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Synthesis and Structure–Activity Relationship of Spiro[isochroman-piperidine] Analogs for Inhibition of Histamine Release. III[1]

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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

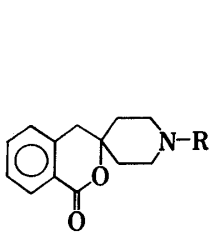
We found that spiro[isochroman-piperidin]-4-ones (**1**) and spiro[sochroman-piperidines] (**2**) inhibited the compound 48/80-induced release of histamine from isolated rat peritoneal mast cells.[1-3] The effect of the substituents (R) of **1** and **2** on the activity[3] and the results of chemical modification of the isochromsn moiety[1] 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.

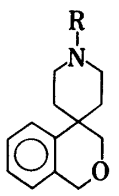
Chemistry

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**).

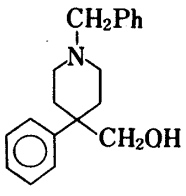
1-Alkyl-4-(4-isochromanylidene)piperidines (**12**) were prepared similarly. The intermediates (**9**) obtained by the Stobbe condensation were converted without purification to 2-(1-benzyl-4-piperiylidene)-2-(2-hydroxymethylphenyl)ethanol derivatives (**11**) by esterification followed by reduction,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



1a : R=Me
1b : R=CH_2Ph



2a : R=Me
2b : R=CH_2Ph



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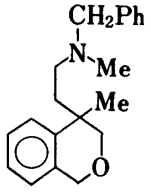

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Chart 1

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-diphenylmethylpiperidine[4] with benzyl chloride.

1-Benzyl-4-(9-fluorenyl)piperidine (**17**) was prepared from 1-benzyl-4-fluorenylidenepiperidine (**16**) obtained according to Nagai and Uno's method[5] 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.

