Synthesis and Antiarrhythmic Activity of 2,2-Dialkyl-1′-(*N*-substituted aminoalkyl)-spiro-[chroman-4,4′-imidazolidine]-2′,5′-diones

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A novel series of 2,2-dialkyl-1′-(*N*-substituted aminoalkyl)-spiro-[chroman-4,4′-imidazolidine]-2′,5′-diones was synthesized and evaluated for antiarrhythmic activity in chloroform- or/and aconitine-induced ventricular arrhythmia in mice. Among these compounds, (−)-6-chloro-2,2-dimethyl-1′-[3-(4-hydroxypiperidino)propyl]-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione was found to be more effective than reference agents and was selected for further development.

Keywords antiarrhythmic activity; 2,2-dialkyl-1′-(*N*-substituted aminoalkyl)-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione; chloroform-induced arrhythmia; acontitine-induced arrhythmia; (−)-6-chloro-2,2-dimethyl-1′-[3-(4-hydroxypiperidino)propyl]-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione; spirohydantoin

Quinidine, lidocaine and disopyramide, which are widely used for the treatment of ventricular arrhythmias, have not been very satisfactory because they produce several side effects like anticholinergic activity.[1] Therefore, we have tried to develop a novel antiarrhythmic agent which could be more effective and exhibit pure class I[2] antiarrhythmic activity. After some studies of lead generation, we found the 2,2-dialkyl-1′-(*N*-substituted aminoalkyl)-spiro-[chroman-4,4′-imidazolidine]-2′,5′-diones having strong antiarrhythmic activity.

We report here our studies on the synthesis and the antiarrhythmic activity of compounds **3**—**47**.

Chemistry The synthetic routes in this study are outlined in Chart 1. As shown, we have developed two general routes, method A (two steps) and B (one step). In method A, the spirohydantoins **1**[3] were derived to the corresponding ω-bromoalkyl derivatives **2a**—**o** with 1,ω-dibromoalkane in the presence of sodium hydride in dimethylformamide (DMF), followed by amination with various amines, HNR_2R_3, to the target compounds. On the other hand, in method B the spirohydantoins **1** were treated with *N*,*N*-disubstituted aminoalkylhalide in the presence of potassium carbonate to afford the target compounds directly. Compound **40** was obtained by acetylation of **33** with acetic anhydride and pyridine. Tables I and II show physical properties of the bromointermediates **2a**—**o** and the target compounds **3**—**47**, respectively.

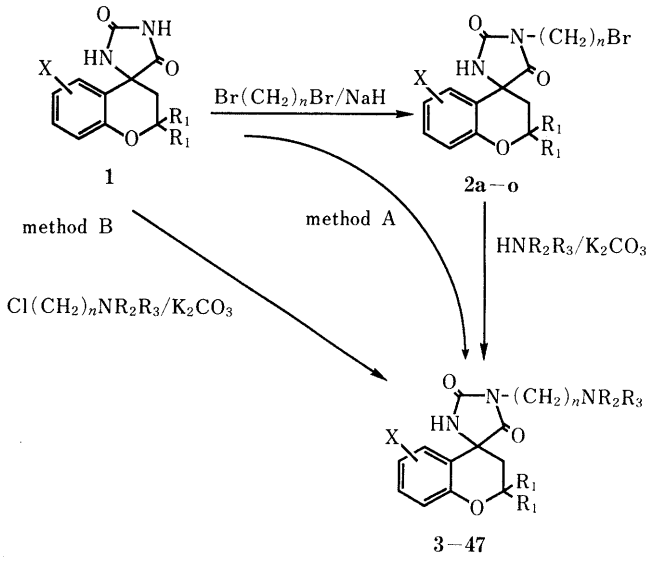


Chart 1

The optically active compounds, **46** [(+)-**42**] and **47** [(−)-**42**] were synthesized from the optically active hydrantoin **1**. Resolution of the racemic hydrantoin **1** (*dl*-6-chloro-2,2-dimethyl-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione) was accomplished by recrystallization of the *N*-methyl cinchonidum salt and the brucine salt[4] to give (+)-hydantoin **1** and (−)-hydantoin **1**, respectively. (+)- and (−)-Hydantoin **1** were converted into **46** and **47** followed by method A, respectively.

