Synthesis and Pharmacological Evaluation in Mice of Halogenated Cannabidiol Derivatives

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Six halogenated derivatives of cannabidiol (CBD, 1) substituted on the aromatic ring at the 3′ and/or 5′ position, 3′-chloro- (2), 3′,5′-dichloro- (3), 3′-bromo- (4), 3′,5′-dibromo- (5), 3′-iodo- (6) and 3′,5′-diiodo-CBD (7) were synthesized and their pharmacological effects of barbiturate-induced sleep prolongation, anticonvulsant effects and locomotor activity were evaluated by intravenous (i.v.) injection in mice. 2 (10 mg/kg, i.v., 69±10 min) significantly prolonged pentobarbital-induced sleeping time by 3.1-fold, compared to control (22±2 min), although other 1 derivatives used did not significantly affect the sleeping time. 2, 4 and 6 (10 mg/kg, i.v.) significantly prolonged hexobarbital-induced sleeping time by 2.0-, 2.0- and 2.3-fold, respectively, compared with control (52±5 min). On the other hand, 1 and all halogenated derivatives did not significantly prolong barbital-induced sleeping time. The monohalogenated derivatives, 2, 4 and 6 were able to prolong pentobarbital and hexobarbital-induced sleeping time, although the dihalogenated derivatives, 3, 5 and 7 did not exhibit a prolongation of the sleeping time. All halogenated derivatives of 1 except for brominated derivatives (2, 3, 6, 7) tended to prolong tonic seizure latency induced by pentylenetetrazol. 1 and its halogenated derivatives did not exhibit any prolongation of seizure latency induced by picrotoxin or strychnine. Maximal electroshock test demonstrated that 1 and 4 exhibited almost the same potency in their anticonvulsant effects, although other 1 derivatives 2, 3, 5, 6 and 7 did not show significant effect up to a dose of 63 mg/kg, i.v. The ED_{50} values (mg/kg, i.v.) of 1 and 4 were 38 and 44, respectively. 1 and 4 also showed anticonvulsant effect in minimal and maximal electroshock-threshold tests. 2, 4 and 6 tended to decrease the total distance (horizontal activity) and number of rearings (vertical activity) of mice, whereas 3, 5 and 7 tended to increase the number of rearings. However, the effects of all derivatives were not statistically significant from the control. 2 and 4 were the most potent derivatives on pharmacological activities among the synthetic cannabinoids examined in the present study. These results indicate that monohalogenation of 1 leads to some modification of the pharmacological profile of CBD.

Key words cannabidiol; halogenated cannabidiol derivative; anticonvulsant; barbiturate-induced sleep prolongation; locomotor activity

Cannabinoids are C_{21} compounds composed of C, H and O, and Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabinol (CBN) and cannabidiol (CBD, **1**) are known as three major cannabinoids in marihuana.[1] In previous studies, we reported synthesis of halogenated Δ^9-THC and CBN derivatives and its pharmacological evaluation in mice.[2] We indicated that these halogenated cannabinoid derivatives had some psychotropic activity in mice, and the pharmacological effects of monohalogenated derivatives of Δ^9-THC and CBN were comparable to those of parent compounds, whereas dihalogenated derivatives were much less active.

1 is known to possess barbiturate-induced sleep prolonging and anticonvulsant effects,[3] although this cannabinoid is devoid of the psychomimetic activity observed in THC. The preclinical studies suggest that **1** is a useful drug in treatment of epilepsy.[4] It is important to know the structure–activity relationship of halogenated cannabinoids for better understanding of cannabinoid effects.

The present study was designed to determine pharmacological effects in mice of halogenated derivatives of **1** on the aromatic ring.

Experimental

1 was isolated and purified from cannabis leaves according to the method of Aramaki *et al.*[5] Its purity used was determined to be at least 98% by gas chromatography. Sodium pentobarbital and sodium hexobarbital were from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan) and pentylenetetrazol (PTZ) and strychnine nitrate were purchased from Aldrich Chem. Co. Inc. (Milwaukee, WI). 18-Crown-6, *m*-chloroperbenzoic acid (MCPBA), picrotoxin and sodium barbital were obtained from Wako Pure Chemical Ind. (Osaka, Japan). All other chemicals and solvents used were of analytical reagent grade.

