A New Series of Antiallergic Agents. II.[1] Synthesis and Activity of New 6,11-Dihydrodibenz[*b*,*e*]-oxepin-carboxylic Acid Derivatives

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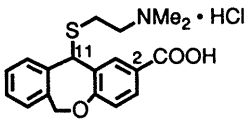
New methods for the preparation of multi-functionallized-6,11-dihydrodibenz[*b*,*e*]oxepins were developed. The structural requirements of KW-4994 (1), a promising orally active antiallergic agent, were defined. A carboxyl group at C-2 was critical for enhanced antiallergic activity of 1. The introduction of bromine atom at C-9 of 1 could elongate the duration of the action of the parent. Antiplatelet activity, a new pharmacological property of this series of compounds, was observed in one of the derivatives of 1.

Keywords antiallergic agent; antiasthmatic agent; H_1-antihistaminic activity; receptor antagonist; anti-passive cutaneous anaphylaxis activity; structure–activity relationship; antiplatelet activity; 6,11-dihydrodibenz[*b*,*e*]oxepin

Effective and orally active antiallergic agents with fewer side effects have been attractive targets for drug research in recent years.[2] In the preceding paper,[1] we reported the synthesis and activity of a new series of 11-substituted-dibenz[*b*,*e*]oxepin derivatives, including KW-4994 (**1**), one of our promising candidates for new antiallergic agents. From the structural point of view,[3] **1** represents a new class of antiallergic agent with both amino and carboxyl moieties in one molecule.



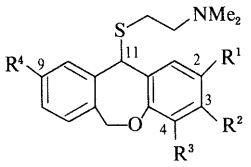
KW-4994 (1)

Fig. 1

In this paper we extended the scope of this novel series of antiallergic agents. The influence of the position of the carboxyl group was examined. Moreover, an additional substituent was introduced in the 4- or 9-position of **1** in order to obtain the compounds with more potent and/or longer duration of action.

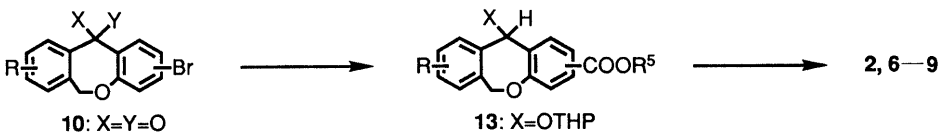
Chemistry Compounds listed in Table I were prepared from appropriate 11-alcohols and 2-(dimethylamino)-ethanethiol by the methods described in the preceding paper.[1] The 11-alcohols possessing a carboxyl group in the varied position of the oxepin ring system were appropriately prepared by the method as outlined in Chart 1. The ketones **10** were reduced with $NaBH_4$ and the resulting alcohols **11** were treated with dihydropyran/

TABLE I. Substituted 6,11-Dihydrodibenz[*b*,*e*]oxepin Derivatives



Compd.[a] No.	R^1	R^2	R^3	R^4	mp (°C)	Recrystn.[b] solvent	H_1 % inhibn. 0.1 μM	M_1 % inhibn. 1 μM	PCA % inhibn. (mg/kg *p.o.*) 100	10
1 (KW-4994)	COOH	H	H	H			59	7	95	87
2	COOH	H	Me	H	243—244 (dec.)	IP	20	2	99	47
3	COOH	H	H	Br	251—253 (dec.)	IP	83	2	70	62
4	COOH	H	H	SMe	230—232 (dec.)	IP	56	−1	N.T.	62
5	COOH	H	H	iso-Pr	215—217	IP	28	0	N.T.	63
6	H	COOH	H	H	95—110 (dec.)	TL	10	−1	16	N.T.
7	H	H	COOH	H	135 (dec.)	IP	0	−2	24	N.T.
8	Me	H	COOH	H	90 (dec.)	IP	−12	−4	28	N.T.
9	H	H	H	COOH	250—251 (dec.)	IP	24	5	38	N.T.

a) All compounds were obtained as HCl salts. *b*) IP, isopropanol; TL, toluene. N.T., not tested.



