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Synthesis and Structure–Activity Relationship of Spiro[isochroman-piperidine] Analogues for Inhibition of Histamine Release. III¹⁾

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Several 1-alkyl-4-piperidylidene analogs were synthesized and tested for inhibitory activity on the compound 48/80-induced release of histamine from mast cells. 4-(4-Isochromanylidene) (12b) and 4-(diphenylmethylene) (14) derivatives of 1-benzylpiperidine were much more active than the lead compounds, 1-benzylspiro[isochroman-piperidines] (1b and 2b).

Keywords——isochroman; piperidine; spiro compound; histamine-release inhibition; compound 48/80; antiallergic activity

We found that spiro[isochroman-piperidin]-4-ones (1) and spiro[isochroman-piperidines] (2) inhibited the compound 48/80-induced release of histamine from isolated rat peritoneal mast cells.¹⁻³⁾ The effect of the substituents (R) of 1 and 2 on the activity³⁾ and the results of chemical modification of the isochroman moiety¹⁾ were described in our previous reports.

In the present work, several compounds with sp^2 and sp^3 carbon atoms in place of the spiro type of carbon atom were prepared and their activities were tested.

Chemistry

4-(4-Alkylcyclohexylidene)isochromans (7) were synthesized as shown in Chart 2: 2-[α -ethoxycarbonyl- α -(4-benzylcyclohexylidene)methyl]benzoic acid obtained by the Stobbe condensation of diethyl homophthalate (5) with 4-alkylcyclohexanone was reduced with lithium aluminum hydride to give 2-(4-alkylcyclohexylidene)-2-(2-hydroxymethylphenyl)ethanol (6). For the cyclization of 6, two methods were tried: heating of 6 over activated alumina at 150°C gave 7 in a high yield, while heating of 6 in benzene in the presence of *p*-toluenesulfonic acid gave not 7 but 4-alkyl-4'-methylenespiro[cyclohexane-1,3'-isochroman] (8).

1-Alkyl-4-(4-isochromanylidene)piperidines (12) were prepared similarly. The intermediates (9) obtained by the Stobbe condensation were converted without purification to 2-(1-benzyl-4-piperidylidene)-2-(2-hydroxymethylphenyl)ethanol derivatives (11) by esterification followed by reduction, and these products were cyclized by heating them over activated alumina to give 12.

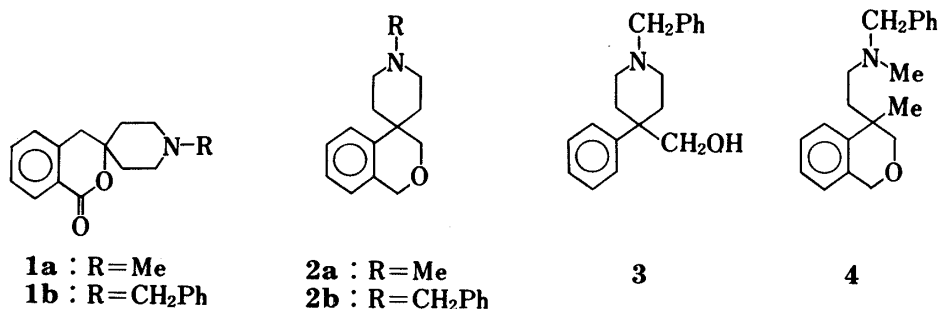


Chart 1

1-Benzyl-4-(4-isochromanylidene)piperidine (**12b**) was hydrogenated over 10% Pd-carbon in ethanol to give 1-benzyl-4-(4-isochromanyl)piperidine (**13**).

1-Benzyl-4-diphenylmethylpiperidine (**15**) was prepared by the reaction of 4-diphenylmethylpiperidine⁴⁾ with benzyl chloride.

1-Benzyl-4-(9-fluorenyl)piperidine (**17**) was prepared from 1-benzyl-4-fluorenylidene-piperidine (**16**) obtained according to Nagai and Uno's method⁵⁾ by hydrogenation over 10% Pd-carbon in ethanol.

