Synthesis and Antiarrhythmic Activity of 2,5-Disubstituted 2,3-Dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-Dioxides

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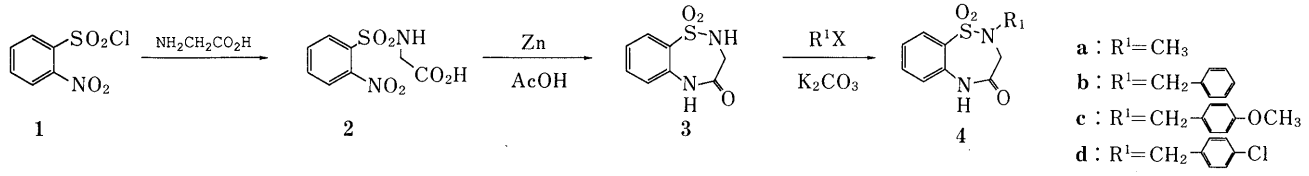
A series of 2,5-disubstituted 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-dioxide derivatives were prepared and evaluated for the antiarrhythmic effect on ouabain-induced arrhythmias in guinea pigs. Most of the synthesized compounds showed the antiarrhythmic activity in this primary screening system. Some of the compounds with 2-(*N*,*N*-dimethylamino)ethyl, 2-(pyrrolidin-1-yl)ethyl and 2-oxo-2-(morpholin-4-yl)ethyl moieties on the 5-position of 1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-dioxide exhibited a potent antiarrhythmic activity. The structure–activity relationship of these compounds was discussed.

Keywords synthesis; 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-dioxide; ouabain-induced arrhythmia; antiarrhythmic activity; structure–activity relationship

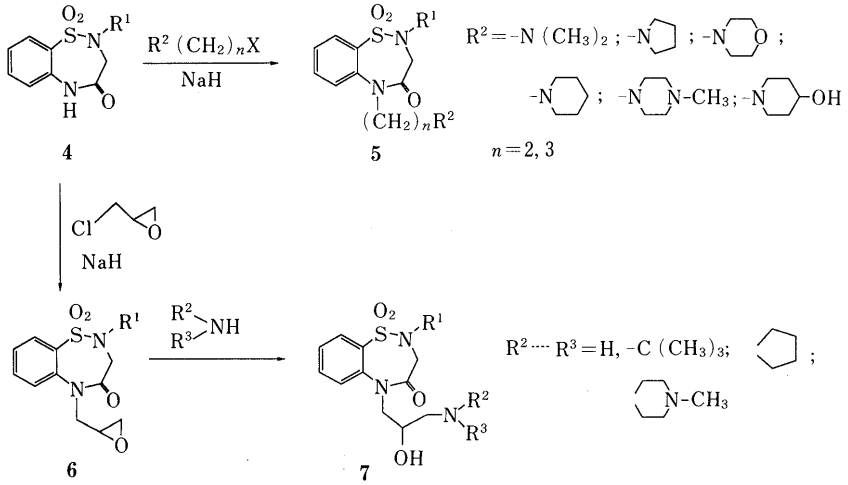
It is believed that sudden cardiac death is caused from ventricular arrhythmia. Over the past decade, the number of patients suffering from this disease has been increasing. Under these circumstances, numerous efforts have been made by many groups[1] to develop new or potent and safe antiarrhythmic agents. Recently, propafenone,[2] mexiletine,[3] cibenzoline,[4] pilisicainide[5] and others have been launched on the Japanese market as class I antiarrhythmic agents. Most of these agents are characterized as having the basic part, such as primary, secondary, or tertiary amine, at the terminal of the bond chain attached to a single aromatic ring. Although there are a few reports[6] of class I antiarrhythmic agents with a bicyclic structure with an aromatic ring fused to a seven- or eight-membered ring system, there is nothing in clinical practice as a class I antiarrhythmic agent with such a structure; in addition to antiarrhythmic activity of main action, the compound[6b] with this ring system possesses interesting properties, *e.g.*, antiaggregatory or antiserotoninergic activities. These observations prompted us to synthesize a structurally novel compound with an aromatic ring fused to the seven-membered ring system. Thus, with the aim of finding a potential and novel antiarrhythmic agent, we synthesized numerous 2,5-disubstituted 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-dioxides, and found that these compounds showed a pronounced antiarrhythmic activity on the ouabain-induced arrhythmia in guinea pigs; moreover, the activity of these compounds varied depending upon the substituents on the benzothiadiazepine skeleton. In this paper, we wish to report on the synthesis of 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one derivatives and the structure–activity relationship between their structure and antiarrhythmic activity.

Chemistry 2-Substituted 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-dioxides (**4**), a key intermediate in the synthesis of 2,5-disubstituted 2,3-dihydro-1,2,5-ben-



1 2 3 4

Chart 1



4 5 6 7

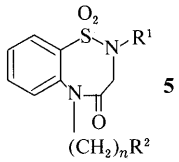
Chart 2

zothiadiazepin-4(5*H*)-one 1,1-dioxides (**5**, **7** and **8**), were prepared according to the pathway as shown in Chart 1.

The condensation of 2-nitrobenzenesulfonyl chloride (**1**) with glycine gave *N*-(2-nitrobenzenesulfonyl)glycine (**2**),[7] which was converted to 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-dioxide (**3**) by the reductive cyclization with zinc powder in acetic acid. Selective alkylation on the 2-position of **3** was accomplished using the appropriate alkyl halides or benzyl halides in the presence of potassium carbonate in *N*,*N*-dimethylformamide (DMF) to give the key intermediates (**4**) in good yield (Chart 1). The alkylation on the 5-position of **4** using the appropriate aminoalkyl halides in the presence of sodium hydride in DMF proceeded smoothly to give the corresponding aminoalkyl derivatives (**5**) in fair yields (Chart 2, Tables I and II).