Results and Discussion

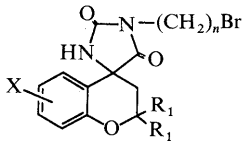
The antiarrhythmic activities of compounds **3**—**47**, quinidine and disopyramide were examined with chloroform- and/or aconitine-induced arrhythmia in male mice[5,6] by oral administration. The results are shown in Table II. The acute toxicity (LD_{50}) tests of quinidine, disopyramide, **46** and **47** were also carried out in male mice by oral administration. Table III shows the ratio of LD_{50} to the effective dose of aconitine-induced arrhythmia of these compounds.

Quinidine showed only weak activity in chloroform- and aconitine-induced arrhythmia, whereas disopyramide showed moderate activity. Most of the new compounds were more potent than quinidine, and quite a few compounds were more potent than disopyramide.

The activity tended to become strong when the substitutent on the benzene ring was an electron withdrawing group (**3** *vs.* **5**; **4** *vs.* **6**, **10**; **36** *vs.* **33**, **42**), and the position of the substituent was more effective on the 6-position than on the 8-position (**5** *vs.* **13**; **37** *vs.* **38**). With regard to the effect of the *N*-substituted amino group NR_2R_3, dimethylamino, diethylamino, piperidino, 4-hydroxypiperidino and its relative derivatives showed potent activity. A dimethyl group was suitable for the substituents on the 2-position. When the effect of chain length (*n*) on antiarrhythmic activity was tested in aconitine-induced arrhythmia in compounds **41**—**45**, the most suitable length was $n=3$.

As compound **42** showed potent and long-lasting activity, it was resolved to test the antiarrhythmic activity and the acute toxicity (LD_{50}). The effective dose (ED) and the ratio of LD_{50} to it of each optically active form were compared with those of quinidine and disopyramide. Even its compound **46** was superior to quinidine and disopyr-

TABLE I. Physical Properties of 2,2-Dialkyl-1′-(ω-bromoalkyl)-spiro-[chroman-4,4′-imidazolidine]-2′,5′-diones **2a**—**o**[a]