Results and Discussion

As previously reported,³⁾ cleavage of the isochroman or piperidine ring of **2b** resulted in loss of the activity: 1-benzyl-4-hydroxymethyl-4-phenylpiperidine (**3**) and 4-[(*N*-benzyl-*N*-methylamino)ethyl]-4-methylisochroman (**4**) were inactive. Since these results suggested that the spiro forms in **1** and **2** contribute to the activity, possibly by maintaining a suitable conformation for interaction with a receptor, a compound with an sp^2 carbon atom in place of the spiro type of carbon atom was prepared. Compound **12b**, in which the piperidine and isochroman rings are linked with a double bond, was more active than the spiro-type compound **2b**. In addition, reduction of the double bond in **12b** resulted in decrease in the potency, as expected.

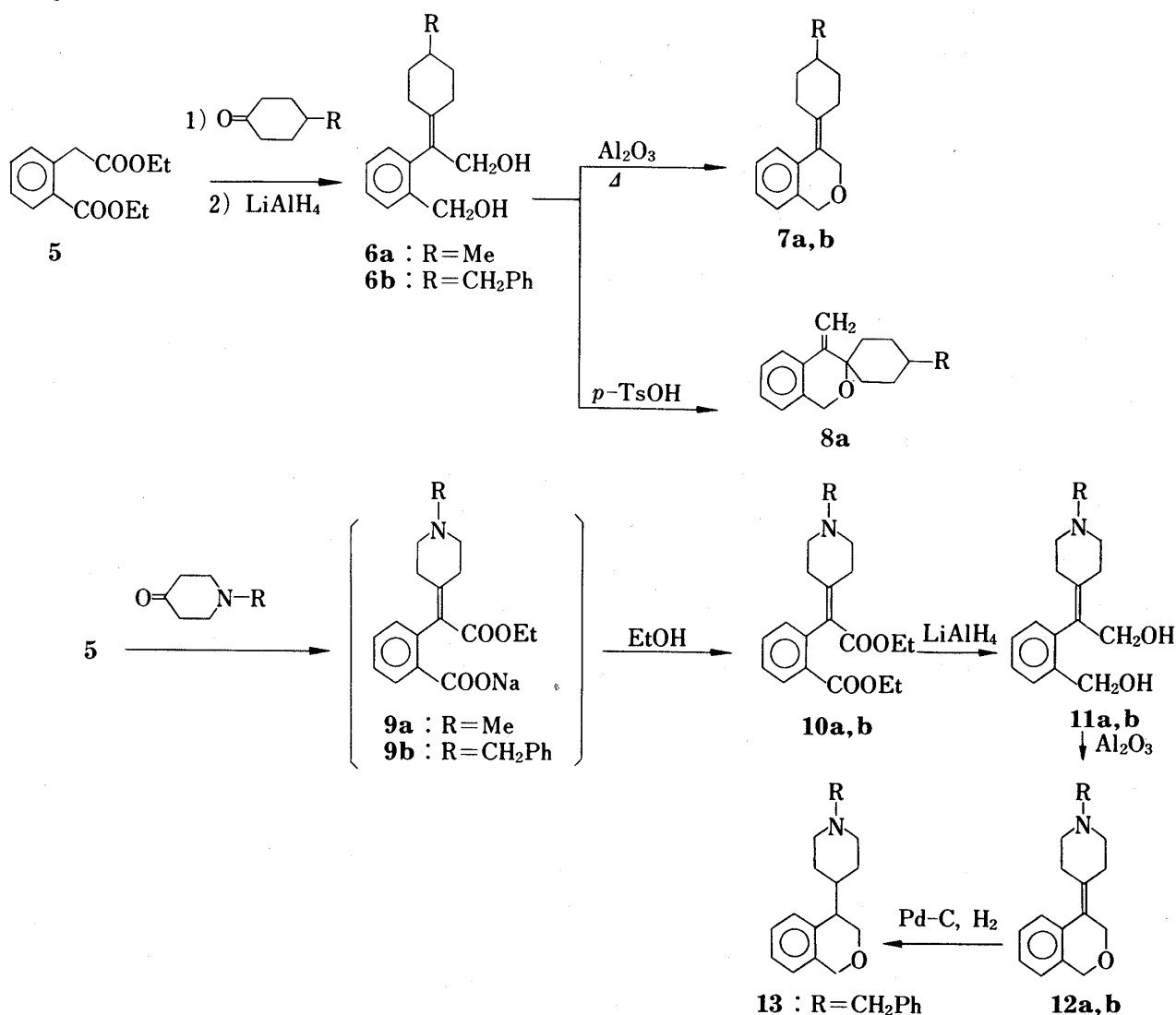


Chart 2

TABLE I. Inhibition of Histamine Release from Isolated Rat Peritoneal Mast Cells by Spiro [isochroman-piperidine] Analogs