The alkylation on the 5-position of **4** with epichlorohydrin afforded the 2,3-epoxypropyl derivatives (**6**), which were treated with the appropriate amines to give the corresponding 3-amino-2-hydroxypropyl derivatives (**7**) (Chart 2, Tables III and IV). 5-Acetamide derivatives (**8**) were prepared from **4** by two different methods as shown in Chart 3. First, a direct alkylation on the 5-position of **4** with the appropriate chloroacetylamino derivatives in the same manner as described for the synthesis of **5** afforded the corresponding 5-acetamides (**8**) in good yield. The compound (**8e**) was also synthesized by this method, but a satisfactory yield was not obtained. Therefore, **8e** was synthesized stepwise by an alternative method, wherein the alkylation on the 5-position of the compound (**4**) with *tert*-butyl bromoacetate, performed in the same manner as described for **5**, afforded *tert*-butyl 2,3-dihydro-2-(4-methoxybenzyl)-4-oxo-1,2,5-benzothiadiazepine-5-acetate

TABLE I. Physical Data of 2,5-Disubstituted 2,3-Dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-Dioxides (**5**)



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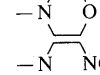
Compd. No.	R^1	*n*	R^2	Yield (%)	Salt[a]	mp (°C) (Recrystn. solvent[b])	Formula	Analysis (%) Calcd (Found) C	H	N
5a	$-CH_3$	2	$-N(CH_3)_2$	55	M	159—161 (Et)	$C_{13}H_{19}N_3O_3S \cdot C_4H_4O_4$	49.39 (49.42)	5.61 5.55	10.16 10.12)
5b	$-CH_3$	3	$-N(CH_3)_2$	53	M	184—185 (Et)	$C_{14}H_{21}N_3O_3S \cdot C_4H_4O_4$	50.57 (50.71)	5.90 6.20	9.83 9.77)
5c	$-CH_3$	2		43	M	162—164 (Et)	$C_{15}H_{21}N_3O_3S \cdot C_4H_4O_4$	51.93 (52.15)	5.73 5.54	9.56 9.52)
5d	$-CH_3$	3		39	H	203—204 (Et–E)	$C_{17}H_{25}N_3O_3S \cdot HCl$	51.44 (51.47)	6.60 6.82	10.59 10.38)
5e	$-CH_3$	2		40	—	143—144 (Et)	$C_{15}H_{21}N_3O_4S$	53.08 (53.16)	6.23 6.22	12.38 12.29)
5f	$-CH_3$	3		29	M	139—141 (Et)	$C_{16}H_{23}N_3O_4S \cdot C_4H_4O_4$	51.16 (50.98)	5.80 5.46	8.95 8.85)
5g	$-CH_3$	3		35	H	215—217 (Et–E)	$C_{17}H_{25}N_3O_4S \cdot HCl$	48.39 (48.13)	6.45 6.78	9.96 9.72)
5h	$-CH_2C_6H_5$	2	$-N(CH_3)_2$	35	M	168—170 (Et)	$C_{19}H_{23}N_3O_3S \cdot C_4H_4O_4$	56.43 (56.37)	5.56 5.72	8.53 8.51)
5i	$-CH_2C_6H_5$	2		49	M	160—162 (Et)	$C_{22}H_{27}N_3O_3S \cdot C_4H_4O_4$	58.97 (58.74)	5.90 5.85	7.93 7.75)
5j	$-CH_2C_6H_5$	3		40	M	185—187 (Et)	$C_{23}H_{30}N_4O_3S \cdot C_8H_8O_8 \cdot H_2O$	53.75 (53.80)	5.82 5.70	8.09 7.87)
5k	$-CH_2C_6H_4$-4-OCH_3	2	$-N(CH_3)_2$	58	M	189—190 (Et)	$C_{20}H_{25}N_3O_4S \cdot C_4H_4O_4$	55.48 (55.38)	5.63 5.69	8.09 8.06)
5l	$-CH_2C_6H_4$-4-OCH_3	2		53	M	170—172 (Et)	$C_{22}H_{27}N_3O_4S \cdot C_4H_4O_4$	57.24 (57.46)	5.73 5.64	7.70 7.68)
5m	$-CH_2C_6H_4$-4-OCH_3	2		39	M	172—173 (Et)	$C_{23}H_{29}N_3O_4S \cdot C_4H_4O_4$	57.95 (58.06)	5.94 5.69	7.51 7.53)
5n	$-CH_2C_6H_4$-4-OCH_3	3		51	H	165—166 (Et–E)	$C_{24}H_{31}N_3O_4S \cdot HCl$	54.38 (54.70)	6.66 6.81	7.93 7.99)
5o	$-CH_2C_6H_4$-4-OCH_3	2		24	M	179—180 (Et)	$C_{22}H_{27}N_3O_5S \cdot C_4H_4O_4$	55.61 (55.84)	5.56 5.67	7.48 7.49)
5p	$-CH_2C_6H_4$-4-OCH_3	3		47	M	180—182 (Et)	$C_{24}H_{32}N_4O_4S \cdot C_8H_8O_8 \cdot H_2O$	53.18 (53.37)	5.86 5.90	7.75 7.75)
5q	$-CH_2C_6H_4$-4-Cl	2	$-N(CH_3)_2$	30	M	153—155 (Et)	$C_{19}H_{22}ClN_3O_3S \cdot C_4H_4O_4$	52.72 (52.96)	5.00 5.01	8.02 7.94)
5r	$-CH_2C_6H_4$-4-Cl	2		34	M	139—140 (Et)	$C_{21}H_{24}ClN_3O_3S \cdot C_4H_4O_4$	54.59 (54.90)	5.13 5.30	7.64 7.58)
5s	$-CH_2C_6H_4$-4-Cl	2		23	M	167—168 (Et)	$C_{21}H_{24}ClN_3O_4S \cdot C_4H_4O_4$	53.03 (52.94)	4.99 5.08	7.42 7.38)

a) Kind of salt: M, maleic acid; H, hydrogen chloride. *b*) Recrystallization solvents: Et, ethanol; E, diethyl ether.