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-GSX400 Fourier transform (FT)-NMR spectrometer using tetramethylsilane as an internal standard. ^{1}H-NMR chemical shift assignments were based on those of **1** reported previously.[6] The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet and br=broad. The mass spectra (MS) were recorded on a JEOL JMS-SX-102A mass spectrometer.

General Halogenation Procedure We carried out the synthesis of halogenated derivatives (**2**, **3**, **4**, **5**) according to the method of Umemoto *et al.*[7] The synthesis of **6** and **7** followed a method described previously for halogenated derivatives of THC and CBN.[2]

3′-Chloro-CBD (**2**) and 3′,5′-Dichloro-CBD (**3**): **2**; 158 mg from **1** (254 mg 56% yield) as a yellow oil. MS *m/z*: 348 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, $C_{5''}$-H), 1.78 (3H, s, C_{10}-H), 2.58 (2H, t, $C_{1''}$-H), 3.97 (1H, m, C_3-H), 4.41, 4.55 (1H×2, s, C_9-H), 5.54 (1H, br s, C_2-H), 6.31 (1H, s, $C_{5'}$-H). **3**; 170 mg from **1** (1.589 g, 8% yield) as a yellow oil. MS *m/z*: 382 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, $C_{5''}$-H), 1.77 (3H, s, C_{10}-H), 2.83 (2H, t, $C_{1''}$-H), 4.04 (1H, m, C_3-H), 4.42, 4.53 (1H×2, s, C_9-H), 5.46 (1H, br s, C_2-H).

3′-Bromo-CBD (**4**) and 3′,5′-Dibromo-CBD (**5**): **4**; 1.42 g from **1** (1.67 g, 68% yield) as a yellow oil. MS *m/z*: 392 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, $C_{5''}$-H), 1.78 (3H, s, C_{10}-H), 2.59 (2H, t, $C_{1''}$-H), 4.00 (1H, m, C_3-H), 4.41, 4.55 (1H×2, s, C_9-H), 5.54 (1H, br s, C_2-H), 6.33 (1H, s, $C_{5'}$-H). **5**; 247 mg from **1** (380 mg, 54 % yield) as a yellow oil. MS *m/z*: 470 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, $C_{5''}$-H), 1.77 (3H, s, C_{10}-H), 2.92 (2H, t, $C_{1''}$-H), 4.07 (1H, m, C_3-H), 4.41, 4.54 (1H×2, s, C_9-H), 5.46 (1H, br s, C_2-H).

3′-Iodo-CBD (**6**) and 3′,5′-Diiodo-CBD (**7**): **6**; 440 mg from **1** (617 mg, 51% yield) as a yellow oil. MS *m/z*: 440 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, $C_{5''}$-H), 1.81 (3H, s, C_{10}-H), 2.59 (2H, t, $C_{1''}$-H), 3.93 (1H, m, C_3-H),

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4.42, 4.56 (1H×2, s, C_9-H), 5.54 (1H, br s, C_2-H), 6.38 (1H, s, $C_{5'}$-H). **7**; 111 mg from **1** (344 mg, 20% yield) as a yellow oil; MS *m/z*: 566 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, $C_{5''}$-H), 1.78 (3H, s, C_{10}-H), 3.07 (2H, t, $C_{1''}$-H), 4.10 (1H, m, C_3-H), 4.38, 4.55 (1H×2, s, C_9-H), 5.49 (1H, br s, C_2-H).

Animals and Drugs Male ddY mice weighing 20—25 g were obtained from Japan SLC Co. Ltd. (Tokyo, Japan) and used in pharmacological experiments. Before use, mice were fed standard laboratory diet (Oriental Yeast, F-2, Tokyo) and water *ad libitum* for at least one week. All halogenated derivatives of **1** were suspended in physiological saline containing 1% Tween 80. Sodium pentobarbital, sodium hexobarbital, sodium barbital, PTZ, picrotoxin and strychnine were dissolved in saline. All animal experiments were carried out at an ambient temperature of 22±2 °C.