Compd. No.	X	R_1	n	Yield (%)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
2a	H	H	3	72	83—84 (Et_2O–hexane)	$C_{14}H_{15}BrN_2O_3$	49.58 (49.54)	4.48 4.43	8.26 8.45)
2b	6-F	Me	2	45	201—203 (AcOEt–hexane)	$C_{15}H_{16}BrFN_2O_3$	48.57 (48.73)	4.35 4.37	7.55 7.51)
2c	6-F	Me	3	72	190—192 (AcOEt–hexane)	$C_{16}H_{18}BrFN_2O_3$	49.89 (49.63)	4.71 4.57	7.27 7.15)
2d	6-F	Me	4	70	144—146 (AcOEt–hexane)	$C_{17}H_{20}BrFN_2O_3$	51.14 (51.38)	5.05 5.16	7.02 7.01)
2e	6-F	H	3	62	109—110 (Et_2O–hexane)	$C_{14}H_{14}BrFN_2O_3$	47.08 (47.33)	3.95 4.09	7.84 8.10)
2f	6-Cl	H	3	66	181—183 (Et_2O–hexane)	$C_{14}H_{14}BrClN_2O_3$	45.01 (45.26)	3.78 3.80	7.50 7.62)
2g	6-Cl	Me	2	38	171—173 (AcOEt–hexane)	$C_{15}H_{16}BrClN_2O_3$	46.48 (46.72)	4.16 4.20	8.06 7.77)
2h	6-Cl	Me	3	72	192—194 (CH_2Cl_2–hexane)	$C_{16}H_{18}BrClN_2O_3$	47.84 (48.10)	4.52 4.53	6.97 7.02)
2i	6-Cl	Me	4	58	183—186 (Et_2O–hexane)	$C_{17}H_{22}BrClN_2O_3$	49.12 (49.37)	4.85 4.89	6.74 6.57)
2j	6-Cl	Me	5	83	181—183 (Et_2O–hexane)	$C_{18}H_{22}BrClN_2O_3$	50.31 (50.19)	5.16 5.17	6.52 6.48)
2k	6-Cl	Me	6	61	121—122 (Et_2O–hexane)	$C_{19}H_{24}BrClN_2O_3$	51.42 (51.37)	5.45 5.37	6.31 6.39)
2l	6-Cl	Et	3	54	171—173 (AcOEt–hexane)	$C_{18}H_{22}BrClN_2O_3$	50.31 (50.27)	5.16 5.08	6.52 6.51)
2m	8-Cl	H	3	70	160—162 (Et_2O–hexane)	$C_{14}H_{14}BrClN_2O_3$	45.01 (45.31)	3.77 3.86	7.50 7.63)
2n	6-NO_2	Me	3	70	236—237 (AcOEt–Et_2O)	$C_{16}H_{18}BrN_3O_5$	46.62 (46.49)	4.40 4.31	10.19 10.22)
2o	7-OMe 8-Me	Me	3	73	211—213 (AcOEt–hexane)	$C_{18}H_{23}BrN_2O_3$	52.56 (52.27)	5.64 5.60	6.81 6.54)

a) Structures of all compounds were confirmed by NMR spectra. For typical example, see Experimental.

amide in the effectiveness (LD_{50}/ED). Moreover, the antiarrhythmic activity of **47** was 8 and 30 times more potent than disopyramide and quinidine, respectively, and its effectiveness was 4 times higher than disopyramide, and 10 times that of quinidine.

Conclusion

We could find a promising compound, **47**, in the SAR (structure–activity relationships) study of spirohydantoin derivatives. Compound **47** was superior to the reference agents in its effectiveness. After more extensive pharmacological and toxicological evaluation, **47** was selected as a clinical candidate.

Experimental

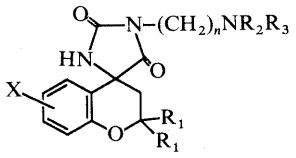
Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured on a JEOL-JNM-FX90Q (90 MHz) instrument. Chemical shifts are given in ppm using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet. Column chromatography was performed on silica gel (Merck, particle size 0.063—0.200 mm for normal chromatography). Elemental analysis were performed at the Analytical Chemistry Section of Eisai Tsukuba Research Laboratories. The yields were not optimized.

General Procedure of Method A. 2,2-Dimethyl-6-fluoro-1′-(3-bromopropyl)-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (2c) Sodium hydride [1.0 g (60% suspension in mineral oil), 25 mmol] was added to a solution of 2,2-dimethyl-6-fluoro-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (6.6 g, 25 mmol)[3] and 1,3-dibromopropane (10.1 g, 50 mmol) in DMF (70 ml) over a period of 5 min at room temperature. The mixture was stirred at room temperature for 2 h and poured into ice-water. After extraction with AcOEt, the organic layer was washed with water, dried over $MgSO_4$ and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (5% EtOH–CH_2Cl_2) to obtain **2c** (6.9 g, 72%). mp 190—192 °C (AcOEt–hexane). *Anal.* Calcd for $C_{16}H_{18}BrFN_2O_3$: C, 49.87; H, 4.71; N, 7.27. Found: C, 49.63; H, 4.59; N, 7.15. NMR ($CDCl_3$) δ: 1.32 (3H, s), 1.50 (3H, s), 2.02 (1H, d, J=16 Hz), 2.24 (2H, q, J=8 Hz), 2.60 (1H, d, J=16 Hz), 3.40 (2H, t, J=8 Hz), 3.74 (2H, t, J=8 Hz), 6.36 (1H, s), 6.45—7.10 (3H, m).