TABLE II. Spectral Data of the Compounds (**5**)

Compd. No.	MS m/z (M^+)	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6)[a] δ ppm
5a	297	1670 (CO), 1340 (SO_2)	2.73 (3H, s), 2.96 (6H, s), 3.37 (2H, t, J=6.8 Hz), 3.51 (2H, s), 4.34 (2H, t, J=6.3 Hz), 6.30 (2H, s), 7.10—8.00 (4H, m)
5b	311	1670 (CO), 1340 (SO_2)	1.60—2.05 (2H, m), 2.61 (3H, s), 2.70 (6H, s), 2.80—3.20 (2H, m), 3.36 (2H, s), 3.90 (2H, t, J=6.0 Hz), 6.03 (2H, s), 7.50—8.00 (4H, m)
5c	323	1670 (CO), 1340 (SO_2)	1.70—2.10 (4H, m), 2.60 (3H, s), 3.10—3.40 (6H, m), 3.39 (2H, s), 4.50 (2H, t, J=7.0 Hz), 6.03 (2H, s), 7.50—8.00 (4H, m)
5d	351	1660 (CO), 1330 (SO_2)	1.20—2.15 (8H, m), 2.61 (3H, s), 2.60—3.40 (6H, m), 3.35 (2H, s), 3.92 (2H, t, J=8.0 Hz), 7.40—8.00 (4H, m), 10.50 (1H, br s)
5e	339	1675 (CO), 1340 (SO_2)	2.20—2.50 (6H, m), 2.58 (3H, s), 3.32 (2H, s), 3.20—3.45 (4H, m), 3.90 (2H, t, J=7.0 Hz), 7.40—7.90 (4H, m)
5f	353	1660 (CO), 1340 (SO_2)	1.60—2.10 (2H, m), 2.61 (3H, s), 2.70—3.25 (6H, m), 3.37 (2H, s), 3.50—3.85 (4H, m), 3.94 (2H, t), 6.06 (2H, s), 7.40—8.00 (4H, m)
5g	367	1660 (CO), 1350 (SO_2)	1.50—2.20 (6H, m), 2.60 (3H, s), 2.70—3.70 (8H, m), 3.36 (2H, s), 3.92 (2H, t), 7.45—8.00 (4H, m), 10.30 (1H, br s)
5h	373	1675 (CO), 1345 (SO_2)	2.78 (6H, s), 3.15 (2H, t, J=6.6 Hz), 3.30 (2H, s), 4.14 (2H, t, J=6.6 Hz), 4.27 (2H, s), 6.04 (2H, s), 7.32 (5H, s), 7.50—8.00 (4H, m)
5i	413	1670 (CO), 1340 (SO_2)	1.30—1.90 (6H, m), 2.90—3.30 (6H, m), 3.31 (2H, s), 4.18 (2H, t, J=7.0 Hz), 4.27 (2H, s), 6.04 (2H, s), 7.32 (5H, s), 7.50—8.00 (4H, m)
5j	442	1675 (CO), 1350 (SO_2)	1.50—1.90 (2H, m), 2.51 (3H, s), 2.60—3.20 (10H, m), 3.26 (2H, s), 3.86 (2H, t, J=7.0 Hz), 4.24 (2H, s), 6.15 (4H, s), 7.32 (5H, s), 7.40—8.00 (4H, m)
5k	403	1675 (CO), 1340 (SO_2)	2.78 (6H, s), 3.15 (2H, t, J=7.0 Hz), 3.26 (2H, s), 3.72 (3H, s), 4.10 (2H, t, J=7.0 Hz), 4.20 (2H, s), 6.87 (2H, d, J=8.8 Hz), 7.22 (2H, d, J=8.8 Hz), 7.50—8.00 (4H, m)
5l	429	1680 (CO), 1340 (SO_2)	1.70—2.20 (4H, m), 3.00—3.50 (6H, m), 3.27 (2H, s), 3.73 (3H, s), 4.12 (2H, t, J=7.5 Hz), 4.20 (2H, s), 6.04 (2H, s), 6.88 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.50—8.00 (4H, m)
5m	443	1680 (CO), 1340 (SO_2)	1.30—1.85 (6H, m), 2.80—3.40 (6H, m), 3.27 (2H, s), 3.72 (3H, s), 4.00—4.30 (2H, m), 4.20 (2H, s), 6.04 (2H, s), 6.88 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.50—8.00 (4H, m).
5n	457	1660 (CO), 1340 (SO_2)	1.10—2.10 (8H, m), 2.60—3.30 (6H, m), 3.24 (2H, s), 3.72 (3H, s), 3.90 (2H, t, J=7.0 Hz), 4.19 (2H, s), 6.90 (2H, d, J=8.2 Hz), 7.25 (2H, d, J=8.2 Hz), 7.40—8.00 (4H, m), 10.40 (1H, br s)
5o	445	1660 (CO), 1340 (SO_2)	2.70—3.10 (6H, m), 3.25 (2H, s), 3.50—3.75 (4H, m), 3.72 (3H, s), 4.08 (2H, t, J=8.0 Hz), 4.18 (2H, s), 6.11 (2H, s), 6.86 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.40—7.90 (4H, m)
5p	472	1670 (CO), 1350 (SO_2)	1.50—1.90 (2H, m), 2.68 (3H, s), 2.80—3.20 (10H, m), 3.22 (2H, s), 3.72 (3H, s), 3.86 (2H, t), 4.17 (2H, s), 6.15 (4H, s), 6.88 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz), 7.35—7.95 (4H, m)
5q	407	1670 (CO), 1340 (SO_2)	2.79 (6H, s), 3.10 (2H, t, J=6.8 Hz), 3.34 (2H, s), 4.08 (2H, t, J=6.8 Hz), 4.27 (2H, s), 6.04 (2H, s), 7.37-8.00 (8H, m)
5r	433	1680 (CO), 1355 (SO_2)	1.75—2.25 (4H, m), 3.34 (2H, s), 3.10—3.50 (6H, m), 3.05 (2H, t, J=7.0 Hz), 4.27 (2H, s), 6.04 (2H, s), 7.37—8.00 (8H, m)
5s	449	1675 (CO), 1350 (SO_2)	2.70—3.10 (6H, m), 3.32 (2H, s), 3.50—3.70 (4H, m), 4.04 (2H, t, J=7.4 Hz), 4.26 (2H, s), 6.12 (2H, s), 7.40—8.00 (8H, m)

