12, methyls), 3.9–4.8 (m, 7).

1,2:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose Sulfamate (18c). A mixture of azidosulfate **18b** (4.94 g, 0.014 mol) in dry methanol (100 mL) was treated with copper powder (2.23 g) and refluxed for 5 h. The reaction mixture was filtered, and the filtrate was concentrated to a syrup, which was purified on a dry column of silica gel with toluene/ethyl acetate (4:1) to give a white foam, **18c** (1.22 g, 27%): IR (KBr) ν_{max} 3320 (NH_2), 1360, 1180 (OSO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3–1.7 (3 s, 12, methyls), 3.9–4.6 (m, 9, including NH_2).

4,5-*O*-Cyclohexylidene-2,3-*O*-(1-methylethylidene)-β-D-fructopyranose Sulfamate (19). Hydrochloric acid (concentrated, 25 mL) was added portionwise during 30 min to a solution of **1** (12.0 g, 0.03 mol) and 1-(trimethylsiloxy)cyclohexene (5.3 g, 0.03 mol) in anhydrous THF (40 mL).[6] After the mixture was stirred for 5 min, it was poured into ice–water and extracted into methylene chloride (2 × 50 mL). The combined organic extracts were washed with water, 5% sodium bicarbonate, and brine, dried, and concentrated to give a solid (7.3 g, 58%). Recrystallization twice from ethyl acetate/hexane yielded **19** as a white solid (5.4 g, 43%): mp 178–179 °C; IR (KBr) ν_{max} 3374 (NH_2), 1366, 1204 (OSO_2) cm^{-1}; 90-MHz ^1H NMR ($CDCl_3$) δ 1.3–1.8 (m, 16), 3.8 (m, 2, H_6), 4.3 (m, 4), 4.5 (dd, 1, H_4), 5.4 (br s, 2, NH_2); 360-MHz ^1H NMR ($CDCl_3$) δ 3.78 (dd, H_6, J = 12.8, 0.7 Hz), 3.88 (dd, H_6', J = 12.9, 1.8 Hz), 4.22 (d, H_1, J = 11.0 Hz), 4.23 (ddd, H_5, J = 0.7, 1.8, 7.9 Hz), 4.30 (d, H_3, J = 2.6 Hz), 4.30 (d, H_1', J = 11.0 Hz), 4.59 (dd, H_4, J = 7.9, 2.6 Hz). These data show that **19** adopts the same conformation that **1** adopts. Also, the two methyl singlets resonated at δ 1.40 and 1.53, indicating a 4,5-cyclohexylidene substitution.

2,3-*O*-(1-Methylethylidene)-β-D-fructopyranose Sulfamate (20). A solution of **4** (20.0 g, 58.9 mmol) in THF (200 mL) and 3 N HCl (200 mL) was stirred at 45 °C for 3.5 h. After cooling to ambient temperature, the reaction mixture was neutralized with anhydrous Na_2CO_3 and saturated with NaCl. The resulting

(29) For the preparation of related compounds, see: Zinner, H.; Lauger, T. *J. Prakt. Chem.* **1978**, *320*, 789.
(30) Avakian, S.; Martin, G. J. U.S. Patent 3 058 981, 1962.

aqueous phase was extracted three times with THF, and the combined organic phases were dried ($MgSO_4$) and evaporated to give 17 g of a pale yellow oil. Column chromatography (flash, silica gel, EtOAc/hexane, 2:1, followed by CH_3CN/CH_2Cl_2, 4:1) gave 7.2 g of colorless oil (41% yield). Crystallization of this oil from EtOAc/hexane gave 5.4 g of **20** (31%) as a white crystalline solid: mp 130–132 °C; IR (KBr) ν_{max} 3482 (OH), 3386 (NH), 1383, 1189 (SO_2) cm^{-1}; 360-MHz ^1H NMR (CD_3OD) δ 1.36 (s, 3), 1.48 (s, 3), 3.65 (dd, 1, J = 11.8, 5.1 Hz), 3.73 (dd, 1, J = 11.5, 9.1 Hz), 3.96 (ddd, 1, J = 8.9, 5.2, 3.4 Hz), 4.13 (dd, 1, J = 3.4, 3.4 Hz), 4.17 (d, 1, J = 3.4 Hz), 4.24 (s, 2); ($CDCl_3$) δ 3.73 (ddd, 1, J = 11.3, 5.2, 0.7 Hz, H_{6a}), 3.82 (dd, 1, J = 11.3, 9.3 Hz, H_{6e}), 4.04 (ddd, 1, J = 3.3, 5.2, 9.3 Hz, H_5), 4.22 (ddd, 1, J = 3.3, 3.3, 0.7 Hz, H_4), 4.26 (d, 1, J = 3.3 Hz, H_3), 4.32 (s, 2).