Barbiturate-Induced Sleep Prolongation Each group of 5 to 15 mice was injected with **1** and its halogenated derivatives (5 or 10 mg/kg, intravenous, i.v.) or the vehicle. Sodium pentobarbital (40 mg/kg, intraperitoneal, i.p.), sodium hexobarbital (100 mg/kg, i.p.) and sodium barbital (300 mg/kg, i.p.) were injected to mice 20 min after injection of cannabinoids. The loss of righting reflex was used as an index of sleep.[8] Control mice were injected with the vehicle instead of cannabinoids.

Anticonvulsant Effect against PTZ-, Picrotoxin- and Strychnine-Induced Seizures PTZ (120 mg/kg, subcutaneous, s.c.), picrotoxin (10 mg/kg, s.c.) and strychnine (2 mg/kg, i.p.) were injected to mice 20 min after the 10 mg/kg, i.v. injection of the cannabinoids or the vehicle. The latency for clonic and tonic seizures was recorded.[9]

Maximal Electroshock (MES) In MES-induced seizures, various doses of **1** and its halogenated derivatives were injected i.v. 15 min prior to administration of an electroshock of 50 mA intensity and 0.2 s duration.[10] The protection against MES-induced tonic seizures was measured. Threshold against minimal and maximal electroshock seizures in mice was measured using a tonic extensor as end point by E.C. stimulator MK-800 (Muromachi Ind., Tokyo) 15 min after the i.v. injection of **1** and **4**.

Locomotor Activity Animals were injected with **1** and its halogenated derivatives (10 mg/kg, i.v.) in groups of 5 to 15 mice, and locomotor activities, consisting of horizontal (total distance moved) and vertical activity (number of rearings) were measured with a Muromachi animal behavior analyzer (Muromachi BTA-1, Muromachi Ind., Tokyo) equipped with an NEC PC-9801 RX microcomputer for 60 min.[11] The control mice received the vehicle only.

Statistical Analyses The statistical significance of variation in data was calculated by Bonferroni multiple-comparison test using one way analysis of variance (ANOVA).

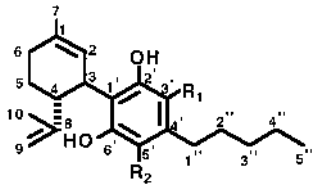
Results

Synthesis of Halogenated 1 Derivatives Structures, MS and NMR of the halogenated derivatives of **1** synthesized in the present study are listed in Table 1. All halogenated derivatives were prepared according to the method described in Materials and Methods. A proton at the 5′-position of **1** (δ 5.57 ppm, 1H) disappeared in the ^{1}H-NMR spectra of monohalogenated derivatives. Two protons at the 3′- and 5′-positions of **1** (δ 5.57 ppm, 2H) disappeared in the ^{1}H-NMR spectra of dihalogenated derivatives. The MS and NMR spectra of the halogenated derivatives support the assigned structures.

Pharmacological Effects Barbiturate-Induced Sleep Prolongation: The effects of the halogenated derivatives of **1** on pentobarbital-, hexobarbital- and barbital-induced sleep are shown in Fig. 1. I.v. administration (10 mg/kg) of **2** (69±10 min) modestly prolonged pentobarbital-induced sleeping time as in the case of **1** (61±13 min) (Fig. 1A). However, the other derivatives did not significantly prolong the sleeping time. At 10 mg/kg, i.v., the sleep of mice treated with **2**, **3**, **4**, **5**, **6** and **7** was 69±10, 42±6, 50±9, 45±4, 45±5 and 44±7 min, respectively, and that of the control group was 22±2 min.