a) Compound **5a** was measured in D_2O.

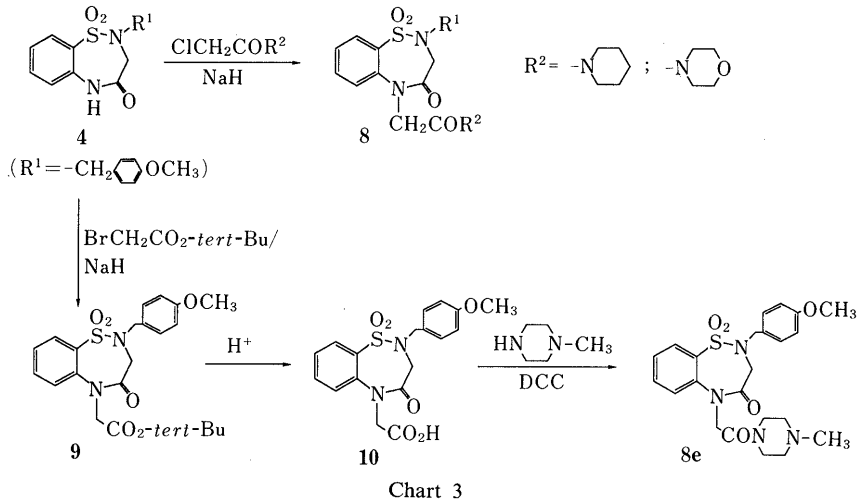
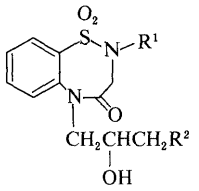


Chart 3

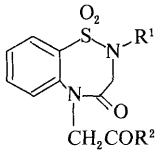
1,1-dioxide (**9**) in 79% yield. The acid-hydrolysis of **9** afforded 5-acetic acid derivative (**10**), which was condensed with *N*-methylpiperazine using dicyclohexylcarbodiimide (DCC) to give the compound (**8e**) (Chart 3, Tables III and IV).

Biological Activity The compounds were evaluated for antiarrhythmic activity on ouabain-induced arrhythmia in guinea pigs as a primary screening according to the literature.[8] In this screening, the compounds were administered intravenously (i.v.) at a dose of 7.5 mg/kg to

TABLE III. Physical Data of 2,5-Disubstituted 2,3-Dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-Dioxides (**7**) and (**8**)



7



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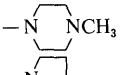
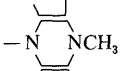
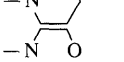
Compd. No.	R^1	R^2	Yield (%)	Salt[a]	mp (°C) (Recrystn. solvent)[b]	Formula	Analysis (%) Calcd (Found)		
							C	H	N
7a	$-CH_3$	$-NHC(CH_3)_3$	48	M	181—182 (IP–E)	$C_{16}H_{25}N_3O_4S \cdot C_4H_4O_4$	50.95 (50.63)	6.20 6.15	8.91 9.26)
7b	$-CH_3$		65	M	178—179 (Et)	$C_{17}H_{26}N_4O_4S \cdot C_8H_8O_8$	48.85 (48.50)	5.58 5.45	9.12 8.92)
7c	$-CH_2C_6H_4$-4-OCH_3		59	H	113—115 (B–Et)	$C_{23}H_{29}N_3O_5S \cdot HCl \cdot H_2O$	53.74 (53.57)	6.27 6.19	8.17 8.11)
7d	$-CH_2C_6H_4$-4-OCH_3		54	M	174—175 (Et)	$C_{24}H_{32}N_4O_5S \cdot C_8H_8O_8$	53.33 (52.91)	5.59 5.40	7.77 7.64)
8a	$-CH_3$		83	—	Oil	$C_{16}H_{21}N_3O_4S$	54.64 (54.50)	6.02 6.23	11.96 11.87)
8b	$-CH_3$		65	—	182—183 (D–IPE)	$C_{15}H_{19}N_3O_5S$	50.98 (51.10)	5.42 5.30	11.89 11.83)
8c	$-CH_2C_6H_4$-4-OCH_3		58	—	122—123 (D–IPE)	$C_{23}H_{27}N_3O_5S$	60.38 (60.23)	5.95 6.17	9.18 9.16)
8d	$-CH_2C_6H_4$-4-OCH_3		62	—	134—135 (Et)	$C_{22}H_{25}N_3O_6S$	57.50 (57.21)	5.48 5.71	9.14 8.96)
8e	$-CH_2C_6H_4$-4-OCH_3		85	—	93—95 (D–IPE)	$C_{23}H_{28}N_4O_5S$	58.46 (58.10)	5.97 5.85	11.86 11.71)

a) Kind of salt: M: maleic acid, H: hydrogen chloride. *b*) Recrystallization solvents: B, benzene; D, dichloromethane; Et, ethanol; E, ethyl ether; IP, isopropanol; IPE, isopropyl ether.