3,6-Dioxa-2-thia-1-azaspiro[4.5]decane-8α,9α,10β-triol 2,2-Dioxide Hydrate and Isomers (21). A mixture of 1 (10 g, 0.029 mol) in trifluoroacetic acid (100 mL, 90%) was stirred for 18 h at room temperature and then concentrated under vacuum to a syrup, which was redissolved in water (200 mL) and treated with Amberlite IR-45 (54 g, anion-exchange resin, hydroxide form). The mixture was filtered, concentrated, and dried under vacuum for 24 h to give **21** (3.0 g, 43%): IR (neat) ν_{max} 3350 (NH), 1360, 1180 (OSO_2) cm^{-1}; ^{13}C NMR (D_2O) δ 59.6, 59.9, 60.5, 60.9, 61.2, 61.6, 65.2, 66.5, 66.7, 66.9, 67.2, 69.1, 71.5, 71.8, 72.5, 73.3, 73.8, 78.4, 79.0, 79.4, 94.1 (2β-pyranose, ca. 45%), 95.5 (2α-pyranose, ca. 25%), 96.9 (2β-furanose, ca. 15%), 98.9 (2α-furanose, ca. 15%);[31] CI-MS (CH_4), m/e 242 (M + 1), 224 (M − OH). To confirm the spirocyclic structure, **21** was silylated with an excess of a mixture of hexamethyldisilazane and chlorotrimethylsilane in pyridine to give a tetrasilylated adduct. This was indicated by a CI-MS (CH_4) spectrum, which had a parent ion at m/e 530 (M + 1), corresponding to silylation of three hydroxyls and the NH group. No molecular ions were present at m/e 547 (i.e., for noncyclized adduct).

Methyl D-Fructofuranoside Sulfamate Hemihydrate (22). Compound 1 (20 g, 0.059 mol) was treated with 6.3% methanolic hydrogen chloride (900 mL) at 23 °C. After 24 h, the reaction mixture was cooled to 0 °C and treated with lead carbonate until it was basic. The mixture was filtered with the aid of Dicalite and concentrated under vacuum to yield **22** as a syrup (15.7 g, 94%): IR (neat) ν_{max} 3350 (NH_2), 1370, 1180 (OSO_2) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.3–3.4 (m, 3, OCH_3), 3.5–4.3 (m, 10), 7.4 (m, 2, NH_2); ^{13}C NMR (D_2O) δ 49.4 (2 C), 49.7, 49.9, 62.3, 63.1, 63.8, 64.5, 65.0, 67.8, 68.5, 68.9, 69.7, 70.1, 71.1, 75.3, 75.6, 77.9, 78.4, 80.8, 81.6, 82.2, 84.6, 97.5 (H_2 in β-pyranose), 99.9 (H_2 in α-pyranose), 102.1 (H_2 in β-furanose), 107.2 (H_2 in α-furanose).[31] On the basis of ^{13}C NMR integration, the mixture comprised α- and β-furanosides and α- and β-pyranosides in the ratio 49:32:11:8, respectively.

Other Derivatives. Sulfamates **9**, **13–15**, **16b**, **17b**, and **23–26** were prepared by reacting the requisite alcohol with NaH and addition of NH_2SO_2Cl. Purified yields were as follows: **9**, 26%; **13**, 56%; **14**, 64%; **15**, 67%; **16b**, 52%; **17b**, 52%; **23**, 56%; **24**, 44%; **25**, 41%; **26**, 70%.

