Bioorganic & Medicinal Chemistry Letters, Vol.3, No.12, pp. 2653-2656, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

ANTICONVULSANT SUGAR SULFAMATES. POTENT CYCLIC SULFATE AND CYCLIC SULFITE ANALOGUES OF TOPIRAMATE

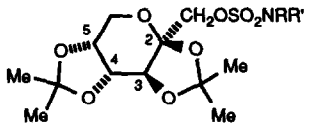
Bruce E. Maryanoff,*,† Michael J. Costanzo,† Richard P. Shank,§
James J. Schupsky,§ Marta E. Ortegon,§ and Jeffry L. Vaught§
Departments of Medicinal Chemistry† and CNS Research,§
The R. W. Johnson Pharmaceutical Research Institute
Spring House, Pennsylvania 19477 USA

(*Received in USA* 5 *August* 1993; *accepted* 7 *September* 1993)

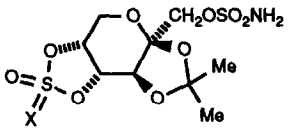
Summary: Exploration of structure-activity relationships surrounding the clinically effective antiepileptic drug topiramate (**1**) led to a series of potent anticonvulsants with a 4,5-cyclic sulfate or 4,5-cyclic sulfite functionality. Key derivative **2** (RWJ-37947) is ca. 8 times more potent than topiramate in mice; it also features a long duration of action and a very favorable neurotoxicity index.

Epilepsy is a chronic neurological disorder characterized by seizures that result from the sudden, disorderly depolarization of neurons in the brain.[1] Anticonvulsant drugs, which function by inhibiting initiation and/or propagation of the causative neuronal discharges, are employed to control epileptic symptoms. However, the available drugs are limited in number, in kind, by various side-effects, and by ineffectiveness in selected patient populations. This has inspired a search for new, more effective, less toxic anticonvulsants.

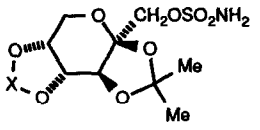
Because of the multiple etiologies of epilepsy, and our lack of understanding about the responsible mechanisms, the discovery of novel antiepileptic drugs often involves empiricism. Indeed, we discovered topiramate (**1**) by using the standard maximal electroshock seizure (MES) test as a screening protocol.[2] Since the antiepileptic efficacy of topiramate has been confirmed through clinical trials in patients refractory to generally prescribed drugs,[3] we have continued to pursue this novel "sugar sulfamate" structural class. In this communication, we report on a series of 4,5-cyclic sulfate and 4,5-cyclic sulfite analogues of topiramate, such as **2** and **3**, which exhibit potent anticonvulsant activity.



1 R = R' = H (topiramate)
30 R = H, R' = Me
31 R = R' = Me



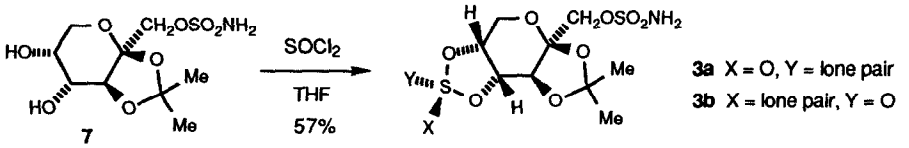
2 X = O
3 X = lone pair



4 X = CRR'
5 X = C(O)
6 X = B-Me

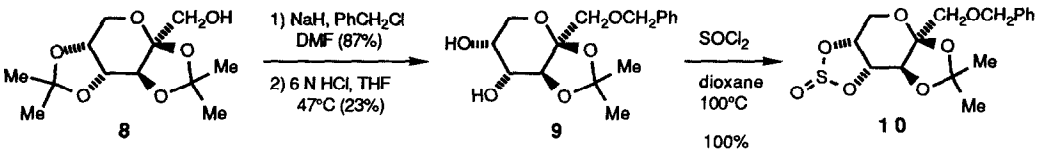
Our early work involved the investigation of various O-alkyl sulfamates as potential anticonvulsants, and was diverse from a structural standpoint.[2] Subsequently, we have conducted structure-activity studies with topiramate that entail more modest, systematic structural changes.[4] We found that a high level of anticonvulsant activity requires the substituents on the 4,5-ring in **4** to be alkyl groups of optimal size in a narrow range (H <

R, R' < Et); furthermore, we found that a planar sp^2 atom in the 4,5-ring (as in **5** and **6**) and a 6-membered 4,5-ring (not shown) are undesirable.[4] These structural requirements seriously constrained our search for topiramate analogues with improved biological properties. Fortunately, our investigation of 1,3,2-dioxasulfolane derivatives (viz. **2** and **3**), commonly referred to as cyclic sulfates and cyclic sulfites, proved rewarding.