TABLE IV. Spectral Data of the Compounds (**7**) and (**8**)

Compd. No.	MS *m/z* (M^+)	IR (KBr) cm^{-1}	^{1}H-NMR[a] δ ppm
7a	356	1660 (CO), 1340 (SO_2)	1.25 (9H, s), 2.61 (3H, s), 2.70—3.15 (2H, m), 3.25, 3.50 (2H, dd, J=11.2 Hz), 3.50—3.80 (1H, m), 3.90—4.30 (3H, m), 5.90 (1H, br s), 6.14 (2H, s), 7.45—8.00 (4H, m), 8.60 (2H, br s)
7b	383	1670 (CO), 1340 (SO_2)	2.61 (3H, s), 2.71 (3H, s), 2.60—3.60 (13H, m), 3.90—4.20 (2H, m), 6.15 (4H, m), 7.40—8.00 (4H, m)
7c	459	1660 (CO), 1340 (SO_2)	1.70—2.10 (4H, m), 2.80—4.20 (9H, m), 3.34 (2H, s), 3.72 (3H, s), 4.20 (2H, s), 6.00 (1H, s), 6.88 (2H, d, J=8.8 Hz), 7.25 (2H, d, J=8.8 Hz), 7.40—8.00 (4H, m)
7d	488	1670 (CO), 1350 (SO_2)	2.70 (3H, s), 2.50—3.50 (13H, m), 3.72 (3H, s), 3.90—4.30 (3H, m), 6.15 (4H, s), 6.88 (2H, d, J=8.4 Hz), 7.23 (2H, d, J=8.4 Hz), 7.40—8.00 (4H, m)
8a	351	1685, 1660 (CO), 1170 (SO_2)	1.65 (6H, br s), 2.74 (3H, s), 3.30—3.75 (4H, br m), 3.47 (2H, s), 4.51 (2H, s), 7.35—8.10 (4H, m)
8b	353	1685, 1660 (CO), 1175 (SO_2)	2.73 (3H, s), 3.45 (2H, s), 3.40—3.85 (8H, m), 4.50 (2H, s), 7.35—8.00 (4H, m)
8c	457	1690, 1660 (CO), 1180 (SO_2)	1.65 (6H, br s), 3.34 (2H, s), 3.43, 3.60 (each 2H, br m), 3.77 (3H, s), 4.25 (2H, s), 4.50 (2H, s), 6.82 (2H, d, J=9.0 Hz), 7.20 (2H, d, J=9.0 Hz), 7.30—8.00 (4H, m)
8d	459	1685, 1665 (CO), 1185 (SO_2)	3.32 (2H, s), 3.40—3.80 (8H, m), 3.77 (3H, s), 4.24 (2H, s), 4.47 (2H, s), 6.84 (2H, d, J=9.0 Hz), 7.30—8.00 (4H, m)
8e	472	1685, 1655 (CO), 1185 (SO_2)	2.32 (3H, s), 2.35—2.65 (4H, m), 3.33 (2H, s), 3.54, 3.68 (each 2H, br t, J=5 Hz), 3.77 (3H, s), 4.24 (2H, s), 4.49 (2H, s), 6.82 (2H, d, J=9.0 Hz), 7.20 (2H, d, J=9.0 Hz), 7.30—8.00 (4H, m)

a) Compounds **7a—d** and **8a—e** were measured in DMSO-d_6 and $CDCl_3$, respectively.

urethane-anesthetized guinea pigs. After three minutes of test compound administration, ouabain was continuously infused and the dose of ouabain required to cause arrhythmia was measured. Potency of the activity was expressed as the increasing percent of ouabain volume at the test compound injection in comparison with that of vehicle injection.

Results and Discussion

Data relative to the antiarrhythmic activity (*in vivo*) of new compounds on an ouabain-induced arrhythmia model in guinea pigs is described in Table V. In the structure–activity relationship between the series of compounds (**5a—s**, **7a—d** and **8a—e**), the series of (**5a—s** and **8a—e**) exhibited antiarrhythmic activity but none of

TABLE V. Antiarrhythmic Activity of Compounds **5a—s**, **7a—d** and **8a—e** on Ouabain-Induced Arrhythmia in the Guinea Pig

