The existence of aqueous shunts in the oil phase may shorten t_L drastically. To examine the validity of t_L as a characteristic time, one plots $C_R(t)$ against t for several values of n for an infinite source (Fig. 8). At long times, $C_R(t)$ asymptotically approaches the equilibrium solution, which for an infinite source is:

$$\lim_{t \to \infty} C_R(t) = C_0 \qquad \text{(Eq. 11)}$$

As shown in Fig. 8, the lag time, t_L, is a reasonable estimate of the time of convergence of the curves for different n.

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Synthesis and Anticonvulsant Properties of Some 2-Aminoethanesulfonic Acid (Taurine) Derivatives

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Abstract □ A series of 2-acylaminoethanesulfonamides were synthesized by treating the corresponding sulfonyl chlorides with ammonia, a primary, or a secondary amine. A few compounds displayed marked anticonvulsant activity in mice when tested for their potency in the maximal electroshock seizure test. The piperidino, benzamido, phthalimido, and phenylsuccinylimido derivatives were active, whereas the succinylimido, saccharinylimido, and norbornendicarboxylimido compounds showed no activity. The interference with the sodium-independent taurine binding to mouse brain synaptic membranes was assessed to elucidate the possible mode of anticonvulsant action.

Keyphrases □ Anticonvulsant agents—potential, 2-aminoethanesulfonic acid (taurine) derivatives, synthesis □ Synthesis—2-aminoethanesulfonic acid (taurine) derivatives, anticonvulsant activity in mice □ Taurine—synthesis of derivatives, anticonvulsant activity in mice

Taurine, 2-aminoethanesulfonic acid, is abundant in excitable mammalian tissues such as the brain, sensory organs, heart, and other muscles (1). In these tissues taurine has recently been considered an essential effector in the regulation of neuronal communication, possibly as an inhibitory synaptic transmitter, neuromodulator, or stabilizer of excitable membranes (2, 3). Taurine effectively prevents seizures when administered intracerebroventricularly to an animal model, but clinical trials with epileptic patients using oral or intravenous administration have been only partially successful (4).

Taurine is quite polar, and its penetration from plasma into brain tissue is apparently hampered by its hydrophilic properties (5). We have attempted to prepare more lipophilic derivatives of taurine which would still possess an inhibitory action at central synapses. Lipophilization of taurine was effected by both acylation and conversion of the sulfonic acid group to various amides. In this way the shape of the molecule and the intramolecular electron distribution, both of which may be essential for the taurine-like inhibitory action (6), were expected to be unchanged. It is also significant that sulfonamides are generally atoxic.

RESULTS AND DISCUSSION

The compounds studied are of the general structures A and B (see Table I for R_1 and R_2 designations).

$R_1CH_2CH_2SO_2NH_2$ (A) $\qquad$ $R_1CH_2CH_2SO_2R_2$ (B)

Although several earlier reports (7–10) have described similar compounds, these studies evaluated the compounds for antibacterial and antimalarial activity. They were either inactive or only slightly active in this respect.

Compounds II, IVa–g, V, and VIIIa–b inhibited maximal electroshock (MES)-induced convulsions in mice (Table II). The most potent compounds were II, IVc, IVd, IVe, IVg, and V, which had ED_{50} values ≤100 mg/kg. It was found that the sodium-independent binding of [^{3}H]taurine to isolated synaptic membranes was inhibited by III, IVa, V, and VIc. In general, no parallelism was observed between anticonvulsant action and inhibition of taurine binding. Only V may act by interfering with the attachment of taurine to its membrane binding sites.

The acyltaurinamides and *N*-substituted acyltaurinamides were synthesized from the corresponding sulfonyl chlorides and ammonia, a primary, or a secondary amine as described previously (7–9, 11). These compounds are colorless, crystalline substances with a somewhat bitter taste. They are insoluble or slightly soluble in water, but soluble in polar organic solvents.