Compd. No.	% inhibition of histamine release at various doses (mol)						
	10^{-6}	5×10^{-6}	10^{-5}	5×10^{-5}	10^{-4}	5×10^{-4}	10^{-3}
1a ·HCl				Inactive			
1b ·HCl	—	—	—	—	20	40 ^{a)}	78
2a ·HCl				Inactive			
2b ·HCl	—	—	—	—	28	96 ^{a)}	100
7a ^{b)}	—	—	1	3	12	9	39
7b ^{b)}	—	—	17	48	86	95	95
12a ·HCl	—	—	4	4	13	41	50
12b ·HCl	—	—	27	33	57	83	—
13 ·HCl	—	—	—	—	19	52	88
14 ·HCl ^{c)}	28	90	91	—	—	—	—
15 ·HCL	—	—	50	73	70	80	92
16 ·HCl ^{d)}	—	—	6	2	24	78	80
17 ·HCl	—	—	10	32	37	46	65
DSCG ^{e)}	—	—	—	—	31	58 ^{a)}	80

a) Dose, 2×10^{-4} mol. b) The compound was suspended in carboxymethylcellulose (CMC).

c) mp, 244–248°C (dec.); for free base, see ref. 6. d) mp 241–243°C (dec.); for free base, see ref. 5. e) Disodium cromoglycate; J. S. G. Cox, *Nature* (London), **216**, 1328 (1967).

In order to examine whether or not the spiro-type compound **2b** and the double-bond compound **12b** interact with an active site in a similar manner, chemical modification of the piperidine moiety in **12b** was undertaken. Information from previous studies on the chemical modification of **1** and **2** shows that the optimum number of carbon atoms in the R group is 4 to 7 and the nitrogen atom in the piperidine ring is not essential to elicit the activity.³⁾ Therefore, 1-methyl-4-(4-isochromanylidene)piperidine (**12a**) and the 1'-methyl (**7a**) or 1'-benzyl (**7b**) derivative of 4-cyclohexylideneisochroman were synthesized. The benzyl analog, **7b**, was similar to **12b** in potency, while the potencies of the methyl analogs, **7a** and **12a**, were much less, analogously to 1'-methylspiro[isochroman-3,4'-piperidine]-4-one (**1b**) and 1'-methylspiro[isochroman-4,4'-piperidine] (**2a**), which lack the activity. The effects of substituents of the piperidine or cyclohexane ring on the activity in **12** and **7** were consistent with those of the spiro compounds (**1** and **2**). These results suggest that both spiro and double-bond types of compounds interact with a receptor in a similar manner.

1-Benzyl-4(diphenylmethylene)piperidine (**14**),⁶⁾ in which the isochromanylidene group in **12b** is replaced by a diphenylmethylene group, was synthesized, because a diphenylmethyl group is generally known to be effective as a carrier and/or lipophilic moiety for drugs. Compound **14** was considerably more active than **12b** and was the most active compound in this series. On the other hand, **16**, which was designed as a conformationally rigid analog, was much less active than **14**. Reduction of the double bond in **14** or **16** resulted in a decrease of the activity. The activities of **13**, **15**, and **17** were less than those of the corresponding parent compounds (**12b**, **14**, and **16**, respectively), suggesting that the existence of the double bond made the molecule a better fit for the receptor site. However, **15**, which is a saturated congener of the double bond of **14**, was more active than the analogs with the double bond (**7b**, **12b**, and **16**) or the spiro compound (**2b**). These results may be explained by assuming that conformational change in **15** would be greatly restricted by the bulky diphenylmethyl group and the preferred conformation of **15** may be similar to that of **14**. CPK molecular models of **14** and **15** supported this view.

Experimental

Melting points (determined on a Yanagimoto micro melting point apparatus) are uncorrected. Proton magnetic resonance (PMR) spectra were obtained on a Hitachi R-24 spectrometer at 60 MHz and ^{13}C -nuclear magnetic resonance (CMR) spectra were obtained on a Hitachi 22-FTS spectrometer at 22.6 MHz, with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 spectrometer, and infrared (IR) spectra on a Nippon Bunko A-102 spectrometer.