As shown in Fig. 1B, administration (10 mg/kg) of **2**, **4** and **6** significantly prolonged hexobarbital-induced sleeping time as well as that of **1**, although the dihalogenated derivatives of **1** did not significantly cause prolongation compared to the control group. At 10 mg/kg, i.v., the sleep of mice treated with **2**, **3**, **4**, **5**, **6** and **7** was 105±15, 76±6, 102±5, 57±4, 119±7 and 57±3 min, respectively, and that of the control group was 52±5 min.

Table 1. Structures of Halogenated CBD Derivatives



	R_1	R_2	MS (*m/z*)	^{1}H-NMR δ (in $CDCl_3$) ppm
1	H	H	314 (M^+)	5.57 (C-3′, s)
2	Cl	H	348 (M^+)	6.31 (C-3′, s)
3	Cl	Cl	382 (M^+)	—
4	Br	H	392 (M^+)	6.33 (C-3′, s)
5	Br	Br	470 (M^+)	—
6	I	H	440 (M^+)	3.68 (C-3′, s)
7	I	I	566 (M^+)	—

Administration (10 mg/kg) of **2** and **4** tended to prolong barbital-induced sleeping time as well as that of **1**, although the effect of neither derivative was statistically significant. The other derivatives did not cause prolongation of barbital-induced sleeping time compared to the control group (Fig. 1C). At 10 mg/kg, i.v., the sleeping of mice treated with **2**, **3**, **4**, **5**, **6** and **7** was 176±42, 132±10, 160±16, 112±13, 133±10 and 133±20 min, respectively, and that of the control group was 133±13 min.

Effect on PTZ-, Picrotoxin- and Strychnine-Induced Seizures: As summarized in Table 2, **1** and all halogenated derivatives, except for **4** and **5**, tended to prolong seizure latency against both the clonic and tonic seizures induced by PTZ, compared to the control group. However, none of the halogenated derivatives exhibited any higher effect of protection against PTZ- induced seizures than did **1**. The prolongation of seizure latency against both clonic and tonic convulsions compared to control were higher in the order of **1**>**2**>**7**>**6**>**3**. In no case was the effect of halogenated derivatives of **1** statistically significant.

In the protection against tonic seizures induced by picrotoxin, **6** (469 s) and **7** (400 s) tended to prolong seizure latency compared to the control group (357 s) and **1** (360 s). Other halogenated derivatives did not exhibit any protection against picrotoxin-induced seizures. However, the protection effect of **4** against tonic convulsion of strychnine-induced seizures was higher than that of **1**, as shown in Table 2, although the effect **4** was not statistically significant.

Anticonvulsant Effects against Electroshock-Induced Seizures: **1** and **4** exhibited potent anticonvulsant effect against MES-induced seizures. ED_{50} values of **1** and **4** in the MES- test were 38 (26—56) and 44 (37—53) mg/kg, i.v., respectively (Table 3). Other **1** derivatives, **2**, **3**, **5**, **6** and **7** showed no significant anticonvulsant effect at any dose up to 200 μmol/kg, i.v. In minimal and maximal electroshock-threshold tests, **4** exhibited the same potency as did **1** (Table 4).