10: X=Y=O
11: X=OH, Y=H
12: X=OTHP, Y=H

13: X=OTHP
14: X=OH

Chart 1

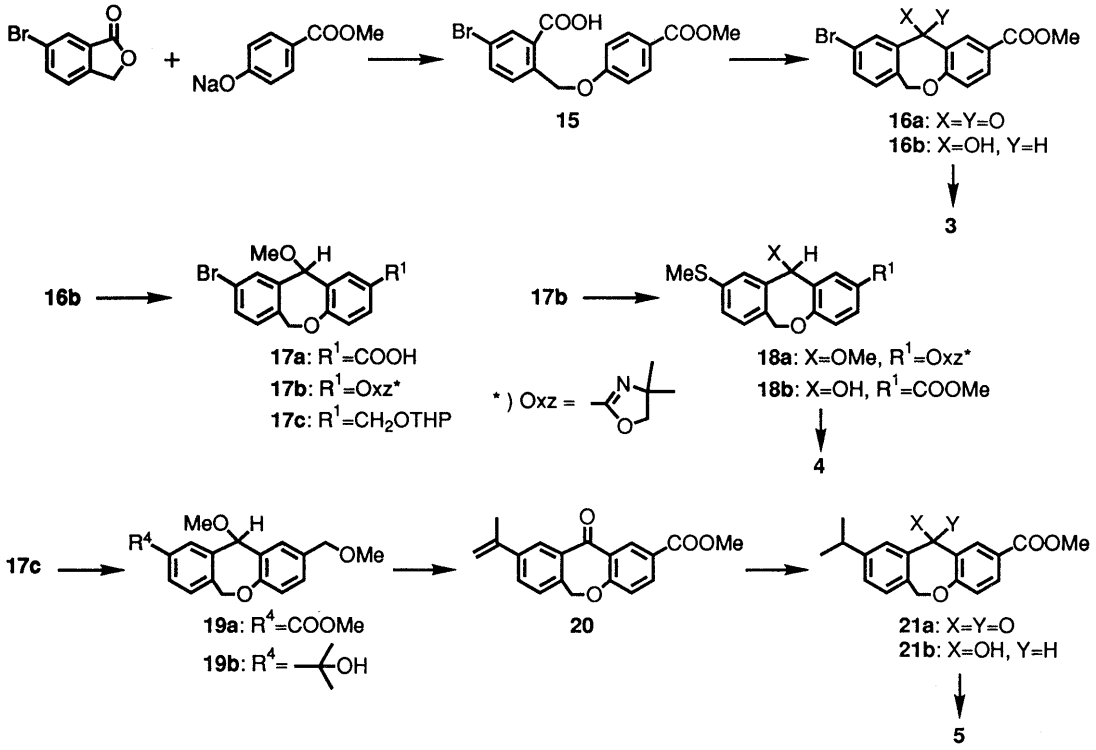


Chart 2

pyridinium *p*-toluenesulfonate (PPTS) to afford the tetrahydropyranyl (THP) ethers **12**. The bromides **12** were treated with 1) *n*-BuLi, 2) $(EtO)_2CO$ [method A] or 1) *n*-BuLi, 2) CO_2, 3) Me_2SO_4 [method B] to provide the esters **13**: Acid treatment of **13** afforded **14**, from which **2** and **6**—**9** were prepared.

The synthesis of **3**—**5** which were the analogues of **1** possessing an additional substituent at C-9 was outlined in Chart 2. For the preparation of the starting ketone **16a**, our newly developed procedure[4] based on the intramolecular Friedel–Crafts acylation of **15** turned out to be quite superior to the previously reported methods.[5,6] Merck and Daiich groups reported the synthetic methods for the preparation of 11-oxo-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic acid, independently. The former method which involved the cyanation of bromide could not be applied for the synthesis of 9-bromo-2-carboxylic acid derivatives. The latter was unsatisfactory in yield. The dicarboxylic acid monoester **15** was treated with equimolecular of trifluoroacetic anhydride and subsequently with a catalytic amount of $BF_3 \cdot Et_2O$ to afford **16a** under very mild conditions.

$NaBH_4$ reduction of **16a** provided the alcohol **16b**, from which **3** was prepared. In addition, **17b** was prepared by the conversion of the hydroxyl and methoxycarbonyl groups of **16b** to methoxy and 4,4-dimethyl-oxazolin-2-yl groups, respectively. The resulting **17b** was treated with *n*-BuLi and then Me_2S to afford the sulfide **18a**. Simultaneous acidic cleavage of the oxazoline and ether groups of **18a** and the subsequent ester exchange reaction provided **18b**, which was converted to **4**. The alcohol **21b**, the precursor of **5**, was obtained by the reduction of the ketone **21a** prepared *via* 9-methoxycarbonyl derivative **19a**. Compound **17a** was reduced with $LiAlH_4$ and the resulting alcohol was protected to **17c**, which was converted to **19a** in a similar manner described in Chart 1. Compound **19b** prepared by the treatment of **19a** with MeMgBr was oxidized and dehydrated to **20**, which was hydrogenated to the final ketone **21a**.

Results and Discussion

The compounds synthesized were tested for their inhibitory effects on the specific binding of [^{3}H]pyrilamine to guinea pig cerebellum histamine-H_1 receptors (H_1),[7] the specific [^{3}H]quinuclidinyl benzilate binding to rat striatum muscarinic acetylcholine receptors (M_1),[8] and 48 h homologous passive cutaneous anaphylaxis (PCA) in rats. The results are summarized and represented by percent inhibition in Table I. Any of the compound synthesized showed negligible M_1 receptor binding affinity which was one of the indices of side effects such as suppression of salivary secretion and mydriasis.[9]

We examined the influence of the position of the carboxyl group on the activity. In the PCA test, 2-carboxylic acid (**1**) was the most potent compound and 9-carboxylic acid (**9**) was less potent than **1**. Compounds with a carboxyl group at C-3 or C-4 (**6**—**8**) were devoid of an inhibitory effect in this test. This tendency was also observed in the H_1 receptor binding assay. Based on the observed difference in potency between 2-COOH and 9-COOH, we presumed that the oxygen in the oxepin ring might play a crucial role for their antiallergic activity.