2,2-Dimethyl-6-fluoro-1′-[3-(4-hydroxypiperidino)propyl]-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (33) A mixture of compound **2c** (6.0 g, 15.6 mmol), 4-hydroxypiperidine (3.15 g, 31.2 mmol) and K_2CO_3 (4.31 g, 31.2 mmol) in DMF (70 ml) was stirred at 80 °C for 5 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and then evaporated under reduced pressure. The residue was recrystallized from EtOH–AcOEt to give **33** (5.85 g, 90%). mp 211—213 °C. *Anal.* Calcd for $C_{21}H_{38}FN_3O_4$: C, 62.20; H, 6.96; N, 10.36. Found: C, 61.92; H, 7.01; N, 10.25. NMR ($CDCl_3$) δ: 1.32 (3H, s), 1.52 (3H, s), 1.5—2.9 (15H, m), 3.6 (2H, t, J=8 Hz), 3.45—3.8 (1H, m), 6.1 (1H, br), 6.5—7.1 (3H, m).

General Procedure of Method B. 8-Chloro-1′-(3-dimethylaminopropyl)-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (13) Sodium hydride [240

TABLE II. Physical Properties and Antiarrythmic Activities of 2,2-Dialkyl-1′-(*N*-substituted aminoalkyl)-spiro-[chroman-4,4′-imidazolidine]-2′,5′-diones **3**—**47**[a]