Compd. No.	Antiarrhythmic activity[a] Mean volume of ouabain (μg/kg) for: Ventricular extrasystole (Δ%)	Ventricular flutter (Δ%)	Fibrillation (Δ%)	Cardiac arrest (Δ%)
Vehicle[b]	202.2	322.2	335.5	362.4
5a	264.1 (31)	387.6 (20)	427.8 (28)	429.2 (18)
5b	279.0 (38)	457.9 (42)	470.4 (40)	501.5 (38)
5c	332.2 (64)	434.8 (35)	452.2 (35)	494.2 (36)
5d	141.4 (−30)	187.5 (−42)	211.0 (−37)	231.6 (−36)
5e	240.6 (19)	346.3 (7)	369.7 (10)	400.1 (10)
5f	220.0 (9)	261.7 (−19)	287.4 (−14)	313.2 (−13)
5g	182.1 (−10)	254.5 (−21)	281.7 (−16)	315.3 (−13)
5h	295.1 (46)	421.9 (31)	442.3 (32)	471.9 (30)
5i	[c]	[c]	[c]	170.4 (−52)
5j	167.2 (−17)	239.0 (−25)	252.2 (−25)	267.8 (−26)
5k	259.0 (28)	441.5 (37)	463.0 (38)	508.1 (40)
5l	294.9 (46)	360.4 (12)	372.8 (11)	419.7 (16)
5m	330.7 (64)	395.9 (23)	408.4 (22)	439.8 (21)
5n	192.3 (−5)	272.4 (−15)	297.3 (−11)	288.1 (−21)
5o	249.8 (23)	389.8 (21)	415.6 (24)	432.0 (19)
5p	208.3 (0)	271.6 (−16)	292.9 (−12)	320.0 (−12)
7a	233.8 (16)	313.8 (−3)	337.0 (0)	351.1 (3)
7b	191.6 (−5)	274.3 (−15)	294.8 (−12)	314.8 (−13)
7c	188.8 (−7)	250.3 (−22)	401.7 (20)	391.1 (8)
7d	255.8 (27)	353.7 (10)	378.1 (13)	358.0 (−1)
Vehicle[d]	178.3	207.9	232.0	266.1
5q	192.9 (8)	316.9 (52)	343.7 (48)	356.4 (34)
5r	267.6 (50)	347.0 (67)	373.4 (61)	388.4 (46)
5s	181.3 (2)	227.0 (9)	302.2 (30)	317.5 (19)
8a	178.7 (0)	268.5 (29)	292.1 (26)	303.6 (14)
8b	228.5 (28)	331.4 (59)	356.5 (54)	376.0 (41)
8c	163.0 (−9)	250.0 (20)	284.2 (23)	303.9 (14)
8d	206.3 (16)	282.1 (36)	303.0 (31)	319.9 (20)
8e	213.3 (20)	319.5 (54)	343.4 (48)	257.4 (−3)

a) See experimental section; dose of the test compounds and vehicle was 7.5 and 1.5 mg/kg, i.v., respectively. *b*) Saline was used as vehicle. *c*) Only this compound induced chronic arrhythmia. *d*) 0.5% PEG 600 in saline was used as vehicle because the compounds of **5q—s** and **8a—e** were dissolved in PEG 600 and diluted with saline.

the compounds (**7a—d**) with the substituent of 3-amino-2-hydroxyalkyl moieties on the 5-position of benzothiadiazepine skeleton exhibited such activity. This observation suggests that the introduction of a hydrophilic substituent such as the hydroxyl group on the alkyl chain between the amino moiety and the N-atom on the 5-position of the benzothiadiazepine skeleton reduced the antiarrhythmic activity. Namely, the alkylamino or 2-oxoalkylamino moieties on the 5-position of this benzothiadiazepine skeleton are important to show such activity. Next, in the series of compounds (**5a—s**) with the alkylamino moiety on the 5-position of the benzothiadiazepine skeleton, the substituents on the 2-position of that skeleton did not affect the antiarrhythmic activity, but the potency of the activity depended upon the kind of amino moiety at the terminal of the alkyl chain on the 5-position of the skeleton. In particular, compounds (**5a, b, k** and **5q**) with an *N,N*-dimethylamino group and compounds (**5c** and **5r**) with pyrrolidine group showed potent antiarrhythmic activity, while, except for **5m**, compounds (**5d—g**, **5j**, **5n—p** and **5s**) with morpholino, piperidino, 4-hydroxypiperidino and 4-methylpiperazino groups showed a tendency to reduce the activity. In this series, **5i** alone induced chronic arrhythmia, and this is assumed to be a side effect caused by the high dose (7.5 mg/kg, i.v.). Finally, in the series of compounds (**8a—e**) with a 2-oxoethylamino moiety on the 5-position of the benzothiadiazepine skeleton, antiarrhythmic activity was almost unvaried by the kind of substituents on the 2- and 5-positions of the benzothiadiazepine skeleton. Although all of the compounds (**8a—e**) showed antiarrhythmic activity, **8b** was the most active compound. In conclusion, we think that the derivatives with a 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-dioxide skeleton have the potential to make a novel class I antiarrhythmic agent. On the basis of the biological results, further investigation for 2,3-dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-dioxide derivatives as antiarrhythmic agents is now continuing.

Experimental

All melting points were recorded with a Yanagimoto micromelting point apparatus and are uncorrected. Spectral data were as follows: infrared (IR) spectra with a Hitachi 260-50 spectrophotometer; mass spectra (MS) with a JEOL LMS-01G-2 spectrometer; proton nuclear maganetic resonance (^{1}H-NMR) spectra with JEOL JMX-FX 100 spectrometer (using tetramethylsilane as the internal standard). Chemical shifts of ^{1}H-NMR signals are given in δ values (ppm). Elemental analysis was carried out with a Yanagimoto C H N Corder MT-2 analyzer.

***N*-(2-Nitrobenzenesulfonyl)glycine (2)**[7] Title compound **2** was prepared from **1** (25.0 g) with glycine (10.0 g) according to the known method. Yield 25.0 g (97.1%), mp 160—161 °C (lit.[7] mp 160 °C).