EXPERIMENTAL[1]

***N*-[2-[(Methylamino)sulfonyl]ethyl]benzamide (IVb), *N*-[2-[(Ethylamino)sulfonyl]ethyl]benzamide (IVc), *N*-[2-[(Dimethylamino)sulfonyl]ethyl]benzamide (IVd), *N*-[2-[[(1-Methylethyl)amino]sulfonyl]ethyl]benzamide (IVe), *N*-[2-[(Butylamino)sulfonyl]ethyl]benzamide (IVf), and *N*-[2-[[(1,1-Dimethylethyl)amino]sulfonyl]ethyl]benzamide (IVg)**—These compounds were prepared as described below for IVg. To *tert*-butylamine (10.92 g, 0.150 mol) was added with cooling and stirring (ice-bath) the substituted sulfonyl chloride (7.66 g, 0.031 mol) over a 25-min period. After 20 min stirring additional *tert*-butylamine (3.64 g, 0.05 mol) was added, and the stirring was continued at room temperature. Water (75 mL) was added, and the excess amine was removed with a stream of air. The precipitate was re-

[1] Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were performed by Janssen Pharmaceutica NV, Analytical Department, Beerse, Belgium. NMR data were recorded on a JEOL FX-60 spectrophotometer.

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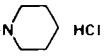
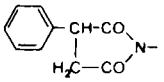
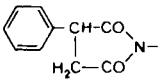
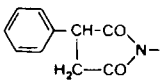
Table I—Taurinesulfonamide Derivatives of $R_1CH_2CH_2SO_2R_2$

Compound	R_1	R_2	Recrystallization Solvent	Melting Point, °C	Formula	Analysis % Calc.	Found
I	H_2N-	$-NH_2$ HCl	90% ethanol	133–136[a]			
II			Ethanol-HCl	222–224[b]			
III			Ethanol-HCl	254–256[c]			
IVa		$-NH_2$	95% ethanol	168–171[d]			
IVb		$-NHCH_3$	Water	116–117	$C_{10}H_{14}N_2O_3S$	C 49.57 H 5.82 N 11.56	49.28 5.74 10.96
IVc		$-NHCH_2CH_3$	33% ethanol	112–114	$C_{11}H_{16}N_2O_3S$	C 51.54 H 6.29 N 10.93	51.45 6.32 11.00
IVd		$-N(CH_3)_2$	33% ethanol	113–115	$C_{11}H_{16}N_2O_3S$	C 51.54 H 6.29 N 10.93	51.72 6.35 11.11
IVe		$-NHCH(CH_3)_2$	33% ethanol	111–113	$C_{12}H_{18}N_2O_3S$	C 53.31 H 6.71 N 10.36	53.15 6.69 10.43
IVf		$-NH(CH_2)_3CH_3$	50% methanol	93–95	$C_{13}H_{20}N_2O_3S$	C 54.91 H 7.09 N 9.85	54.98 7.10 9.97
IVg		$-NHC(CH_3)_3$	75% methanol	91–94	$C_{13}H_{20}N_2O_3S$	C 54.91 H 7.09 N 9.85	54.77 7.03 9.93
V		$-NHCH_3$	95% ethanol	142–144	$C_{11}H_{12}N_2O_4S$	C 49.25 H 4.51 N 10.44	49.32 4.40 10.44
VIa		$-NH_2$	Acetone	195–197	$C_9H_{10}N_2O_5S_2$	C 37.24 H 3.47 N 9.65	37.12 3.48 9.68
VIb		$-NHCH_3$	Acetonitrile	179–182	$C_{10}H_{12}N_2O_5S_2$	C 39.47 H 3.97 N 9.20	39.43 4.01 9.22
VIc		$-NH(CH_2)_3CH_3$	Cyclohexane–ethylacetate (1:1)	72–77	$C_{13}H_{18}N_2O_5S_2$	C 45.07 H 5.24 N 8.09	44.86 5.07 7.92
VIIa		$-NH_2$	Water	189–191	$C_6H_{10}N_2O_4S$	C 34.95 H 4.89 N 13.58	34.75 4.88 13.60
VIIb		$-NHCH(CH_3)_2$	95% ethanol	101–102	$C_9H_{16}N_2O_4S$	C 43.54 H 6.50 N 11.28	43.46 6.54 11.28
VIIc		$-NH_2CH_2$ 	95% ethanol	110–112	$C_{13}H_{16}N_2O_4S$	C 52.69 H 5.44 N 9.45	52.78 5.48 9.48
VIIIa		$-NH_2$	95% ethanol	157–159	$C_{12}H_{14}N_2O_4S$	C 51.05 H 5.00 N 9.52	50.50 4.91 9.66
VIIIb		$-NHCH(CH_3)_2$	50% methanol	68–73	$C_{15}H_{20}N_2O_4S$	C 55.54 H 6.21 N 8.64	54.95 6.09 8.55
VIIIc		$-NHC(CH_3)_3$	95% ethanol	113–116	$C_{16}H_{22}N_2O_4S$	C 56.79 H 6.55 N 8.28	56.62 6.57 8.46
IX		$-NH_2$	Ethanol–dimethylformamide	242–245	$C_{14}H_{12}N_2O_4S$	C 55.26 H 3.97 N 9.21	55.06 3.90 9.21
Xa		$-NH_2$	Acetonitrile	206–209	$C_{11}H_{14}N_2O_4S$	C 48.88 H 5.22 N 10.36	48.89 5.21 10.21
Xb		$-NHCH(CH_3)_2$	Acetonitrile	131–134	$C_{14}H_{20}N_2O_4S$	C 53.83 H 6.45 N 8.97	53.93 6.52 8.88