We next examined the influence of the introduction of an additional substituent at C-4 or C-9 of **1**. Such kind of modification had succeeded in improvement of the antiallergic activities of 5-oxo-5*H*-[1]benzopyrano[2,3-*b*]-pyridines[10] and pyrido[2,1-*b*]quinazolinecarboxylic acids.[11] Contrary to our expectation, compounds **2**—**5** failed to enhance the antiallergic activity of **1**. Comparative oral PCA duration studies for compounds **1**—**5** were performed in rats. All compounds were administered orally

at 1 mg/kg. Each inhibition of the PCA response was measured at various times following drug administration. Compound **3** exhibited significant inhibitory effect at 12 h after the dosing and its duration of action was longer than that of **1** (6—9 h). Therefore, the introduction of a bromine atom at C-9 as an additional substituent to **1** resulted in elongation of the action. The long duration of action is beneficial if an agent is to be useful in the clinical prophylaxis of allergic diseases, and the details of the effect of the additional substituent on the improved pharmacokinetics of **3** is now under investigation.

Of all the synthesized compounds in this study including **1**, only **8** was found to possess a potent antiplatelet activity in our screening experiments. It significantly inhibited a collagen-induced aggregation of rabbit platelet rich plasma at 3 μg/ml, whereas it showed negligible antiallergic and antihistaminic activities as described above.

In conclusion, we developed new procedures for the preparation of a new series of multi-functionallized-6,11-dihydrodibenz[*b*,*e*]oxepins and defined the structural requirements of KW-4994 (**1**). A carboxyl group at C-2 was critical for the enhanced antiallergic activity of **1**. Some of the compounds synthesized showed potent antiallergic activities, of which compound **3** exhibited a longer duration of action than **1**. Additionally, compound **8** is a new lead as an antiplatelet agent. Further modifications of these compounds are now in progress in our research laboratories.

Experimental

Synthetic Procedures Melting points were determined with a Büchi-510 melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IR-400 spectrometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a JEOL PMX-60 (60 MHz), a Hitachi R-90H (90 MHz), or a JEOL GX-270 (270 MHz) spectrometer with Me_4Si as internal standard. Mass spectra (MS) were recorded on a JEOL D300 mass spectrometer. Elemental analyses were performed by the analytical department of our laboratories.

Methyl 9-Bromo-11-oxo-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylate (16a) To a solution of methyl 4-hydroxybenzoate (11.9 g, 78.2 mmol) was added 28% MeONa in MeOH (5 ml, 78.2 mmol) and the solution was stirred. After being evaporated to dryness, 6-bromophtalide (20 g, 93.9 mmol) was added. The mixture was heated at 120 °C for 8 h. Acetic acid (5 ml, 78.2 mmol) and MeOH (30 ml) were added and stirring was continued at 50 °C for 1 h. The reaction mixture was diluted with water and adjusted to pH 5.6 with 2 N HCl. The resultant precipitate was collected and recrystallized from isopropanol to give 12.1 g (42%) of **15** as crystals, mp 184—187 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.88 (s, 3H), 5.49 (s, 2H), 6.8—8.2 (m, 7H). IR (KBr): 3400, 1700 cm^{-1}. To a suspension of **15** (12.0 g, 32.9 mmol) in CH_2Cl_2 (300 ml) was added trifluoroacetic anhydride (4.7 ml, 32.9 mmol) under Ar atmosphere and the mixture was stirred at room temperature for 1 h. $BF_3 \cdot Et_2O$ (1 ml, 8.1 mmol) was added and the stirring was continued for a further 2 h under the same conditions. The reaction mixture was poured into ice-water. The organic layer was separated, washed successively with aqueous $NaHCO_3$ and brine, dried and concentrated. The residue was recrystallized from AcOEt to give 8.86 g (78%) of **16a** as crystals, mp 199—200 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.93 (s, 3H), 5.19 (s, 2H), 7.09 (d, J=8.6 Hz, 1H), 7.27 (d, J=8.0 Hz, 1H), 7.70 (dd, J=2.0, 8.0 Hz, 1H), 8.01 (d, J=2.0 Hz, 1H), 8.14 (dd, J=2.2, 8.6 Hz, 1H), 8.90 (d, J=2.2 Hz, 1H). *Anal.* Calcd for $C_{16}H_{11}BrO_4$: C, 55.36; H, 3.19. Found: C, 55.55; H, 3.19.

Methyl 9-Bromo-11-hydroxy-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylate (16b) To a solution of **16a** (11.90 g, 34 mmol) in MeOH (150 ml) was added $NaBH_4$ (0.79 g, 21 mmol) and the solution was stirred at room temperature for 3 h. After concentration, water was added and the mixture was extracted with AcOEt. The extract was washed with brine, dried, and concentrated to give **16b** (11.9 g, 100%), as a solid, mp 132—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.81 (s, 4H), 4.96 and 5.76 (AB, J_{AB}=14.1 Hz, 2H), 5.70 (s, 1H), 6.80 (d, J=8.5 Hz, 1H), 7.02—7.46 (m, 3H), 7.79 (dd, J=2.2, 8.5 Hz, 1H), 8.02 (d, J=2.2 Hz, 1H).