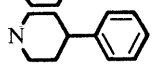
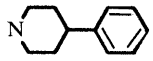
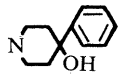
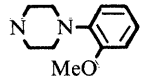
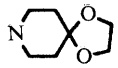
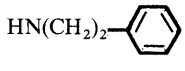
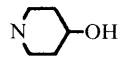
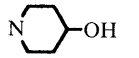
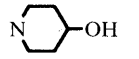
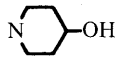
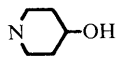
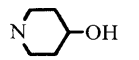
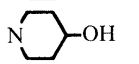
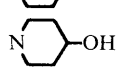
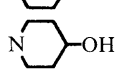
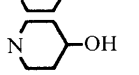
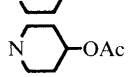
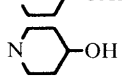
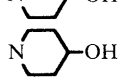
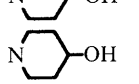
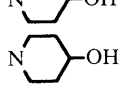
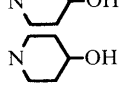
Compd. No.	X	R_1	*n*	NR_2R_3	Yield (%) (Method)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	Antiarrhymic activity[b] Chloroform aconitine (mg/kg, *p.o.*)
3	H	H	3	$N(Me)_2$	63 (B)	118—119 (Et_2O–hexane)	$C_{16}H_{21}N_3O_3$	63.35 (63.31)	6.98 6.91	13.85 13.81)	>100
4	H	Me	3	$N(Me)_2$	41 (B)	135—137 (Et_2O–hexane)	$C_{18}H_{25}N_3O_3$	65.23 (65.31)	7.60 7.72	12.68 12.69)	>100
5	6-Cl	H	3	$N(Me)_2$	64 (B)	131—133 (Et_2O–hexane)	$C_{16}H_{20}ClN_3O_3$	56.89 (56.78)	5.97 5.82	12.44 12.65)	25
6	6-Cl	Me	3	$N(Me)_2$	55 (B)	269—270 (EtOH–Et_2O)	$C_{18}H_{24}ClN_3O_3$ ·HCl	53.73 (53.84)	6.26 6.19	10.44 10.35)	12.5
7	6-F	Me	2	$N(Me)_2$	14 (B)	234—235 (EtOH–hexane)	$C_{17}H_{22}FN_3O_3$ ·HCl	54.91 (54.75)	6.23 6.11	11.30 11.21)	100
8	6-F	Me	2	$N(Et)_2$	57 (B)	154—156 (Et_2O–hexane)	$C_{19}H_{26}FN_3O_3$	62.79 (62.74)	7.21 7.28	11.56 11.49)	25
9	6-F	Me	2	$N(iso\text{-}Pr)_2$	45 (B)	122—124 (Et_2O–hexane)	$C_{21}H_{30}FN_3O_3$	64.43 (64.43)	7.72 7.82	10.73 10.67)	50
10	6-F	Me	3	$N(Me)_2$	45 (B)	166—169 (AcOEt–hexane)	$C_{18}H_{24}FN_3O_3$	56.17 (56.23)	6.55 6.51	10.92 10.75)	12.5
11	6-F	Me	3	$N(Et)_2$	30 (B)	99—100 (EtOH–hexane)	$C_{20}H_{28}FN_3O_3$	63.64 (63.43)	7.48 7.53	11.13 11.13)	50
12	6-F	Me	3	$N(n\text{-}Pr)_2$	49 (A)	235—237 (EtOH–Et_2O)	$C_{22}H_{32}FN_3O_3$ ·HCl	59.79 (59.57)	7.30 7.25	9.51 9.27)	50
13	8-Cl	H	3	$N(Me)_2$	79 (B)	158—159 (EtOH)	$C_{16}H_{20}ClN_3O_3$	56.89 (56.84)	5.97 5.93	12.44 12.39)	>100
14	6-Br	Me	3	$N(Me)_2$	65 (B)	277—279 (MeOH–Et_2O)	$C_{18}H_{24}BrN_3O_3$	48.50 (48.29)	5.65 5.73	9.43 9.21)	100
15	6-Cl	Et	3	$N(Me)_2$	71 (B)	203—205 (MeOH–Et_2O)	$C_{20}H_{28}ClN_3O_3$ ·HCl	60.98 (60.73)	7.16 7.08	10.67 10.62)	50
16	6-Cl	*n*-Pr	3	$N(Me)_2$	75 (B)	112—115 (EtOH–Et_2O)	$C_{22}H_{32}ClN_3O_3$ ·HCl	57.64 (57.59)	7.26 7.31	9.17 9.25)	>100
17	6-Cl	$(CH_2)_5$	3	$N(Me)_2$	35 (B)	230—231 (EtOH–Et_2O)	$C_{21}H_{28}ClN_3O_3$ ·HCl	57.01 (56.95)	6.38 6.27	9.50 9.61)	50
18	6-F	Me	3		79 (A)	256—258 (EtOH–hexane)	$C_{21}H_{28}FN_3O_3$ ·HCl	59.22 (59.15)	6.86 6.78	9.87 10.01)	25
19	6-F	H	3		35 (A)	175—177 (EtOH–Et_2O)	$C_{25}H_{28}FN_3O_3$ ·HCl·1/2H_2O	62.16 (62.39)	6.26 6.29	8.70 8.57)	50
20	6-F	Me	3		23 (A)	131—132 (Et_2O–hexane)	$C_{27}H_{32}FN_3O_3$	69.66 (69.50)	6.93 6.91	9.03 8.93)	100
21	6-F	H	3		31 (A)	169—172 (EtOH–Et_2O)	$C_{27}H_{32}FN_3O_4$ ·HCl	62.60 (62.57)	6.42 6.51	8.11 8.23)	100
22	6-F	Me	3		43 (A)	235—238 (EtOH–Et_2O)	$C_{20}H_{26}FN_3O_4$ ·HCl	56.14 (55.94)	6.13 6.40	9.82 9.54)	100
23	6-F	Me	3	$NH(CH_2)_3OH$	34 (A)	138—139 (AcOEt–hexane)	$C_{19}H_{26}FN_3O_4$	60.14 (59.87)	6.91 6.85	11.07 10.91)	100
24	6-F	Me	3	$N(CH_2CH_2OH)_2$	16 (A)	198—200 (EtOH–Et_2O)	$C_{20}H_{30}FN_3O_5$ ·HCl·H_2O	53.38 (53.18)	7.18 6.98	9.34 9.15)	100
25	5-F	Me	3		50 (A)	195—197 (EtOH–Et_2O)	$C_{27}H_{33}FN_4O_4$ ·HCl	60.84 (60.75)	6.43 6.33	10.51 10.37)	50
26	6-F	Me	3		44 (A)	154—156 (AcOEt–hexane)	$C_{21}H_{26}FN_3O_4$	62.52 (62.37)	6.50 6.46	10.42 10.32)	25
27	6-F	Me	3		80 (A)	146—148 (AcOEt–hexane)	$C_{23}H_{30}FN_3O_4$	61.73 (61.57)	6.76 6.91	9.39 9.27)	25
28	6-Cl	Me	3		57 (A)	173—175 (EtOH–Et_2O)	$C_{21}H_{29}ClN_4O_3$	59.92 (59.90)	6.94 6.90	13.31 13.21)	>100
29	6-Cl	Me	3		42 (A)	129—131 (AcOEt–hexane)	$C_{23}H_{26}ClN_3O_3$	64.56 (64.35)	6.12 6.33	9.82 9.71)	>100