2-Cyclohexylidene-2-(2-hydroxymethylphenyl)ethanols (6b)—2-(4-Benzylcyclohexylidene)-2-(2-hydroxymethylphenyl)ethanol (**6b**): A 50% dispersion of NaH (1 g, 21 mmol) in mineral oil was added portionwise to a solution of diethyl homophthalate (**5**) (4.2 g, 18 mmol), and the mixture was stirred for 30 min at room temperature. Then, a solution of 4-benzylcyclohexanone (2 g, 18 mmol) in dry benzene (50 ml) was added over a 20 min period. The mixture was stirred for 4 h at room temperature, made acidic with 10% HCl, and extracted with AcOEt. Evaporation of the solvent gave 3.4 g of a mixture of 2-[α -ethoxycarbonyl- α -(4-benzylcyclohexylidene)methyl]benzoic acid and 2-[α -ethoxycarbonyl- α -(4-benzyl-1-cyclohexenyl)methyl]benzoic acid, as a viscous oil. IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 2900 (OH), 1720 (CO), 1690 (CO). PMR (CDCl_3) δ : 1.22, 1.33 (3H, t, $J=6$ Hz, CH_2CH_3), 3.75–4.66 (2.4H, m, CH_2CH_3 and $>\text{CHCH}_2\text{OH}$), 5.43–5.60 (0.4H, m, olefin H), 8.15 (1H, dd, $J=2, 8$ Hz, C_6H), 10.15 (1H, br, COOH). The mixture was used without purification.

The oil (3.4 g) in dry Et_2O (100 ml) was added dropwise at 0°C to a suspension of LiAlH_4 (0.7 g, 18 mmol) in Et_2O (100 ml). The mixture was allowed to reflux for 3.5 h, then decomposed with H_2O , and extracted with Et_2O . The solvent was evaporated off and the residue was chromatographed on a column of silica gel. First elution with AcOEt–petr. ether (1:1) gave 1.2 g (42%) of **6b**, as a viscous oil. Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{O}_2$: C, 81.95; H, 8.13. Found: C, 81.72; H, 7.91. IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 3300 (OH). PMR (CDCl_3) δ : 1.29–2.16 (9H, m, cyclohexane H), 2.49 (2H, d, $J=6$ Hz, CH_2Ph), 3.42–3.74 (2H, br, $\text{OH}\times 2$), 3.75–4.74 (4H, m, $\text{CH}_2\text{OH}\times 2$), 6.92–7.37 (9H, m, aromatic H). MS m/e : 304 ($\text{M}^+ - \text{H}_2\text{O}$).

Further elution gave 0.8 g (27%) of 2-(4-benzyl-1-cyclohexenyl)-2-(2-hydroxymethylphenyl)ethanol, as a viscous oil. Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{O}_2$: C, 81.95; H, 8.13. Found: C, 81.84; H, 8.07. IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 3350 (OH). PMR (CDCl_3) δ : 1.34–2.15 (7H, m, cyclohexene H), 2.55 (2H, d, $J=6$ Hz, CH_2Ph), 2.63–3.14 (2H, br, $\text{OH}\times 2$), 3.64–4.19 (3H, m, CHCH_2OH), 4.50 and 4.83 (2H, ABq, $J=12$ Hz, CH_2OH), 5.41–5.60 (1H, m, olefin H), 7.23 (4H, s, aromatic H), 7.30 (5H, s, Ph). MS m/e : 304 ($\text{M}^+ - \text{H}_2\text{O}$).

2-(2-Hydroxymethylphenyl)-2-(4-methylcyclohexylidene)ethanol (**6a**) and 2-(2-hydroxymethylphenyl)-2-(4-methyl-1-cyclohexenyl)ethanol were similarly prepared. **6a**: yield 47%. Viscous oil. Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2$: C, 78.01; H, 9.00. Found: C, 78.15; H, 8.95. IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 3300 (OH). PMR (CCl_4) δ : 0.93 (3H, d, $J=7$ Hz, CH_3), 1.38–2.12 (9H, m, cyclohexane H), 3.79–4.58 (4H, m, $\text{CH}_2\text{OH}\times 2$), 4.53–4.85 (2H, br, $\text{OH}\times 2$), 6.83–7.38 (4H, m, aromatic H).