4-Bromo-11-tetrahydropyranyloxy-6,11-dihydrodibenz[*b*,*e*]oxepin (12a) The ketone **10a** (4-Br, R=H, mp 129—132 °C) was prepared from phtalide and 2-bromophenol by the same method as described in the preparation of **16a** (75%). The ketone **10a** was reduced to **11a** (4-Br, R=H), mp 94—96 °C) by the same method as described in the preparation of **16b**. The alcohol **11a** (17 g, 0.059 mmol) was treated with 2,3-dihydropyran (49.3 g, 0.59 mol) and pyridinium *p*-toluenesulfonate (PPTS) (1.47 g, 5.9 mol) in CH_2Cl_2 at room temperature for 2.5 h. The reaction mixture was washed with aqueous $NaHCO_3$, dried, and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 5:1) to give 21.3 g (97%) of **12a** as an oil. ^{1}H-NMR ($CDCl_3$) δ:1.59 (br s, 6H), 3.24—4.13 (m, 2H), 4.53 and 4.73 (each br s, total 1H), 5.00 and 5.94 (AB, J_{AB}=12.0 Hz, 1H), 5.04 and 5.95 (AB, J_{AB}=12.5 Hz, 1H), 5.55 and 5.63 (each br s, total 1H), 6.66 (t, J=7.5 Hz, 1H), 7.03—7.54 (m, 6H). MS *m/z*: 376 and 374 (M^+).

Compounds **12b** (3-Br, R=H, oil), **12c** (4-Br, R=2-Me, mp 114—116 °C), **12d** (9-Br, R=H, oil), and **12e** (2-Br, R=4-Me, oil) were prepared by the same method as described above.

Ethyl 11-Hydroxy-6,11-dihydrodibenz[*b*,*e*]oxepin-4-carboxylate (14a) [Method A] To a solution of **12a** (41.5 g, 0.11 mol) in tetrahydrofuran (THF 330 ml) was added dropwise a 1.5 M solution of *n*-BuLi in hexane (73.3 ml, 0.11 mol) at −78 °C under Ar atmosphere. After being stirred for 10 min, the solution was added dropwise to a solution of diethyl carbonate (133 ml, 1.1 mol) in THF (220 ml) at −78 °C. The mixture was gradually warmed to room temperature with stirring. After an addition of H_2O (500 ml), the mixture was extracted with AcOEt. The extract was washed with H_2O, dried, and concentrated. The residue containing crude **13a** (4-COOEt, R=H) and *p*-TsOH·H_2O (2.1 g, 11 mmol) was dissolved in the mixture of 1,4-dioxane (220 ml) and H_2O (80 ml) and the mixture was stirred at 60 °C for 2.5 h. The mixture was extracted with AcOEt and the extract was washed successively with aqueous $NaHCO_3$ and brine. The organic layer was dried and concentrated. The residue was chromatographed on silica gel (toluene–AcOEt, 5:1) to give **14a** (4-COOEt, R=H, 10.0 g, 32%) as crystals, mp 147—148.5 °C (toluene). IR (KBr): 3350, 1660, 1595, 1440, 1220 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (t, J=7.0 Hz, 3H), 3.53 (d, J=6.0 Hz, 1H), 4.32 (q, J=7.0 Hz, 2H), 5.21 and 5.58 (AB, J_{AB}=14.5 Hz, 2H), 5.73 (d, J=6.0 Hz, 1H), 6.78—7.75 (m, 5H). *Anal.* Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.78; H, 5.88.

Compounds **14c** (4-COOEt, R=H, oil) and **14e** (2-COOEt, R=4-Me, mp 159.5—160 °C) were prepared by the same method as described above from **12c** and **12e**, respectively.

Methyl 11-Hydroxy-6,11-dihydrodibenz[*b*,*e*]oxepin-9-carboxylate (14d) [Method B] To a solution of **12d** (20.8 g, 55 mmol) in THF (180 ml) was added dropwise a 1.5 M solution of *n*-BuLi in hexane (36.8 ml, 55 mmol) at −78 °C under Ar atmosphere. After being stirred for 10 min, the mixture was poured onto dry ice (50 g) and stirred at room temperature for 2 h. Then dimethyl sulphate (5.8 ml, 60.5 mmol) was added and the mixture was refluxed for 1 h. After addition of 1 N NaOH (20 ml) and H_2O (300 ml), the mixture was extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue obtained and *p*-TsOH·H_2O (2.6 g, 13.7 mmol) were dissolved in a mixture of 1,4-dioxane (300 ml) and H_2O (150 ml) and the solution was stirred at 60 °C for 4 h. The mixture was extracted with AcOEt and the extract was washed successively with aqueous $NaHCO_3$ and brine. The organic layer was dried and concentrated. The residue was chromatographed on silica gel (toluene–AcOEt, 10:1 and then 2:1) to give **14d** (6.0 g, 49%) as a viscous oil. IR (neat): 3380, 1720, 1605, 1485, 1435, 1280, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.57 (s, 3H), 4.95 and 5.73 (AB, J_{AB}=13.0 Hz, 2H), 5.63 (s, 1H), 6.64—8.04 (m, 7H). High resolution MS *m/z*: Calcd for $C_{16}H_{14}O_4$ 270.0892. Found: 270.0888 (M^+).

Compound **14b** (3-COOMe, R=H, mp 101—103 °C) was prepared by the same method as described above from **12b**.