TABLE II. (continued)

Compd. No.	X	R_1	n	NR_2R_3	Yield (%) (Method)	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	Antiarrhymic activity[b] Chloroform aconitine (mg/kg, *p.o.*)	
30	H	H	3		45 (A)	150—152 (Et_2O–hexane)	$C_{19}H_{25}N_3O_4$	63.49 (63.53	7.01 7.15	11.69 11.66)	100	
31	6-F	Me	2		40 (A)	169—170 (EtOH–hexane)	$C_{20}H_{26}FN_3O_4$	61.37 (61.34	6.70 6.80	10.73 10.56)	>100	80
32	6-F	H	3		72 (A)	204—206 (AcOEt–hexane)	$C_{19}H_{24}FN_3O_4$	60.46 (60.19	6.40 6.45	11.13 11.01)	50	
33	6-F	Me	3		90 (A)	211—213 (Et_2O–hexane)	$C_{21}H_{28}FN_3O_4$	62.20 (61.92	6.96 7.01	10.36 10.25)	25	5
34	6-F	Me	4		80 (A)	186—187 (EtOH–hexane)	$C_{22}H_{30}FN_3O_4$ ·HCl	57.96 (57.77	6.85 6.84	9.22 9.06)	50	
35	6-NO_2	Me	3		47 (A)	173—175 (CH_2Cl_2–hexane)	$C_{21}H_{28}N_4O_6$	58.32 (58.02	6.53 6.53	12.96 12.96)	100	
36	7-OMe 8-Me	Me	3		86 (A)	156—158 (EtOH–Et_2O)	$C_{23}H_{33}N_3O_5$	64.01 (63.98	7.71 7.59	9.74 9.80)	100	
37	8-Cl	H	3		54 (B)	144—146 (EtOH–Et_2O)	$C_{19}H_{24}ClN_3O_4$	57.94 (57.71	6.14 6.08	10.67 10.51)	>100	
38	6-Cl	H	3		75 (A)	219—221 (EtOH–Et_2O)	$C_{19}H_{24}ClN_3O_4$	57.94 (57.67	6.14 6.12	10.67 10.60)	100	
39	6-Cl	Et	3		54 (A)	174—177 (Et_2O–hexane)	$C_{23}H_{32}ClN_3O_4$	61.39 (61.29	7.12 7.22	9.34 9.26)	25	
40	6-F	Me	3		65 (from **33**)	216—219 (EtOH–Et_2O)	$C_{23}H_{30}FN_3O_5$ ·HCl	57.08 (56.90	6.46 6.27	8.68 8.63)	25	
41	6-Cl	Me	2		75 (A)	159—161 (Et_2O–hexane)	$C_{20}H_{26}ClN_3O_4$	58.89 (58.82	6.43 6.40	10.30 10.54)	>100	
42	6-Cl	Me	3		93 (A)	154—156 (EtOH–AcOEt)	$C_{21}H_{28}ClN_3O_4$	59.78 (59.77	6.69 6.42	9.96 9.89)	25	5
43	6-Cl	Me	4		53 (A)	87—89 (Et_2O–hexane)	$C_{22}H_{30}ClN_3O_4$	60.61 (60.57	6.94 6.75	9.64 9.58)		10
44	6-Cl	Me	5		47 (A)	136—139 (AcOEt–hexane)	$C_{23}H_{32}ClN_3O_4$	61.39 (61.25	7.17 7.27	9.34 9.35)		40
45	6-Cl	Me	6		40 (A)	131—134 (AcOEt–hexane)	$C_{24}H_{34}ClN_3O_4$	62.13 (62.18	7.39 7.28	9.06 9.01)		40
46	(+)-**42**				(A)	165—167 (AcOEt–hexane)						40
47	(−)-**42**				(A)	164—166 (AcOEt–hexane)						5
Quinidine sulfate											>100	160
Disopyramide phosphate											50	40