2-(2-Hydroxymethylphenyl)-2-(4-methyl-1-cyclohexenyl)ethanol: Yield 20%. Viscous oil. Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2$: C, 78.01; H, 9.00. Found: C, 77.95; H, 9.04. IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 3300 (OH). PMR (CCl_4) δ : 1.03 (3H, d, $J=7$ Hz, CH_3), 1.43–2.14 (7H, m, cyclohexene H), 3.38–4.15 (3H, m, $>\text{CHCH}_2\text{OH}$), 4.43 and 4.80 (2H, ABq, $J=12$ Hz, CH_2OH), 5.34–5.51 (1H, m, olefin H), 7.15 (4H, s, aromatic H).

4-(Cyclohexylidene)isochromans (7)—4-(4-Benzylcyclohexylidene)isochroman (**7b**): A mixture of **6b** (7 g, 28 mmol) and activated Al_2O_3 (for column chromatography, abt. 300 mesh, Wako Chemical Ind. Co., Ltd., Tokyo, Japan; 60 g) was stirred for 23 h at 150°C , then washed with Et_2O . The Et_2O washings were concentrated and the residue was chromatographed on a column of silica gel. Elution with benzene–cyclohexane (1:1) gave 4 g (62%) of **7b** as a viscous oil. Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{O}$: C, 86.80; H, 7.95. Found: C, 87.01; H, 7.85. IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 1640 (C=C). PMR (CCl_4) δ : 1.29–2.28 (7H, m, cyclohexane H), 2.53 (2H, d, $J=6$ Hz, CH_2Ph), 2.69–3.42 (2H, m, cyclohexane H), 4.38 (2H, s, C_3H_2), 4.54 (2H, s, C_1H_2), 7.06–7.28 (9H, m, aromatic H). MS m/e : 304 (M^+).

4-(4-Methylcyclohexylidene)isochroman (**7a**): Yield 58%. Viscous oil. Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}$: C, 84.16; H, 8.83. Found: C, 84.01; H, 8.95. IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 1630 (C=C). PMR (CCl_4) δ : 0.91 (3H, d, $J=6$ Hz, CH_3), 1.21–2.06 (7H, m, cyclohexane H), 2.43–3.28 (2H, m, cyclohexane H), 4.32 (2H, s, C_3H_2), 4.47 (2H, s, C_1H_2). MS m/e : 228 (M^+).

4-Methyl-4'-methylenespiro[cyclohexane-1,3'-isochroman] (8a)—A mixture of **6a** (10 g, 40 mmol), *p*-toluenesulfonic acid (0.3 g), and dry benzene was allowed to reflux for 2 h in a flask fitted with a modified Soxhlet extractor containing anhyd. MgSO_4 in the thimble. After cooling, the mixture was made basic with 20% KOH and extracted with AcOEt. The solvent was evaporated off and the residue was chromatographed on a column of silica gel. Elution with cyclohexane–benzene (1:1) gave 6.4 g (69%) of **8a** as a viscous oil. Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}$: C, 84.16; H, 8.83. Found: C, 84.50; H, 8.72. IR $\nu_{\text{max}}^{\text{liq.}}$ cm^{-1} : 1630 (C=C). PMR (CCl_4) δ : 1.02 (3H, d, $J=6$ Hz, CH_3), 1.42–2.11 (9H, m, cyclohexane H), 4.70 (2H, s, C_1H_2), 5.10 (1H, s, $=\text{CH}_2$), 5.49 (1H, s, $=\text{CH}_2$), 6.92–7.55 (4H, m, aromatic H). CMR (CDCl_3) δ : 28.58 (q), 36.53 (t) $\times 2$, 38.48 (d), 40.18 (t) $\times 2$, 67.87 (t), 80.02 (s), 112.00 (t), 130.20 (d), 130.55 (d), 132.91 (d), 133.52 (d), 138.00 (s), 140.50 (s), 153.24 (s). MS m/e : 228 (M^+).