9-Bromo-11-methoxy-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic Acid (17a) A mixture of **16b** (11.5 g, 33 mmol) and *p*-TsOH·H_2O (0.3 g, 1.6 mmol) in MeOH (165 ml) was refluxed for 1 h. NaOH (1 N, 50 ml) was added and the mixture was refluxed for 2 h. After concentration, the residue was dissolved in H_2O and acidified with 4 N HCl. The resultant precipitate was collected by filtration, washed with H_2O, and dried to give **17a** (11.3 g, 98%) as a solid, mp 249—250 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.32 (s, 3H), 5.06 and 5.95 (AB, J_{AB}=12.6 Hz, 2H), 5.30 (s, 1H), 6.83—8.25 (m, 6H). MS *m/z*: 348 and 350 (M^+). *Anal.* Calcd for $C_{16}H_{13}BrO_4$: C, 55.04; H, 3.75. Found: C, 55.00; H, 3.85.

9-Bromo-2-(4,4-dimethyl-2-oxazolin-2-yl)-11-methoxy-6,11-dihydrodibenz[*b*,*e*]oxepin (17b) To a solution of **17a** (10.0 g, 28.6 mmol) and

pyridine (4.7 ml, 57.2 mmol) in CH_2Cl_2 (100 ml) was added a solution of $SOCl_2$ (2.7 ml, 37.2 mmol) in CH_2Cl_2 (20 ml) at 0 °C and the mixture was stirred at the same temperature for 30 min and then at room temperature for 2 h. After concentration, the residue was dissolved in CH_2Cl_2 (20 ml) and the solution was added to a solution of 2-amino-2-methyl-1-propanol (17.8 g, 200 mmol) in CH_2Cl_2 (150 ml) at 0 °C. The mixture was stirred at the same temperature for 1 h and then at room temperature overnight. The mixture was diluted with CH_2Cl_2. The organic solution was washed successively with aqueous $NaHCO_3$ and brine, dried, and concentrated to give a crude *N*-(1,1-dimethyl-2-hydroxy)ethyl-9-bromo-11-methoxy-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxamide (9.93 g) as an oil. This crude amide and pyridine (5 ml) were dissolved in CH_2Cl_2 (120 ml) and a solution of $SOCl_2$ (1.7 ml, 23.6 mmol) in CH_2Cl_2 (10 ml) was added at 0 °C. The mixture was refluxed for 6 h. Upon cooling, the mixture was washed with water, dried, and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1) to give **17b** (6.25 g, 54% from **17a**) as an amorphous solid. IR ($CHCl_3$): 2950, 1640, 1480, 1070 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (s, 6H), 3.26 (s, 3H), 3.99 (s, 2H), 4.78 and 5.91 (AB, J_{AB} = 11.7 Hz, 2H), 4.91 (s, 1H), 6.76 (d, J = 8.5 Hz, 1H), 6.97—7.84 (m, 5H). *Anal.* Calcd for $C_{20}H_{20}BrNO_3$: C, 59.71; H, 5.01; N, 3.48. Found: C, 59.60; H, 5.12; N, 3.30.

9-Methylthio-2-(4,4-dimethyl-2-oxazolin-2-yl)-11-methoxy-6,11-dihydrodibenz[*b*,*e*]oxepin (18a) To a solution of **17b** (5.70 g, 14 mmol) in THF (56 ml) was added *n*-BuLi (1.5 M in hexane, 9.3 ml, 14 mmol) at −78 °C. After being stirred at the same temperature for 5 min, methyldisulfide (1.35 ml, 15 mmol) was added. The mixture was gradually warmed to room temperature over 4 h with stirring. After the addition of water, the mixture was extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 2 : 1) to give **18a** (2.29 g, 44%) as a viscous oil. IR (neat): 2960, 1735, 1645, 1490, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (s, 6H), 2.38 (s, 3H), 3.24 (s, 3H), 3.98 (s, 2H), 4.75 and 5.96 (AB, J_{AB} = 12.1 Hz, 2H), 4.91 (s, 1H), 6.75 (d, J = 8.5 Hz, 1H), 7.04—7.27 (m, 3H), 7.66 (dd, J = 2.2, 8.5 Hz, 1H), 7.84 (d, J = 2.2 Hz, 1H). *Anal.* Calcd for $C_{21}H_{23}NO_3S$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.00; H, 6.51; N, 3.55.

Methyl 11-Hydroxy-9-methylmercapto-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylate (18b) A mixture of **18a** (2.0 g, 54 mmol), conc. HCl (0.7 ml), H_2O (6 ml), and 1,4-dioxane (18 ml) was heated at 90 °C for 2 h. Upon cooling, the mixture was extracted with AcOEt. The extract was washed successively with aqueous $NaHCO_3$ and brine, dried and concentrated. The residue was dissolved in MeOH (20 ml) and 28% MeONa in MeOH (0.2 ml) was added. After being refluxed for 3 h, the mixture was diluted with H_2O and extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was chromatographed (flash chromatography) on silica gel (hexane–AcOEt, 5 : 1 and then 2 : 1) to give **18b** (0.60 g, 35%) as an amorphous solid. IR (neat): 3400, 1710, 1605, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (s, 3H), 3.83 (s, 3H), 4.96 and 5.87 (AB, J_{AB} = 12.3 Hz, 2H), 5.64 (s, 1H), 6.79 (d, J = 8.5 Hz, 1H), 7.10—7.30 (m, 3H), 7.77 (dd, J = 2.2, 8.5 Hz, 1H), 8.01 (d, J = 2.2 Hz, 1H). *Anal.* Calcd for $C_{17}H_{16}O_4S$: C, 64.54; H, 5.10. Found: C, 64.20; H, 5.33.