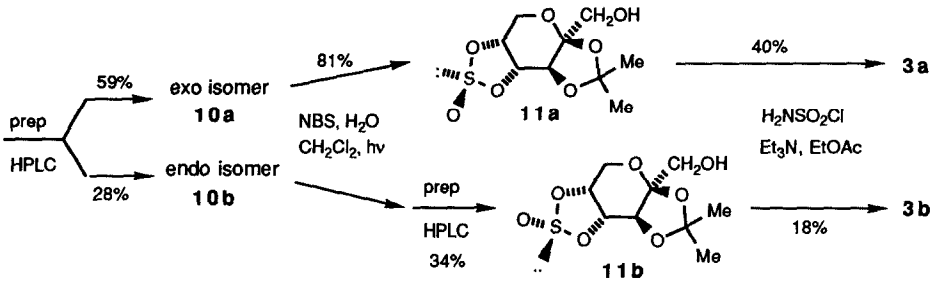


7

At the outset, cyclic sulfite **3** was prepared from diol **7**[2] and thionyl chloride, as a 5.3:1 mixture of "exo" and "endo" diastereomers, **3a** and **3b** (from EtOH, mp 148-151°C; $[\alpha]^{25}_D$ -19.8°, c 0.883, MeOH).[5] The potency of the **3a**:**3b** mixture in the MES test was about eight times that of topiramate (Table). Since separation of the diastereomers was problematic, we used an alternative synthesis to obtain isomerically enriched samples.

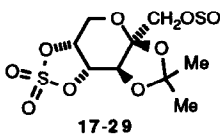


8 **9** **10**

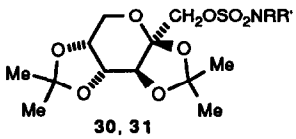


Diacetone fructose **8** was converted to diol **9**,[6] which was condensed with thionyl chloride to give **10**. Reaction in THF at 5°C afforded a 12:1 mixture of **10a**:**10b**, whereas reaction in dioxane at 100°C afforded a 1.6:1 mixture. Equilibration is precluded since **10a** and **10b** did not interconvert under the reaction conditions. The isomers from the dioxane reaction were separated by preparative HPLC (silica gel; EtOAc-hexane, 1:9) and each was debenzylated by free-radical bromination and solvolysis.[7] The exo isomer **11a**, obtained with 17:1 enrichment, was converted to target **3a**, which was diastereomerically pure following recrystallization (from EtOH, mp 151-153°C; $[\alpha]^{25}_D$ -14.9°, c 1.00, MeOH). For the endo case, debenzylation unfortunately resulted in epimerization, such that a 2.4:1 mixture of **11b**:**11a** was obtained. This was subjected to preparative HPLC (silica gel; Et_2O-hexane, 2:3), and pure **11b** was converted to target **3b** (from EtOH, mp 197-199°C, dec; $[\alpha]^{25}_D$ -43.5°, c 1.00, MeOH). Examination of **3a** and **3b** in the MES test revealed no difference in anticonvulsant potency relative to stereochemistry; the isomers were eight times more potent than topiramate (Table).

Table. Compounds and Their Anticonvulsant Activity



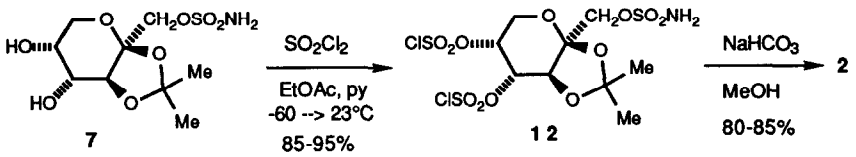
17-29



30, 31

compd[8]	R	R'	mp, °C	dosage mg/kg, p.o.	MES test (mice, 4 h) % block (ED_{50})
2	H	H	139-141	10	80% (ED_{50} = 6.3 mg/kg)
3a/3b	H	H	148-151	10	70% (ED_{50} = 5.7 mg/kg)
3a	H	H	151-153	10	70% (ED_{50} = 6.3 mg/kg)
3b	H	H	197-199	10	70% (ED_{50} = 6.5 mg/kg)
17	H	Me	151-153	10	100% (ED_{50} = 7.4 mg/kg)
18	H	Et	glass	3; 35	0%; 100% (ED_{50} = 14.4 mg/kg)
19	H	Bu	111-113	10; 35	30%; 100%
20	H	allyl	75-77	1; 10	0%; 70%
21	H	octyl	syrup	10; 75	0%; 100%
22	H	Ph	foam	75; 300	0%; 0%
23	H	benzyl	foam	10; 75	0%; 100%
24	H	*c*-C_3H_5	foam	1; 10	0%; 90% (ED_{50} = 7.3 mg/kg)
25	H	*c*-C_4H_7	foam	1; 10	0%; 90%
26	H	cyclooctyl	foam	10; 75	0%; 30%
27	H	CH_2CF_3	125-127	10; 75	40%; 90%
28	Me	Me	109-111	10; 35	70%; 100% (ED_{50} = 6.9 mg/kg)
29	Et	Et	foam	10; 75	10%; 100%
30[2]	H	Me		75; 200[2]	60%; 100%
31[2]	Me	Me		75; 200[2]	0%; 80%
topiramate (**1**)[2]	H	H		60	60% (ED_{50} = 53.5 mg/kg)
phenytoin					ED_{50} = 6.4 mg/kg