2,3-Dihydro-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-Dioxide (3) Zinc powder (40 g) was added to a solution of **2** (23 g) in acetic acid (40 ml) over a period of 1 h at 70 °C. The reaction mixture was stirred for 7 h under refluxing and during reflux a catalytic amount of anhydrous zinc chloride (**4g**) was added in several portions. After standing overnight, the reaction mixture was filtered and then the filtrate was evaporated under reduced pressure to give an oily residue, which was triturated with ice-water. The resulting precipitate was collected by filtration, followed by recrystallization from ethanol to give **3** (8.0 g, 42.7%), mp 218—219 °C. MS *m/z*: 212 (M^+). *Anal.* Calcd for $C_8H_8N_2O_3S$: C, 45.28; H, 3.80; N, 13.20. Found: C, 45.21; H, 3.78; N, 13.23.

2,3-Dihydro-2-methyl-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-Dioxide (4a) Methyl iodide (6.0 g) was added to a mixture of **3** (5.0 g) and potassium carbonate (2.0 g) in DMF (50 ml). After stirring for 20 h at room temperature, the reaction mixture was evaporated under reduced pressure and then the residual oil was acidified with 1 N HCl. The resulting precipitate was collected by filtration, followed by recrystallization from ethanol to give **4a** (4.0 g, 75.0%), mp 214—125 °C. IR (KBr): 1675 (CO), 1340, 1170 (SO_2) cm^{-1}. MS *m/z*: 226 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 2.71 (3H, s), 4.23 (2H, s), 7.10—7.90 (4H, m), 10.64 (1H, br s). *Anal.* Calcd for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.46; N, 12.38. Found: C, 47.68; H, 4.48; N, 12.15. Compounds **4b**, **4c** and **4d** were prepared from **3** with the appropriate alkyl halide in the same manner as described for **4a**. **4b**: yield 84%, mp 141—142 °C. IR (KBr): 1640 (CO), 1340, 1150 (SO_2) cm^{-1}. MS *m/z*: 362 (M^+). *Anal.* Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.72. Found: C, 59.65; H, 4.65; N, 9.20. **4c**: yield 68%, mp 174—176 °C. IR (KBr): 1660 (CO), 1340, 1160 (SO_2) cm^{-1}. MS *m/z*: 332 (M^+). *Anal.* Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.92; H, 5.06; N, 8.40. **4d**: yield 95%, mp 201—202 °C. IR (KBr): 1680 (CO), 1340, 1170 (SO_2) cm^{-1}. *Anal.* Calcd for $C_{15}H_{13}ClN_2O_3S$: C, 53.49; H, 3.89; N, 8.32. Found: C, 53.63; H, 3.83; N, 8.33.

2,3-Dihydro-5-[2-(*N,N*-dimethylamino)ethyl]-2-methyl-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-Dioxide Maleate (5a) Compound **4a** (0.5 g) was gradually added to a suspension of sodium hydride (about 60%, in oil) (0.12 g) in DMF (30 ml) under ice-cooling. The reaction mixture was stirred for 2 h at room temperature and then 2-(*N,N*-dimethylamino)ethyl chloride (0.7 g) [obtained by treatment of 2-(*N,N*-dimethylamino)ethyl chloride hydrochloride with 10% NaOH solution] was added to the whole mixture. After stirring for 5 h at 60 °C, the reaction mixture was evaporated under reduced pressure and the resulting residue was extracted with chloroform (30 ml × 2). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The obtained oily product was

purified by chromatography on a silica gel column with chloroform–ethanol (10 : 1) as an eluent to give the free base of **5a** (0.49 g), which converted into the maleate (**5a**) (0.5 g, 55%) by th treatment with maleic acid in ether solution, mp 159—160 °C. Other physical and spectral data are listed in Tables I and II. Compounds **5b—s** were prepared from the corresponding **4a—d** with the appropriate aminoalkyl halide in the same manner as described for **5a**. Their physical and spectral data are listed in Tables I and II.

2,3-Dihydro-5-(2,3-epoxypropyl)-2-methyl-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-Dioxide (6a) Compound **4a** (1.0 g) was gradually added to a suspension of sodium hydride (about 60% in oil) (0.26 g) in DMF (20 ml) under ice-cooling. After stirring for 1 h at room temperature, epichlorohydrin (0.5 g) and a catalytic amount of sodium iodide were added to the whole mixture. After stirring for 3 d at room temperature, the reaction mixture was evaporated under reduced pressure and the resulting residue was extracted with chloroform (30 ml × 2). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The obtained crude product was purified by chromatography on a silica gel column with chloroform–ethanol (20 : 1) as an eluent, followed by recrystallization from ethanol to give **6a** (0.6 g, 48%), mp 141—142 °C. MS *m/z*: 282 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.55—2.65 (1H, m), 2.80—2.95 (1H, m), 2.74 (3H, s), 3.20—3.60 (3H, m), 4.47 (2H, q, J=6.0 Hz), 7.30—8.00 (4H, m). *Anal.* Calcd for $C_{12}H_{14}N_2O_4S$: C, 51.05; H, 5.00; N, 9.92. Found: C, 50.89; H, 5.02; N, 9.71. Compound **6b** was prepared from **4c** with epichlorohydrin in the same manner as described for **6a**. **6b**: yield 51%. Colorless oil. MS *m/z*: 388 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 2.90—3.60 (2H, m), 3.30 (3H, s), 3.72 (3H, s), 3.90—4.20 (3H, m), 6.85 (2H, d, J=6.0 Hz), 7.20 (2H, d, J=6.0 Hz), 7.20—8.00 (4H, m).