Methyl 11-Methoxy-2-methoxymethyl-6,11-dihydrodibenz[*b*,*e*]oxepin-9-carboxylate (19a) To a solution of **17a** (11.16 g, 30.7 mmol) in ether (120 ml) was added $LiAlH_4$ (1.17 g, 30.7 mmol) portionwise at 0 °C. After being stirred for 1 h, water (3 ml) was added dropwise at 0 °C. The resultant inorganic salts were filtered off and the filtrate was concentrated. A mixture of the residue obtained, dihydropyran (3.2 ml, 35 mmol), and PPTS (0.73 g, 2.9 mmol) in CH_2Cl_2 (150 ml) was stirred at room temperature for 3 h. The mixture was washed successively with aqueous $NaHCO_3$ and water, dried, and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 4 : 1) to give **17c** (7.23 g, 59%) as a viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 3.21 (s, 3H), 4.43 (s, 2H), 4.76 and 5.80 (AB, J_{AB} = 12.5 Hz, 2H), 4.90 (s, 1H), 6.70—7.41 (m, 6H). To a solution of **17c** (4.0 g, 9.5 mmol) in THF (47.5 ml) was added dropwise a solution of 1.5 M *n*-BuLi in hexane (6.7 ml, 10.0 mmol) at −78 °C. After being stirred for 5 min at the same temperature, the mixture was poured onto dry ice (50 g) and warmed gradually to room temperature with stirring. Dimethyl sulfate (0.98 ml, 10.5 mmol) was added and the mixture was refluxed for 2.5 h. Upon cooling, the mixture was diluted with AcOEt. The organic solution was washed successively with aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue and catalytic amount of *p*-TsOH·H_2O was dissolved in MeOH and the mixture was refluxed for 2 h. After concentration, the residue was poured into aqueous $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (hexane–AcOEt, 5 : 1) to give **19a** (1.92 g, 61%) as crystals, mp 93.5—95 °C. IR ($CHCl_3$): 1725, 1500, 1445, 1290 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.31 (s, 6H), 3.88 (s, 3H), 4.35 (s, 2H), 4.88 and 5.97 (AB, J_{AB} = 12.3 Hz, 2H), 5.07 (s, 1H), 6.73—7.38 (m, 4H), 7.87—8.07 (m, 2H). *Anal.* Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.29; H, 6.40.

Methyl 11-Oxo-9-isopropenyl-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylate (20) To a solution of **19a** (1.57 g, 4.8 mmol) in THF (20 ml) was added dropwise MeMgBr (1 M in THF, 24.5 ml, 24.5 mmol) at 0 °C. The mixture was stirred at the same temperature for 2 h and then saturated NH_4Cl was added. The mixture was diluted with AcOEt. The organic solution was washed with brine, dried, and concentrated to give crude **19b** (1.54 g, 98%) as a viscous oil. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (s, 6H), 3.27 (s, 6H), 4.31 (s, 2H), 4.77 and 5.93 (AB, J_{AB} = 12.2 Hz, 2H), 4.94 (s, 1H), 6.67—7.43 (m, 6H). To a solution of the crude **19b** (1.52 g, 4.6 mmol) in absolute MeOH (20 ml) was added portionwise dried ceric ammonium nitrate (CAN) (5.07 g, 9.3 mmol) at room temperature and the mixture was stirred for 2 h. After the addition of H_2O (50 ml), the mixture was extracted with AcOEt. The extract was washed with brine, dried, and concentrated. The residue was chromatographed (flash chromatography) on silica gel (hexane–AcOEt, 2 : 1) to give 9-(1-hydroxy-1-methyl)ethyl-11-methoxy-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carbaldehyde (0.81 g, 56%) as an amorphous solid. IR ($CHCl_3$): 3500, 2960, 1680, 1600, 1565, 1490 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (s, 6H), 3.30 (s, 3H), 4.88 and 6.05 (AB, J_{AB} = 12.1 Hz, 2H), 5.02 (s, 1H), 6.86 (d, J = 8.5 Hz, 1H), 7.12—7.82 (m, 5H), 9.76 (s, 1H). *Anal.* Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.98; H, 6.61. To a solution of the aldehyde (0.80 g, 2.6 mmol) in acetone (10 ml) was added Jones reagent at 0 °C. After the addition of isopropanol to destroy the excess Jones reagent, the resultant insoluble solid was filtered off and the filtrate was concentrated. The residue was dissolved in AcOEt and the organic solution was washed with H_2O, dried, and concentrated. The obtained crude crystals were triturated with diisopropylether to afford 9-(1-hydroxy-1-methyl)ethyl-11-oxo-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylic acid (0.64 g, 79%), mp 186.5—188 °C. *Anal.* Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.10; H, 5.00. The mixture of the carboxylic acid (0.14 g, 0.45 mmol) and 2 drops of conc. H_2SO_4 in MeOH (4 ml) was refluxed for 5 h. Toluene (10 ml) was added and the mixture was heated to evaporate MeOH. After evaporation of MeOH was completed, the mixture was refluxed for 1 h. Upon cooling, the mixture was diluted with AcOEt. The organic solution was washed with brine, dried, and concentrated to give **20** (0.14 g, 100%) as a viscous oil. IR (neat): 1720, 1640, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (s, 3H), 3.88 (s, 3H), 5.14 (br s, 1H), 5.17 (br s, 1H), 5.42 (br s, 1H), 7.03 (d, J = 8.5 Hz, 1H), 6.95—7.33 (m, 2H), 7.61 (dd, J = 2.2, 8.5 Hz, 1H), 7.90 (d, J = 2.2 Hz, 1H), 8.06 (dd, J = 2.4, 8.9 Hz, 1H), 8.78 (d, J = 2.4 Hz, 1H). High resolution MS *m*/*z*: Calcd for $C_{19}H_{16}O_4$ 308.1049. Found: 308.1051 (M^+).