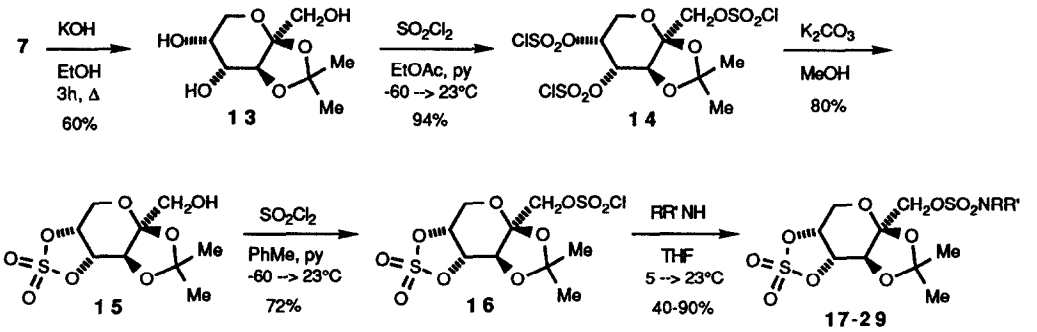
Conversion of **7** to bis-chlorosulfate **12**,[9,10] followed by dechlorosulfation furnished cyclic sulfate **2** (from 50% EtOH:H_2O, mp 139-141°C, dec; $[\alpha]^{25}_D$ -27.7°, c 1.00, MeOH). MES testing of **2** showed it to be



about eight times more potent than topiramate (Table). Consequently, a series of N-substituted analogues was synthesized by preparing key chlorosulfate cyclic sulfate **16** from **7**, as shown, and reacting it with various

amines. These compounds, **17-29**, are listed in the Table along with their MES data.[11]

Use of a 4,5-cyclic sulfate group in place of a 4,5-acetonide group substantially enhances anticonvulsant potency for the fructopyranose structural series (cf. **2** with **1**, **17** with **30**, and **28** with **31**). Hence, robust activity is realized for cyclic sulfates that have alkyl substituents on nitrogen (**17**, **18**, **20**, **24**, **25**, and **28**). Inspection of the monoalkylated analogues reveals that MES activity is optimal when the size of R' is relatively small. However, a cycloalkyl group confers better potency to moderately sized alkyl groups (cf. **25** and **19**). Potency was lower for R' = CH_2CF_3 (cf. **27** and **18**), and fell off dramatically for R' = Ph (**22**).



At 16 h in mice p.o., **2** (RWJ-37947) had an ED_{50} of 41.5 mg/kg, compared to an ED_{50} of 720 mg/kg for **1**, showing **2** to be a potent anticonvulsant with a long duration of action. Compound **2** also shows an excellent therapeutic index relative to neurotoxicity in the rotarod test: ED_{50}/TD_{50} >150.

^1H NMR spectral data for **2** are consistent with a skew conformation ($^3S_0$) for the pyranose ring, as was reported for topiramate.[2] This conformation is also observed for **2** in the solid state by X-ray crystallography.[4]

Acknowledgment. We thank Samuel Nortey and Delene Mitchell for technical assistance.

References and Notes

1. For a recent review on epilepsy and antiepileptic drugs, see: Rogawski, M. A.; Porter, R. J. *Pharmacol. Rev.* **1990**, *42*, 223-285.
2. Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F.; Shank, R. P.; Dodgson, S. P. *J. Med. Chem.* **1987**, *30*, 880-887.
3. Maryanoff, B. E.; Margul, B. L. *Drugs Future* **1989**, *14*, 342-344. Also, *Ibid.* **1993**, *18*, 397-398.
4. Maryanoff, B. E.; Costanzo, M. J.; Nortey, S. O.; Shank, R. P.; Schupsky, J. J.; Ortegon, M. E.; Vaught, J. L., unpublished results, manuscript in preparation.
5. The S=O stereochemistry was assigned by H-1 NMR chemical shifts. The 4,5-protons syn to the sulfinyl group are deshielded relative to the anti 4,5-protons. See: Wang, Y.; Hogenkamp, H. P. C. *Carbohydr. Res.* **1979**, *76*, 131-140; Pritchard, J. G.; Lauterbur, P. C. *J. Am. Chem. Soc.* **1961**, *83*, 2105-2110.
6. The hydrolysis also produced the tetraol product (43%), resulting from removal of both acetonide groups.
7. Binkley, R. W.; Hehmann, D. G. *J. Org. Chem.* **1990**, *55*, 378-380.
8. All new compounds, except **10**, were purified by chromatography on silica gel; all target sulfamates were characterized by H-1 NMR, C-13 NMR, MS, and elemental analysis (C, H, N, S).
9. Martin, O. R.; Korppi-Tommola, S.-L.; Szarek, W. A. *Can. J. Chem.* **1982**, *60*, 1857-1862.
10. We could also prepare **2** from **3** by use of $NaIO_4/RuCl_3$ (Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538-7539); however, we tend to favor the direct condensation method.
11. ED_{50} values are reported for reference drugs and several noteworthy test compounds. Data for other test compounds are reported as % block, with high and low doses to afford a sense of relative potency.