Diethyl α -(Piperidylidene)homophthalates (10)—Diethyl α -(1-Benzyl-4-piperidylidene)homophthalate (**10b**): A 50% dispersion of NaH (3.4 g, 70 mmol) in mineral oil was added portionwise to a solution of **5** (16.4 g, 70 mmol) in dry benzene (200 ml), and the mixture was stirred for 30 min at room temperature. Then, a solution of 1-benzyl-4-piperidone (13 g, 70 mmol) in dry benzene (50 ml) was added over a 20 min period, and the mixture was stirred for 4 h at room temperature. Most of the benzene was evaporated off to give a solid, to which abs. EtOH was added. The mixture was allowed to reflux for 10 h while dry HCl was bubbled through it, then it was concentrated. The residue was made basic with 20% KOH and extracted with AcOEt. The solvent was evaporated off and the residue was chromatographed on a column of alumina. First elution with AcOEt-petr. ether gave 12.3 g (54%) of **10b** as a viscous oil. *Anal.* Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.90; H, 7.01; N, 3.59. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1} : 1720 (CO), 1705 (CO). PMR ($CDCl_3$) δ : 1.15 (3H, t, $J=7$ Hz, CH_2CH_3), 1.37 (3H, t, $J=7$ Hz, CH_2CH_3), 1.93–3.27 (8H, m, piperidine H), 3.56 (2H, s, NCH_2Ph), 4.14 (2H, q, $J=7$ Hz, CH_2CH_3), 4.33 (2H, q, $J=7$ Hz, CH_2CH_3), 8.06 (1H, dd, $J=2, 8$ Hz, C_6H). MS m/e : 407 (M^+).

Further elution gave 5.4 g (24%) of diethyl α -[1-benzyl-4-(1,2,5,6-tetrahydropyridyl)]homophthalate as a viscous oil. *Anal.* Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.52; H, 7.09; N, 3.30. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1} : 1720 (CO), 1705 (CO). PMR ($CDCl_3$) δ : 1.25 (3H, t, $J=7$ Hz, CH_2CH_3), 1.38 (3H, t, $J=7$ Hz, CH_2CH_3), 1.80–2.28 (2H, m, C_5H_3), 2.41–2.72 (2H, m, C_6H_2), 3.52 (2H, s, NCH_2Ph), 4.14 (2H, q, $J=7$ Hz, CH_2CH_3), 4.34 (2H, q, $J=7$ Hz, CH_2CH_3), 5.36–5.57 (1H, m, olefin H), 7.96 (1H, dd, $J=2, 7$ Hz, C_6H). MS m/e : 407 (M^+).

2-(2-Hydroxymethylphenyl)-2-(4-piperidylidene)ethanols (11)—2-(1-Benzyl-4-piperidylidene)-2-(2-hydroxymethylphenyl)ethanol (**11b**): A solution of **10b** (8.1 g, 20 mmol) in Et_2O (50 ml) was added dropwise to a suspension of $LiAlH_4$ (1 g, 25 mmol) in Et_2O (150 ml) and the mixture was allowed to reflux for 3 h, then decomposed with H_2O , and extracted with AcOEt. The solvent was evaporated off and the residue was chromatographed on a column of alumina to give 5.3 g (82%) of **11b** as a viscous oil. *Anal.* Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.15; H, 7.92; N, 4.27. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1} : 3350 (OH). PMR ($CDCl_3$) δ : 1.78–2.12 (2H, m, piperidine H), 2.21–2.54 (2H, m, piperidine H), 2.50 (4H, s, piperidine H), 3.45 (2H, s, NCH_2Ph), 3.73 (2H, br, $OH \times 2$), 3.90 and 4.56 (2H, ABq, $J=12$ Hz, CH_2OH), 4.21 and 4.64 (2H, ABq, $J=12$ Hz, CH_2OH), 7.32 (5H, s, Ph). MS m/e : 323 (M^+).

2-(2-Hydroxymethylphenyl)-2-(1-methyl-4-piperidylidene)ethanol (**11a**): Yield 85%. Viscous oil. *Anal.* Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 12.94. Found: C, 72.64; H, 8.62; N, 13.01. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1} : 3300 (OH). PMR ($CDCl_3$) δ : 1.70–2.10 (2H, s, piperidine H), 2.52 (3H, s, NCH_3), 2.20–2.60 (6H, m, piperidine H), 3.92 and 4.46 (2H, ABq, $J=12$ Hz, CH_2OH), 4.24 and 4.67 (2H, ABq, $J=12$ Hz, CH_2OH), 4.80–5.20 (2H, br, $OH \times 2$). MS m/e : 247 (M^+).

4-(4-Isochromanylidene)piperidines (12)—These compounds were prepared in the same manner as described for the preparation of **7b**.