Methyl 11-Hydroxy-9-isopropyl-6,11-dihydrodibenz[*b*,*e*]oxepin-2-carboxylate (21b) A suspension of **20** (0.14 g, 0.45 mmol) and 10% Pd–C (14 mg) in EtOH (3 ml) was stirred under H_2 atmosphere for 2 h. The catalyst was filtered off and the filtrate was concentrated to give **21a** (0.14 g, 100%) as a viscous oil. IR ($CHCl_3$): 2960, 1710, 1610, 1255 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (d, J = 7.0 Hz, 6H), 2.93 (q, J = 7.0 Hz, 1H), 3.89 (s, 3H), 5.18 (s, 2H), 7.04 (d, J = 8.5 Hz, 1H), 7.27—7.43 (m, 2H), 7.73 (d, J = 1.8 Hz, 1H), 8.09 (dd, J = 2.2, 8.5 Hz, 1H), 8.92 (d, J = 2.2 Hz, 1H). To a solution of **21a** (0.14 g, 0.45 mmol) in MeOH (3 ml) was added portionwise $NaBH_4$ (10 mg, 0.27 mmol) at room temperature. The mixture was stirred for 5 h and then diluted with AcOEt. The organic solution was washed with H_2O, dried, and concentrated to give **21b** (0.13 g, 93%) as an amorphous solid. IR ($CHCl_3$): 3400, 2950, 1705, 1615, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (d, J = 7.0 Hz, 6H), 2.85 (q, J = 7.0 Hz, 1H), 3.83 (s, 3H), 4.96 and 5.99 (AB, J_{AB} = 12.3 Hz, 2H), 5.66 (s, 1H), 6.83 (d, J = 8.5 Hz, 1H), 7.18 (br s, 3H), 7.80 (dd, J = 2.2, 8.5 Hz, 1H), 8.04 (d, J = 2.2 Hz, 1H). *Anal.* Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.12; H, 6.66.

11-[2-(Dimethylamino)ethyl]thio-6,11-dihydrodibenz[*b*,*e*]oxepin-3-carboxylate Hydrochloride (6) **14b** (3-COOMe, R = H, 6.8 g, 25 mmol) was dissolved in dry CH_2Cl_2 (100 ml), to which was added $SOCl_2$ (3.6 ml, 50 mmol) dropwise at 0 °C and the mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated to dryness. A mixture of the resulting residue, 2-(dimethylamino)ethanethiol hydrochloride (90%, 7.1 g, 45 mmol), and dimethylformamide (DMF 100 ml) was stirred at 120 °C under nitrogen atmosphere for 3 h. The solvent was evaporated under reduced pressure and the residue was dissolved in H_2O (100 ml). The solution was acidified to pH 1.0 with 4 N HCl, washed twice with ether and subsequently adjusted to pH 12.0 with 10 N NaOH. The reaction mixture was extracted with ether. The extract was washed with

brine, dried, and concentrated. The residue was chromatographed on silica gel (AcOEt–triethylamine, 10:1) to give 7.7 g (86%) of methyl 11-[2-(dimethylamino)ethyl]thio-6,11-dihydrodibenz[*b*,*e*]oxepin-3-carboxylate as an oil. IR (neat): 2940, 1720, 1435, 1415, 1030 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.11 (s, 6H), 2.3—2.8 (m, 4H), 3.76 (s, 3H), 4.78 and 6.21 (AB, J_{AB} = 12.5 Hz, 2H), 4.94 (s, 1H), 6.9—7.6 (m, 7H). MS *m/z*: 357 (M^+). A mixture of this ester obtained (2.0 g, 5.6 mol), 1 N NaOH (10 ml), and EtOH (80 ml) was refluxed for 2 h. The reaction mixture was concentrated and diluted with H_2O. The solution was acidified to pH 5.7 with 4 N HCl. After stirring for 1 h at room temperature, the resultant precipitate was filtered, washed with water and dried to give 1.7 g (89%) of the crude free base of **6**. This crude free base (1.5 g, 4.4 mmol) was dissolved in isopropanol (15 ml). To the solution was added 8.2 N HCl in isopropanol (0.8 ml, 6.6 mmol) and the mixture was stirred at room temperature for 1 h. The resultant precipitate was collected and recrystallized from toluene to give 1.3 g (78%) of **6** as crystals. *Anal.* Calcd for $C_{19}H_{21}NO_3S \cdot HCl \cdot 0.75H_2O$: C, 58.01; H, 6.02; N, 3.56. Found: C, 58.18; H, 6.40; N, 3.71.