Locomotor Activity: Locomotor activities were analyzed

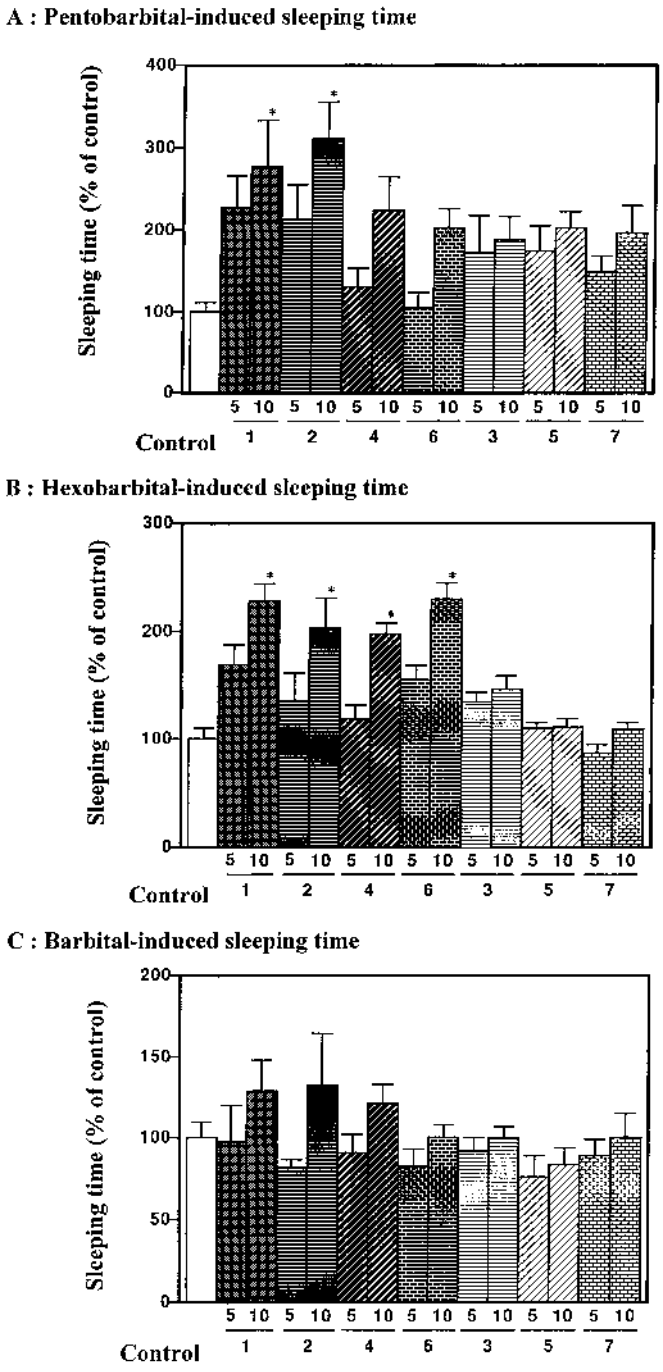


Fig. 1. Effects of CBD and Its Halogenated Derivatives on Pentobarbital-, Hexobarbital- and Barbital-Induced Sleeping Time in Mice by I.v. Injection

Pentobarbital, hexobarbital and barbital were injected to mice i.p. at 40, 100 and 300 mg/kg, respectively, 20 min after the injection of the cannabinoids (5 or 10 mg/kg, i.v.). The mean sleeping times in control mice were 22±2, 52±5 and 133±13 min (i.v.). Each group consisted of 5—15 mice. **1**, CBD; **2**, 3′-Cl-CBD; **3**, 3′,5′-di-Cl-CBD; **4**, 3′-Br-CBD; **5**, 3′,5′-di-Br-CBD; **6**, 3′-I-CBD; **7**, 3′,5′-di-I-CBD. * Significantly different from control ($p<0.01$).

separately into vertical and horizontal components. The horizontal activity measured the total distance of an animal's movement. In this index, as well as for the vertical activity, the time period for recording the mouse behaviors was divided into total terms of 60 min for each component. Both activities tended to increase upon injection of **5** and **7**, although significant activity was not observed. The horizontal and vertical activities for the groups treated with **1**, **2**, **3**, **4**, **5**,

Table 2. Effects of CBD and Its Halogenated Derivatives on PTZ-, Picrotoxin- and Strychnine-Induced Seizures in Mice by I.v. Injection

	Treatment	*n*	Latency for PTZ-induced seizures (s)	
			Clonic seizures	Tonic seizures
	Control	21	139±17	393±53
1		11	286±50*	695±107
2		10	233±30	667±110
4		10	115±13	361±52
6		10	189±29	641±92
3		10	144±53	522±130
5		10	122±13	376±57
7		10	221±41	679±127

	Treatment	*n*	Latency for Picrotoxin-induced seizures (s)	
			Clonic seizures	Tonic seizures
	Control	8	327±17	357±23
1		8	302±20	360±25
2		8	303±20	351±20
4		8	293±19	389±38
6		8	387±18	469±40
3		8	312±16	368±27
5		8	312±21	392±44
7		8	327±15	400±32