Maximal Electroshock Seizure (MES) Test.[9] Male albino mice of the Swiss Webster strain (Royalhart Laboratories, New Hampton, NY) weighing 18–24 g were used. Animals had free access to food and water except during the actual test. Where applicable, doses are expressed in terms of the anhydrous, unsolvated compound. Compounds were administered in aqueous solution or in suspension, ca. 0.1% Tween 80 and distilled water.

The effects of the test compounds on electrically induced seizures in mice were determined in the maximal electroshock seizure threshold (MEST) test and in the maximal electroshock seizure (MES) test. Maximal electroshock threshold seizures were induced by the delivery of an 8-mA current (60 Hz, 0.25-s duration) through ear-clip electrodes. This current strength was found to be the CS_{97} in the mice used. Supramaximal electroshock seizures were induced by the delivery of a 50-mA current (60 Hz, 0.20-s duration) through corneal electrodes. In both procedures, the electrical stimulus induced tonic extension of the hind limbs. An inhibition of this component of the maximal and supramaximal seizures is taken as an indication of activity. In the MEST test, mice were tested at 30 min and in some cases at 240 min following intraperitoneal injection; in the MES test, mice were tested at 30, 60, 120, and 240 min (sometimes 45 min) following intraperitoneal and oral administration. Ten mice were used for each time point. ED_{50} values are for time points in the range of 30–60 min.

Determination of Carbonic Anhydrase Activity. Carbonic anhydrase activity was assayed by the ^{18}O-exchange technique of Mills and Urey, as modified and described previously.[16] In all cases, the carbonic anhydrase activity was calculated from the rate of disappearance of $C^{16}O^{18}O$ (mass 46) from the reaction mixture, which contained 25 mM ^{18}O-labeled $NaHCO_3$ at 25 °C, at either pH 7.2 (for lysed erythrocytes) or pH 7.4 (for intact erythrocytes). The mass spectrometer was set to record the mass-46 peak and the mass-44 peak alternately every 15 s. The continuous readout of the mass-44 peak gives a continuous record of the constancy of the pH of the reaction medium since the height of the mass-44 peak is very sensitive to pH. The pH of the medium was read from the pH meter and used to calibrate the mass-44 peak at regular intervals. Data for **5**, **6**, **9**, **14**, **16b**, and **24** derive from single experiments, while data for 1 are from two experiments. The K_I values were calculatd from linear regression analysis of Dixon plots, obtained by using four to eight concentrations for test compounds. The value reported for 1 is an average of the two K_I values, 1.1 and 2.9 μM.

Modeling of 1. The stereoview of 1 (Figure 1) was generated by using the SYBYL molecular modeling program (Tripos Associates, Inc., St. Louis, MO, Version 3.3). The structure was entered by starting with the tetrahydropyran fragment. After the ring was altered into a twist conformation, the appropriate substituents were appended with the "sketch" command. The structure was then minimized with the "maximin" command (energy = 27.0 kcal). The two distinct chair conformations were explored similarly (energy = 27.8 and 22.4 kcal). We did not exhaustively search the total conformational space to ensure global minima. Thus, these energy values and the associated geometries must be considered unoptimized. (Our goal was a reasonable geometry for the twist conformer of 1.) The van der Waals surface was calculated and displayed with the "dots" command.

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(31) For background on ^{13}C NMR assignments involving the chemical shift of the anomeric carbons, see: Que, L., Jr.; Gray, G. R. *Biochemistry* **1974**, *13*, 146. Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27. Gray, G. R. *Acc. Chem. Res.* **1976**, *9*, 418. Funcke, W.; von Sonntag, C.; Triantaphylides, C. *Carbohydr. Res.* **1979**, *75*, 305. Crawford, T. C.; Andrews, G. C.; Faubl, H.; Chmurny, G. N. *J. Am. Chem. Soc.* **1980**, *102*, 2220. Pfeffer, P. E.; Valentine, K. M.; Parrish, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 1265.