1-Benzyl-4-(4-isochromanylidene)piperidine (**12b**): Yield 45%. Viscous oil. *Anal.* Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.27; H, 7.88; N, 4.39. PMR ($CDCl_3$) δ : 2.10–2.80 (8H, m, piperidine H), 3.50 (2H, s, NCH_2Ph), 4.51 (2H, s, C_3H_2), 4.65 (2H, s, C_1H_2), 7.37 (5H, s, Ph). MS m/e : 305 (M^+). The salt was formed in Et_2O by treatment with dry HCl to give **12b**·HCl, mp 238–242°C (dec.).

4-(4-Isochromanylidene)-1-methylpiperidine (**12a**): Yield 51%. Viscous oil. *Anal.* Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.31; H, 8.20; N, 5.97. IR $\nu_{\max}^{\text{liq.}}$ cm^{-1} : 1640 ($C=C$). PMR (CCl_4) δ : 2.23 (3H, s, NCH_3), 2.20–2.50 (2H, m, piperidine H), 2.40 (4H, s, piperidine H), 2.55–2.85 (2H, m, piperidine H), 4.39 (2H, s, C_3H_2), 4.58 (2H, s, C_1H_2). The salt was formed in Et_2O by treatment with dry HCl to give **12a**·HCl, mp 200–210°C (dec.).

1-Benzyl-4-(4-isochromanyl)piperidine (13)—Compound **12b** (1.5 g, 5 mmol) was hydrogenated over 5% Pd-carbon (0.2 g) in EtOH. The catalyst was removed and the filtrate was concentrated to give 1.2 g (80%) of **13b** as a viscous oil. *Anal.* Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.51; H, 8.30; N, 4.37. PMR (CCl_4) δ : 1.32–3.05 (10H, m, piperidine H and C_4H), 3.42 (2H, s, NCH_2Ph), 3.65 (1H, dd, $J=3.5, 13$ Hz, C_3H), 4.15 (1H, dd, $J=2.5, 13$ Hz, C_3H), 4.71 (2H, s, C_4H_2), 7.27 (5H, s, Ph). MS m/e : 307 (M^+). The salt was formed in Et_2O by treatment with dry HCl and the crude hydrochloride was recrystallized from EtOH– Me_2CO to give **13**·HCl, mp 231–234°C (dec.).

1-Benzyl-4-(diphenylmethyl)piperidine (15)—A mixture of diphenylmethylpiperidine⁴⁾ (1 g, 4 mmol), benzyl chloride (0.51 g, 4 mmol), K_2CO_3 (1.2 g, 9 mmol) and dry N,N -dimethylformamide (DMF) (20 ml) was heated for 2 h at 60°C, poured into H_2O , and extracted with Et_2O . The Et_2O was evaporated off and the residue was chromatographed on a column of alumina. Elution with AcOEt-petr. ether (1:2) gave **15** as a viscous oil. *Anal.* Calcd for $C_{25}H_{27}N$: C, 87.93; H, 7.97; N, 4.10. Found: C, 88.09; H, 8.01; N, 4.05. PMR ($CDCl_3$) δ : 0.85–2.99 (9H, m, piperidine H), 3.44 (2H, s, NCH_2Ph), 3.48 (1H, d, $J=11$ Hz, $CHPh_2$), 7.32 (15H, s, aromatic H). MS m/e : 341 (M^+). The salt was formed in Et_2O by treatment with dry HCl to give **15**·HCl, mp 142–150°C (dec.).

1-Benzyl-4-(9-fluorenyl)piperidine (17)—This compound was prepared from 1-benzyl-4-fluorenylidene-piperidine⁵⁾ (**16**) in the same manner as described for the preparation of **13b**, mp 147.5–149°C, yield 1.2 g (80%). *Anal.* Calcd for $C_{25}H_{25}N$: C, 88.45; H, 7.42; N, 4.13. Found: C, 88.70; H, 7.63; N, 4.19. PMR ($CDCl_3$) δ : 1.30–2.30 (5H, m, piperidine H), 2.60–3.00 (4H, m, piperidine H), 3.48 (2H, s,

NCH₂Ph), 3.93 (1H, d, $J=2$ Hz, C₉H), 7.25 (5H, s, Ph). MS m/e : 339 (M^+). The salt was formed in Et₂O by treatment with dry HCl to give **17**·HCl, mp 185—190°C (dec.).

Inhibition of Histamine Release——Assay of inhibition of histamine release was carried out as described previously.²⁾

References and Notes

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