5-(3-*tert*-Butylamino-2-hydroxypropyl)-2,3-dihydro-2-methyl-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-Dioxide Maleata (7a) An excess of *tert*-butylamine (1 ml) was added to a solution of **6a** (0.15 g) in dichloromethane (5 ml). After stirring for 24 h under reflux, the reaction mixture was evaporated under reduced pressure and then the resulting residue was extracted with chloroform (20 ml × 2). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The obtained oily product was purified by chromatography on a silica gel column with chloroform–ethanol (10 : 1) as an eluent to give the free base of **7a** (0.23 g), which converted into the maleate (**7a**) (0.12 g, 48%) by the treatment with maleic acid in ethanol solution, mp 181—182 °C. The other physical and spectral data are listed in Tables III and IV. Compounds **7b—d** were prepared from the corresponding **6a** and **6b** with appropriate amines in the same manner as described for **7a**. Their physical and spectral data are listed in Tables III and IV.

2,3-Dihydro-2-methyl-5-[2-oxo-2-(morpholin-4-yl)ethyl]-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-Dioxide (8b) Sodium hydride (about 60%, in oil) (0.15 g) was added to a solution of **4a** (0.5 g) in DMF (5 ml) in a several portions at room temperature. After stirring for 0.5 h at 50 °C, *N*-chloroacetylmorpholine[9] (0.5 g) was added to the whole mixture at room temperature. After further stirring for 2 h at 50 °C, the reaction mixture was poured into ice-water (50 ml) and extracted with ethyl acetate (30 ml × 2). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The resulting residue was purified by chromatography on silica gel column with chloroform–ethanol (20 : 1) as an eluent, followed by recrystallization from dichloromethane–isopropyl ether to give **8b** (0.51 g, 65%), mp 182—183 °C. Compounds **8a**, **8c** and **8d** were prepared from the corresponding **4a** and **4c** with the appropriate chloroacetyl derivatives in the same manner as described for **8b**. The physical and spectral data of **7** and **8** are listed in Tables III and IV.

***tert*-Butyl 2,3-Dihydro-2-(4-methoxybenzyl)-4-oxo-1,2,5-benzothiadiazepine-5-acetate 1,1-Dioxide (9)** Title compound was prepared from **4c** (2.5 g) with *tert*-butyl bromoacetate (1.92 g) in the same manner as described for **8b**. The obtained crude oil was purified by chromatography on silica gel column with chloroform–ethyl acetate (9 : 1) as an eluent, followed by recrystallization from chloroform–*n*-hexane to give **9** (2.7 g, 79%). mp 126—127 °C. MS *m/z*: 446 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s), 3.32 (2H, s), 3.77 (3H, s), 4.24 (2H, s), 4.31 (2H, s), 6.82 (2H, d, J=9.0 Hz), 7.20 (2H, d, J=9.0 Hz), 7.20—8.00 (4H, m). *Anal.* Calcd for $C_{22}H_{26}N_2O_6S$: C, 59.18; H, 5.87; N, 6.27. Found: C, 59.50; H, 5.74; N, 6.32.

2,3-Dihydro-2-(4-methoxybenzyl)-4-oxo-1,2,5-benzothiadiazepine-5-acetic Acid (10) Compound **9** (2.55 g) was added to a solution of 1 N HCl (15 ml) in acetic acid (15 ml). After stirring for 0.5 h at 110 °C, the reaction mixture was cooled to room temperature and the resulting precipitate was collected by filtration, washed with water, followed by recrystallization from dichloromethane–isopropyl ether to give **10** (1.77 g, 79%), mp 171—173 °C. MS *m/z*: 390 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 3.34 (2H, s), 3.72 (3H, s), 4.20 (2H, s), 4.34 (2H, s), 6.88 (2H, d, J=9.0 Hz), 7.25 (2H, d, J=9.0 Hz), 7.30—7.90 (4H, m), 13.05 (1H, br s). *Anal.* Calcd for $C_{18}H_{18}N_2O_6S$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.38; H, 4.71; N, 7.14.

2,3-Dihydro-2-(4-methoxybenzyl)-5-[2-oxo-2-(4-methylpiperazin-1-yl)-ethyl]-1,2,5-benzothiadiazepin-4(5*H*)-one 1,1-Dioxide (8e) DCC was added to a solution of **10** (0.4 g) and *N*-methylpiperazine (0.2 g) in dichloromethane (10 ml). After stirring for 2 d at room temperature, the resulting precipitate was filtered off and the filtrate was evaporated under reduced pressure. The obtained pale yellowish oil was purified by chromatography on silica gel column with chloroform–methanol (8 : 1) as an eluent, followed by recrystallization from dichloromethane–isopropyl ether to give **8e** (0.16 g, 33.0%), mp 93—95 °C.

Antiarrhythmic Activity[8] Male Dunkin–Hartley guinea pigs (300—500 g, 5 guinea pigs/group) were used to determine antiarrhythmic activity of the test compound. A test compound at a dose of 7.5 mg/kg or vehicle (0.5% PEG 600 in saline or saline, 1.5 mg/kg) were injected intravenously during a period of 2 min, to urethane-anesthetized guinea pigs. Three minutes after cessation of drug injection, ouabain solution (7.5 μg/ml) was infused at an appropriate rate (approximately 0.33 μg/min) into the femoral vein. The dose of ouabain required to cause ventricular extrasystole, ventricular flutter or fibrillation and cardiac arrest were determined as indicated by ECG (lead II) recording. The activity is expressed as follows:

$$\text{increasing } (\Delta\%) = \frac{A-B}{B} \times 100$$

A: ouabain volume required to cause an arrhythmia at the test compound injection

B: ouabain volume required to cause an arrhythmia at the vehicle injection

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