Compounds **2**—**5** and **7**—**9** were prepared by the same method as described above from **14e**, **16b**, **18b**, **21b**, **14a**, **14c**, and **14d**, respectively. **2**: *Anal.* Calcd for $C_{20}H_{23}NO_3S \cdot HCl$: C, 60.98; H, 6.14; N, 3.56. Found: C, 60.79; H, 6.28; N, 3.35. **3**: *Anal.* Calcd for $C_{19}H_{20}BrNO_3S \cdot HCl$: C, 49.74; H, 4.61; N, 3.05. Found: C, 49.61; H, 4.51; N, 3.20. **4**: *Anal.* Calcd for $C_{20}H_{23}NO_3S_2 \cdot HCl$: C, 56.39; H, 5.68; N, 3.29. Found: C, 56.20; H, 5.77; N, 3.29. **5**: *Anal.* Calcd for $C_{22}H_{27}NO_3S \cdot HCl \cdot 0.5H_2O$: C, 61.31; H, 6.78; N, 3.25. Found: C, 61.35; H, 6.66; N, 3.20. **7**: *Anal.* Calcd for $C_{19}H_{21}NO_3S \cdot HCl \cdot 0.25H_2O$: C, 59.37; H, 5.90; N, 3.64. Found: C, 59.53; H, 6.19; N, 3.33. **8**: *Anal.* Calcd for $C_{20}H_{23}NO_3S \cdot HCl$: C, 60.98; H, 6.14; N, 3.56. Found: C, 61.00; H, 6.49; N, 3.26. **9**: *Anal.* Calcd for $C_{19}H_{21}NO_3S \cdot HCl \cdot 0.25H_2O$: C, 59.37; H, 5.90; N, 3.64. Found: C, 59.48; H, 5.82; N, 3.36.

Biological Evaluation Procedures. Histamine-1 (H_1) Receptor Binding Assay H_1 binding assay was performed according to the previously reported method[7] with minor modification. The cerebellum of male Hartley guinea pig was homogenized in 40 volumes (w/v) of ice cold 50 mM sodium–potassium phosphate buffer, pH 7.5, (abbreviated as buffer) by a polytron homogenizer (Kinematica). The homogenate was centrifuged at $35500 \times g$ for 10 min at 4 °C and the precipitate was homogenized again in the same volumes of buffer by the polytron homogenizer and centrifuged at $35000 \times g$ for 10 min. The resulting precipitate was resuspended in 100 volumes of buffer by a teflon homogenizer. Tissue homogenates (10 mg wet weight), 3.8 nM of [^{3}H]-pyrilamine and various concentrations of drugs in a total volume of 1.1 ml were added to a polypropylene tube and incubated for 30 min at 25 °C. Ice cold buffer (4 ml) was added to a reaction tube and reaction was stopped by rapid vacuum filtration (cell harvester Brandel M-24-R) through a Whatman GF/C glass fiber filter. The filter was washed 3 times with 5 ml of ice cold buffer. The filter was transferred to a scintillation vial, to which 0.5 ml of MeOH and 8 ml of scintisol EX-H (Wako Pure Chemicals) were added to determine radioactivity by a liquid scintillation counter (Packard 4530). Nonspecific binding was determined in the presence of 1 μM astemizole.

Muscarinic Acetylcholine (M_1) Receptor Binding Assay The binding assay was carried out as in the previously described method[8] with minor modification. The striatum of the rat was homogenized in 10 volumes of distilled water with a Potter-El-vehjem homogenizer. This homogenate preparation was diluted to 200 volumes of the wet tissue weight with 50 mM sodium-potassium phosphate buffer, pH 7.4. The homogenate (5 mg wet weight), 1.26 nM of [^{3}H]quinuclidinyl benzilate, and various concentrations of drugs in a total volume of 1.1 ml were incubated at 37 °C for 60 min. Nonspecific binding was determined by the addition of 1 μM unlabeled dexetimide. The assay was terminated by rapid filtration under reduced pressure over a Whatman GF/B filter. The filters were washed three times with 5 ml of ice-cold 50 mM sodium–potassium phosphate buffer, pH 7.4 and the radioactivity was counted by a liquid scintillation counter.

Effects on 48 h Homologous Passive Cutaneous Anaphylaxis (PCA) in Rats Rats reaginic antibody (IgE) raised to ovalbumin (OA) was prepared by the method of Stotland and Share.[12] Briefly, Wistar strain male rats were immunized by a subcutaneous injection of 1 ml of a suspension containing 1 mg OA, 20 mg aluminum hydroxide gel and 10^{10} killed Bordetella pertussis organisms and then bled 14 d after this sensitization. The antiserum was separated and kept at −80 °C. Groups of 3 Wistar male rats were used and 0.05 ml of anti-OA rat serum, diluted 1:8 with 0.9% saline, was injected intradermally at two points on the dorsum. After 48 h, the PCA reaction was induced by intravenous administration of an aqueous solution containing 2 mg of OA and 5 mg of Evans blue. Test compounds were administered orally 1 h before injection of the antigen. After 30 min, the animals were anesthetized with ethyl ether and the dorsal skin was removed to determine the extravasated dye at each reaction site. The amount of dye was extracted by the method of Katayama[13] and was quantified by spectrometry. The percent inhibition of the PCA reaction was then calculated.

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