a) Structures of all compounds were confirmed by NMR spectra. For typical example, see Experimental. *b*) For the antiarrhythmic activity, see Experimental.

TABLE III. The Ratio of Acute Toxicity (LD_{50}) to Effective Dose (ED) of Aconitine-Induced Arrhythmia in Mice

	ED (mg/kg, *p.o.*)	LD_{50} (mg/kg, *p.o.*)	LD_{50}/ED
Quinidine sulfate	160	700	4.3
Disopyramide phosphate	40	400	10
46	40	700	17.5
47	5	200	40

mg (60% suspension in mineral oil), 6 mmol] was added to a solution of 8-chloro-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (1.52 g, 6 mmol)[3] at 5 °C. After stirring for 10 min, a solution of 3-dimethylaminopropyl chloride (802 mg, 6.6 mmol) in DMF (3 ml) was added dropwise to the mixture at room temperature over a period of 10 min. The reaction mixture was stirred at 80—90 °C for 5 h, poured into ice-water and then extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (5% EtOH–CH_2Cl_2) to obtain **13** (1.6 g, 79%). mp 158—159 °C (EtOH). *Anal.* Calcd for $C_{16}H_{20}ClN_3O_3$: C, 56.89; H, 5.97; N, 12.44. Found: C, 56.84; H, 5.93; N, 12.39. NMR ($CDCl_3$) δ: 1.6—1.96 (2H, m), 2.14 (6H, s), 2.0—2.44 (4H, m), 3.58 (2H, t, J=8 Hz), 4.18—4.44 (1H, m), 4.64—4.98 (1H, m), 6.16 (1H, s), 6.6—7.02 (2H, m), 7.16—7.36 (1H, m).

6-Fluoro-2,2-dimethyl-1′-[3-(4-acetoxypiperidino)propyl]-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (40) A mixture of **33** (1.5 g) and Ac_2O (2 ml) in pyridine (20 ml) was stood overnight at room temperature and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (5% EtOH–CH_2Cl_2) to give **40** (1.4 g, 84%). NMR ($CDCl_3$) δ: 1.3 (3H, s), 1.5 (3H, s), 1.5—2.8 (14H, m), 2.0 (3H, s), 3.6 (2H, t, J=8 Hz), 4.6—4.9 (1H, m), 6.3 (1H, br), 6.5—7.0 (3H, m). The compound **40** (1.4 g) was converted into hydrochloride salt by ethanolic HCl solution and the salt was recrystallized from EtOH–Et_2O to give the salt (1.2 g). mp 216—219 °C. *Anal.* Calcd for $C_{23}H_{30}FN_3O_5$·HCl: C, 57.08; H, 6.46; N, 8.68. Found: C, 56.90; H, 6.27; N, 8.63.