[a] Lit. (8) mp 130–134°C. [b] Lit. (12) mp 202–206°C. [c] Lit. (12) mp 250–252°C. [d] Lit. (8) mp 169.5–170.5°C.

moved by filtration, washed with water, and recrystallized from the appropriate solvent (Table I).

1,3-Dihydro-*N*-methyl-1,3-dioxo-2*H*-isoindoleethanesulfonamide (V)—To methylene chloride (30 mL) were added the previously described sulfonyl chloride (2.74 g, 0.01 mol) (8) and methylamine hydrochloride (1.36 g, 0.02 mol). Then, 7 mL of 6 M K_2CO_3 was added with continuous stirring and cooling (~10°C) over a 10-min period. Water (25 mL) was added, and the organic phase was washed with water and dried over magnesium sulfate. The solvent was evaporated, and the product was recrystallized from the appropriate solvent (Table I).

3-Oxo-1,2-benzisothiazole-2(3*H*)-ethanesulfonamide 1,1-Dioxide (VIa), *N*-Methyl-3-oxo-1,2-benzisothiazole-2(3*H*)-ethanesulfon-

Table II—Anticonvulsant Activities (ED_{50}) of Taurinesulfonamide Derivatives in the Maximal Electroshock Test in Mice and the Effects on Sodium-Independent Taurine Binding in Mouse Brain Membrane Fractions

Compound	ED_{50}, mg/kg ip	Taurine Binding[a]
I	>300	102 ± 7 (5)
II	69	113 ± 6 (4)
III	>300	74 ± 10 (4)
IVa	209	80 ± 10 (5)
IVb	150	126 ± 10 (5)
IVc	84	140 ± 12 (4)
IVd	75	109 ± 10 (5)
IVe	77	121 ± 11 (5)
IVf	150	115 ± 11 (4)
IVg	82	136 ± 10 (5)
V	105	67 ± 4 (10)
VIa	>300	98 ± 9 (5)
VIb	>300	102 ± 9 (5)
VIc	>300	75 ± 10 (4)
VIIa	>300	
VIIb	>300	
VIIc	>300	
VIIIa	209	101 ± 13 (4)
VIIIb	244	84 ± 5 (3)
VIIIc	>300	
IX	>300	
Xa	>300	
Xb	>300	