	Treatment	*n*	Latency for Strychnine-induced seizures (s)
			Tonic seizures
	Control	16	162±15
1		8	136±7
2		8	161±10
4		12	238±59
6		8	156±25
3		8	128±7
5		11	180±28
7		8	162±23

PTZ (120 mg/kg, s.c.), picrotoxin (10 mg/kg, s.c.) and strychnine (2 mg/kg, i.p.) were injected into mice 20 min after the i.v. injection of the cannabinoids (10 mg/kg) or vehicle (physiological saline containing 1% Tween 80). * Significantly different from control ($p<0.05$).

Table 3. Anticonvulsant Effects of CBD and Its Halogenated Derivatives Against MES in Mice

Treatment	Peak effect time (min)	MES seizures[a] ED_{50} mg/kg (95% confidence limits)
1	15	38 (26—56)
2	15	>100
4	15	44 (37—53)
6	15	>100
3	15	>100
5	15	>100
7	15	>100

a) 50 mA, 0.2 s duration. Anticonvulsant effects of **1** and its halogenated derivatives against MES in mice were measured using a tonic extensor as end point by E.C. stimulator MK-800 15 min after the i.v. injection of the cannabinoids. E.C. stimulator MK-800 conditions: output, 50 mA; output time, 0.2 s; pulse interval, 10 msec; pulse width, 5.0 msec. Each group consisted of 8—26 mice.

6 and **7** were 2680±404, 2574±315, 3054±553, 2616±430, 2579±905, 3994±652 and 4364±795 cm (total distances), and 53±16, 41±9, 35±14, 49±12, 69±22, 88±15 and 87±18 (number of rearings), respectively. The horizontal and vertical activities for the control were 3812±471 cm (total distances) and 52±8 (number of rearings), respectively.

Discussion

The pharmacology and toxicology of **1** is important for at least two reasons: first, **1** is a major constituent of marihuana, though it causes no significant psychic effects and has low toxicity;[12] secondly, the preclinical evaluation of its anticonvulsant properties suggests that the drug may be a useful anti-epileptic agent.[13] The clinical potential of **1** is enhanced by its apparent lack of toxicity; for example, in man, massive intravenous doses of **1** do not produce the psychotoxic and cardiovascular effects of marihuana or Δ^9-THC.[14] However, animal studies have demonstrated that **1** can prolong barbiturate sleeping time, which was subsequently shown to be the result of the ability of **1** to inhibit barbiturate metabolism by the liver.[15]

Since the pioneering synthetic work of Adams,[16] it has been evident that structural modifications of the cannabinoid molecule profoundly influence the potency of this class of compounds. A major advancement in this field was achieved when the search brought about a therapeutic cannabinoid, devoid of THC-like psychotropic effects.[17] To attain this aim necessitates further knowledge on the structure–activity relationship of **1** derivatives. Charalambous *et al.*[18] and Martin *et al.*[19] reported the pharmacological effects of halogenated derivatives of Δ^8- and Δ^9-THC, although systematic evaluation of these effects of halogenated THC had not been carried out at that time. Martin *et al.*[19] reported the enhanced and decreased potency of 2-iodo-Δ^8-THC and 4-bromo-Δ^8-THC, respectively, in their pharmacological effects such as rectal temperature, analgesia, spontaneous activity and immobility index. Previous studies in our laboratory demonstrated that halogenated derivatives of CBN and Δ^9-THC exhibited cannabimimetic activity to some extent.[2]