(+)-6-Chloro-2,2-dimethyl-1′-[3-(4-hydroxypiperidino)propyl]-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (46) A solution of *dl*-6-chloro-2,2-dimethyl-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (140 g) in MeOH (3 l) was mixed with a solution of cinconidine methohydroxide (163 g) in MeOH (2 l) and MeOH was distilled off under reduced pressure.

The residue was crystallized from acetone to yield the salt of pure (+)-enantiomer (94 g). The salt was dissolved in water, made acidic with hydrochloric acid and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and then evaporated under reduced pressure. The residue was recrystallized from AcOEt to give (+)-6-chloro-2,2-dimethyl-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (23.8 g). mp 238—239.5 °C. $[\alpha]_D$: +56° (c=1.0, MeOH). The above (+)-enantiomer (12 g) was converted into **46** (9.0 g, 50%) by a similar procedure to that described in method A. mp 165—167 °C (AcOEt–*n*-hexane). $[\alpha]_D$: +35.7° (c=1.0, MeOH). NMR ($CDCl_3$) δ: 1.3 (3H, s), 1.5 (3H, s), 1.5—2.9 (15H, m), 3.64 (2H, t, J=8 Hz), 3.5—3.8 (1H, m), 6.24 (1H, br), 6.8 (1H, d, J=12 Hz), 6.86 (1H, d, J=3 Hz), 7.16 (1H, dd, J=12, 3 Hz).

(−)-6-Chloro-2,2-dimethyl-1′-[3-(4-hydroxypiperidino)propyl]-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (47) A solution of 6-chloro-2,2-dimethyl-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (28.2 g) in MeOH (1 l) was mixed with a solution of brucine·$2H_2O$ (43.1 g) in MeOH (1 l) and MeOH was distilled off under reduced pressure. The residue was recrystallized from MeOH–Et_2O to give the salt of pure (−)-enantiomer. The salt was dissolved in water, made acidic with hydrochloric acid and then extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from AcOEt to give (−)-6-chloro-2,2-dimethyl-spiro-[chroman-4,4′-imidazolidine]-2′,5′-dione (9 g). mp 236—237 °C. $[\alpha]_D$: −55.5° (c=1.0, MeOH). The above (−)-enantiomer (1.4 g) was converted to **47** (0.89 g, 42%) by a similar procedure to that described in method A. mp 164—166 °C (AcOEt–*n*-hexane) $[\alpha]_D$: −35° (c=1.0, MeOH).

Chloroform-Induced Arrhythmia[5] Mice were placed in a device filled with chloroform vapor. After expiring, the ventricular beats were counted from an electrocardiogram. The antiarrhythmic activity of the test compound was determined based on its effect of relieving tachycardia. Groups of three male mice were used to test each compound at doses of 12.5, 25, 50 and 100 mg/kg. The test compounds were administrated to mice orally as an aqueous solution or an acidic aqueous solution 1 h before the treatment with chloroform. An effective dose is defined as the dose that suppressed ventricular tachycardia in all animals out of three mice.

Aconitine-Induced Arrhythmia[6] Ventricular arrhythmia was induced in mice by an intraperitoneal injection of 0.1 mg/kg of aconitine. The tachycardia and ventricular premature beats were determined from an electrocardiogram. The compounds were orally administered 1 h before the aconitine injection. Groups of three male mice were used to test each compound at doses of 5, 10, 20, 40, 80 and 160 mg/kg. An effective dose is defined as the dose that decreased ventricular premature beats to half of that of the control animals.

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