[a] The binding of 0.1 μM [^{3}H]taurine to membrane fractions isolated from mouse whole brain in the presence of the compounds tested (concentration in the incubation medium: 1.0 mM except III and VIc, 0.5 mM, and IVg, 0.1 mM) is given as percentage of that in the control incubations without effectors (2.22 ± 0.32 nmol/kg fresh weight of synaptic membranes, n = 40, mean ± SEM). The number of experiments is in parentheses.

amide 1,1-Dioxide (VIb), and *N*-Butyl-3-oxo-1,2-benzisothiazole-2(3*H*)-ethanesulfonamide 1,1-Dioxide (VIc)—Sodium 1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (the sodium salt of saccharin) (205.2 g, 1 mol) and 1,2-dichloroethane (792 g, 8 mol) in dimethyl sulfoxide (1 L) were heated at 105°C for 6 h. The mixture was poured into water, and from the organic phase was isolated 153 g of the corresponding *N*-2-chloroethyl derivative, mp 63–66°C. This material was heated at 120°C for 2 h with thiourea (30.4 g, 0.4 mol). Dimethylformamide (20 mL) was added to the melt, and the mixture was allowed to cool. The material was slurried with acetone, filtered, and the resulting product washed with ethanol to give 38.9 g of the thiuronium hydrochloride, mp 210°C (dec.). This salt (83.2 g, 0.259 mol) was dissolved in warm water (1.9 L), and the mixture was filtered to remove the undissolved material (5.2 g). The solution was cooled to 5°C, and a stream of chlorine gas was bubbled through the solution over a 6-h period with cooling and stirring. The precipitate was isolated and recrystallized from toluene to give 56.2 g of 3-oxo-1,2-benzisothiazole-2(3*H*)-ethanesulfonyl chloride 1,1-dioxide.

Preparation of VIa—The aforementioned substituted sulfonyl chloride (9.66 g, 0.031 mol) was dissolved in methylene chloride (120 mL). With cooling and stirring, gaseous ammonia was introduced over a 15-min period. The solvent was removed by distillation, and the residue was slurried with water and then filtered. Recrystallization from acetone gave 2.09 g of VIa.

Preparation of VIb—The aforementioned substituted sulfonyl chloride (9.0 g, 0.029 mol) was dissolved in methylene chloride (100 mL), and methylamine (3.2 g, 0.19 mol) in isopropyl alcohol (16 mL) was added. After 3 min the mixture was poured into 200 mL of 0.3 M HCl, and after thorough mixing the organic layer was separated, dried, and the solvent evaporated. Several recrystallizations from acetonitrile gave 2.64 g of VIb.

Preparation of VIc—The aforementioned substituted sulfonyl chloride (9.3 g, 0.033 mol) was dissolved in methylene chloride (120 mL). *n*-Butylamine (2.44 g, 0.033 mol) in Na_2CO_3 solution (30 mL, 1.4 M) was added, the mixture was stirred for 6 min, and then water (50 mL) was added. The organic layer was separated and washed twice with water, dried over magnesium sulfate, and the solvent evaporated. The material was slurried with petroleum ether, filtered, and then recrystallized several times from a cyclohexane–ethyl acetate mixture (1:1) to give 0.95 g of VIc.

2,5-Dioxo-1-pyrrolidineethanesulfonamide (VIIa), *N*-(1-Methylethyl)-2,5-dioxo-1-pyrrolidineethanesulfonamide (VIIb), and 2,5-Dioxo -*N*- (phenylmethyl) -1- pyrrolidineethanesulfonamide (VIIc)—A mixture of 2-aminoethanesulfonic acid (taurine) 46.5 g, 0.37 mol), potassium acetate (49.0 g, 0.5 mol), succinic anhydride (50 g, 0.5 mol), and glacial acetic acid (300 mL) were heated at reflux for 2 h, with stirring. Acetic anhydride (25 mL) was added, and the heating was continued. The mixture was cooled overnight, and then the product was removed by filtration and washed with ethanol to give 54 g of the potassium salt of the succinylamide, which was used without purification.