In the present study, we synthesized six halogenated derivatives of **1** on the aromatic ring and their pharmacological activities in mice were compared with those of **1** using the anticonvulsant effect, barbiturate-induced sleep prolongation and locomotor activity as indices for systematic evaluation. All halogenated derivatives were successfully synthesized by halogenation of **1** with potassium halides, 18-crown-6 and MCPBA in the methylene chloride as previously reported.[20] Comparison of pharmacological effects of CBD and its halogenated derivatives in mice investigated in the present study are summarized in Table 5. The results indicate that introduction of halogens modified the pharmacological effects of **1**. Compound **2** significantly prolonged pentobarbital-induced sleeping time. Monohalogenated derivatives of **1** (10 mg/kg, i.v.) also significantly prolonged hexobarbital-induced sleeping time. In particular, **1** and **2** prolonged both hexobarbital- and pentobarbital-induced sleeping time, but not barbital-induced sleeping time. Dihalogenated derivatives also showed the prolonging effect of pentobarbital-induced sleep, but to lesser extents. These results suggest that **1** and its monohalogenated derivatives prolonged barbiturate-induced sleep by inhibition of the hepatic metabolism of barbiturates. The lack of prolongation effect of **1** and its halogenated derivatives on barbital-induced sleeping time may be related to the fact that metabolic degradation does not seem to be important for termination of action of barbital. **1** showed a significant anticonvulsant effect against PTZ-induced clonic seizures, although halogenated derivatives of **1** were not active in protecting against picrotoxin- and strychnine-induced seizures. Some of the halogenated derivatives of **1** tended to prolong seizure latency induced by PTZ (**2**, **6**, **7**), that by picrotoxin (**6**) and that by strychnine (**4**), whereas the anticonvulsant effect was statistically not significant. Compound **1** is known to possess anticonvulsant effects against MES-induced seizures.[3b,13] In the present study, **4** showed almost the same potency in the MES-test, although other halogenated derivatives were less active than **1**. The previous studies from our laboratories also

Table 4. Minimal and MES-Threshold Tests for CBD and 3′-Bromo-CBD

Treatment	Minimal electroshock		MES	
	Control (mA)	Treated (mA)	Control (mA)	Treated (mA)
1	7.4	8.4	10.9	13.7
4	7.4	8.4	10.9	13.4

Values are median-effective electroshock. Threshold against minimal and MES seizures in mice were measured by a tonic extensor as end point by E.C. stimulator MK-800 15 min after the i.v. injection of **1** and **4**. Each group consisted of 8 mice.

Table 5. Comparison of Pharmacological Effects of CBD and Its Halogenated Derivatives in Mice

Compound	Barbiturate synergism			Anticonvulsant effect						Locomotor activity	
				PTZ		Picrotoxin		Strychnine	MES		
	Pentobarbital	Hexobarbital	Barbital	Clonic	Tonic	Clonic	Tonic			Rearing	Total distance
1	++**	++**	±	++*	+	±	±	−	+	−	−
2	++**	++**	±	+	+	±	±	±	−	−	−
4	+	++**	±	±	±	±	±	±	+	−	−
6	+	++**	±	+	+	+	+	±	−	+	−
3	+	+	±	±	+	±	±	−	−	±	±
5	+	±	±	±	±	±	±	±	−	±	±
7	+	±	±	+	+	±	±	±	−	+	±

++; Implies significant prolongation of barbiturate-induced sleep or seizure latency against both clonic and tonic seizures induced by convulsants. +; Implies tendency to prolong barbiturate-induced sleep or seizure latency against both the clonic and tonic seizures, and tendency to increase locomotor activity of mice. −; Implies tendency to shorten seizure latency against both clonic and tonic seizures induced by convulsants, and decrease of locomotor activity of mice. ±; No change. Significantly different from control: *, $p<0.05$; **, $p<0.01$.

demonstrated that brominated derivatives of CBN and Δ^9-THC showed relatively higher pharmacological effects in some cases.[2)] The lack of significant effects of **1** and its halogenated derivatives on locomotor activity of mice indicated that change in this activity may be related to the central nervous system effect of cannabinoids.

The results indicate that pharmacological effects of monohalogenated derivatives such as **2** were comparable to those of **1**; introduction of bromine may be especially useful for modification of the anticonvulsant effect of **1**; whereas dihalogenated derivatives were much less active. In conclusion, we synthesized six **1** halogenated on the aromatic ring, and evaluated that some pharmacological effects of **1** could also be modified by its halogenation as previously studied in the CBN and Δ^9-THC.

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