A mixture of the aforementioned potassium salt (80 g, 0.41 mol), phosphorus pentachloride (115.8 g, 0.56 mol), and methylene chloride (689 mL) was stirred at 15–20°C for 5 h, and was then allowed to stand at room temperature for 48 h. The mixture was poured into ice-water (500 mL), and the organic layer was separated, washed with water, and dried over magnesium sulfate. The solvent was removed under reduced pressure, the residue was slurried with ether (150 mL), and the product was removed by filtration. Recrystallization from toluene gave 40 g of the sulfonyl chloride, mp 133–134°C.

Preparation of VIIa—The aforementioned sulfonyl chloride (11.25 g, 0.05 mol) was added with stirring and cooling (5–10°C) to a mixture of 15 mL of 6 M K_2CO_3, 15 mL of concentrated ammonium hydroxide, and methylene chloride (100 mL). The crystalline material was removed by filtration and washed with two 10-mL portions of cold water. Recrystallization gave 6 g of VIIa, mp 189–191°C. *N*-(1-Methylethyl)-2,5-dioxo-1-pyrrolidineethanesulfonamide (VIIb) and 2,5-dioxo-*N*-(phenylmethyl)-1-pyrrolidineethanesulfonamide (VIIc) were prepared in an analogous manner using isopropyl- and benzylamines, respectively.

2,5-Dioxo-3-phenyl-1-pyrrolidineethanesulfonamide (VIIIa), *N*-(1-Methylethyl)-2,5-dioxo-3-phenyl-1-pyrrolidineethanesulfonamide (VIIIb), and *N*-(1,1-Dimethylethyl)-2,5-dioxo-3-phenyl-1-pyrrolidineethanesulfonamide (VIIIc)—2-Phenylsuccinylimidoethanesulfonyl chloride was synthesized using the method described for phthalimidoethanesulfonyl chloride (7). Chloroethylphenylsuccinimide (87.3 g, 0.367 mol) gave the corresponding phenylsuccinylimidoethanethiuronium chloride in a yield of 56 g, mp 205–216°C. This material (49.4 g, 0.157 mol) afforded 39.4 g, of phenylsuccinylimidoethanesulfonyl chloride, mp 146–148°C, after recrystallization from toluene. Treatment of the aforementioned sulfonyl chloride with concentrated ammonium hydroxide gave VIIIa, while treatment with isopropylamine or *tert*-butylamine gave VIIIb or VIIIc, respectively.

In a similar fashion 1,3-dioxo-1*H*-benz[*de*]isoquinoline-2(3*H*)-ethanesulfonamide (IX) was prepared from the corresponding sulfonyl chloride (mp 164–165°C), and also 1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2*H*-isoindole-2-ethanesulfonamide (Xa) and 1,3,3a,4,7,7a-hexahydro-*N*-(1-methylethyl)-1,3-dioxo-4,7-methano-2*H*-isoindole-2-ethanesulfonamide (Xb) were prepared from the sulfonyl chloride, mp 158–160°C.

Anticonvulsant activity—All compounds were tested for anticonvulsant activity using the maximal electroshock seizure (MES) test which was carried out on mice subjected for 0.2 s to a current of 50 mA (60 Hz) delivered through corneal electrodes (13). The effect of the compounds on the sodium-independent binding of [^{3}H]taurine (0.1 mol/L, specific activity 0.33 PBq/mol) was measured in 0.05 M Tris buffer, pH 7.1, at 5°C (incubation time: 1 min) (14).

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