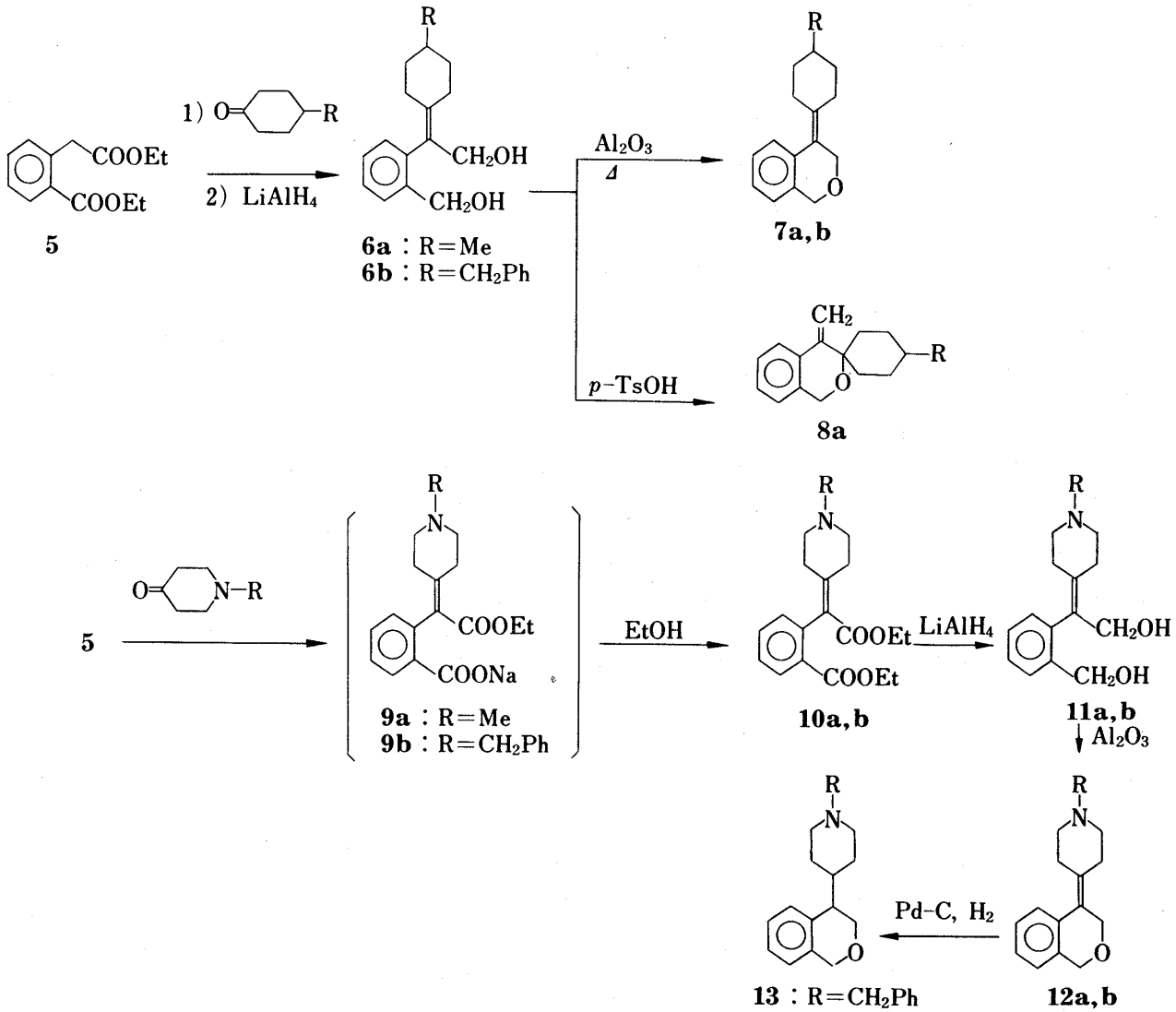

Chart 2

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**) snd 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 (6)——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)methy]benzoic acid and 2-[α-ethoxycarbonyl-α-(4-benzyl-1-cyclohexenyl)methyl]-benzoic acid, as a viscous oil. IR $\nu_{max}^{liq.}$ cm^{-1}: 2900 (OH), 1720 (CO), 1690 (CO). PMR ($CDCl_3$) δ: 1.22, 1.33 (3H, t, J=6 Hz, $CH_2C\underline{H}_3$), 3.75—4.66 (2.4H, m, $C\underline{H}_2CH_3$ and >$C\underline{H}CH_2OH$), 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 $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.72; H, 7.91. IR $\nu_{max}^{liq.}$ cm^{-1}: 3300 (OH). PMR ($CDCl_3$) δ: 1.29—2.16 (9H, m, cyclohexane H), 2.49 (2H, d, J=6 Hz, $C\underline{H}_2Ph$), 3.42—3.74 (2H, br, OH×2), 3.75—4.74 (4H, m, $C\underline{H}_2OH$×2). 6.92—7.37 (9H, m, aromatic H). MS m/e: 304 (M^+-H_2O).

Further elution gave 0.8 g (27%) of 2-(4-benzyl-1-cyclohexenyl)-2-(2-hydroxymethylphenyl)ethanol, as a viscous oil. *Anal.* Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.84; H, 8.07. IR $\nu_{max}^{liq.}$ cm^{-1}: 3350 (OH). PMR ($CDCl_3$) δ: 1.34—2.15 (7H, m, cyclohexene H), 2.55 (2H, d, J=6 Hz, $C\underline{H}_2Ph$), 2.63—3.14 (2H, br, OH×2), 3.64—4.19 (3H, m, $C\underline{H}C\underline{H}_2OH$), 4.50 and 4.83 (2H, ABq, J=12 Hz, $C\underline{H}_2OH$), 5.41—5.60 (1H, m, olefin H), 7.23 (4H, s, aromatic H), 7.30 (5H, s, Ph). MS m/e: 304 (M^+-H_2O).

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 $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.15; H, 8.95. IR $\nu_{max}^{liq.}$ 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, $C\underline{H}_2OH$×2), 4.53—4.85 (2H, br, OH×2), 6.83—7.38 (4H, m, aromatic H).

2-(2-Hydroymethylphenyl)-2-(4-methyl-1-cyclohexenyl)ethanol: Yield 20%. Viscous oil. *Anal.* Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.95; H, 9.04. IR $\nu_{max}^{liq.}$ 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, >$C\underline{H}C\underline{H}_2OH$), 4.43 and 4.80 (2H, ABq, J=12 Hz, $C\underline{H}_2OH$), 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 $C_{22}H_{24}O$: C, 86,80; H, 7.95. Found: C, 87.01; H, 7.85. IR $\nu_{max}^{liq.}$ cm^{-1}: 1640 (C=C). PMR (CCl_4) δ: 1.29—2.28 (7H, m, cyclohexane H), 2.53 (2H, d, J=6 Hz, $C\underline{H}_2Ph$), 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 $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.01; H, 8.95. IR $\nu_{max}^{liq.}$ 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 Soxlet 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 $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.50; H, 8.72. IR $\nu_{max}^{liq.}$ 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, =CH_2), 5.49 (1H, s, =CH_2), 6.92—7.55 (4H, m, aromatic H). CMR ($CDCl_3$) δ: 28.58 (q), 36.53 (t)×2, 38.48 (d), 40.18 (t)×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 $\nu_{max}^{liq.}$ cm^{-1}: 1720 (CO), 1705 (CO). PMR ($CDCl_3$) δ: 1.15 (3H, t, J=7 Hz, $CH_2\underline{C}_3$), 1.37(3H, t, J=7 Hz, $CH_2C\underline{H}_3$),1.93—3.27 (8H, m, piperidine H), 3.56 (2H, s, $NC\underline{H}_2Ph$), 4.14 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.33 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$),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 $\nu_{max}^{liq.}$ cm^{-1}: 1720 (CO), 1705 (CO). PMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.38 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.80—2.28 (2H, m, $C_5'H_3$), 2.41—2.72 (2H, m, $C_6'H_2$), 3.52 (2H, s, $NC\underline{H}_2Ph$), 4.14 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.34 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 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 $\nu_{max}^{liq.}$ 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, $NC\underline{H}_2Ph$), 3.73 (2H, br, OH×2), 3.90 and 4.56 (2H, ABq, J=12 Hz, $C\underline{H}_2OH$), 4.21 and 4.64 (2H, ABq, J=12 Hz, $C\underline{H}_2OH$), 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 $\nu_{max}^{liq.}$ 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, $C\underline{H}_2OH$),4.24 and 4.67 (2H, ABq, J=12 Hz, $C\underline{H}_2OH$), 4.80—5.20 (2H, br, OH×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, piperidne H), 3.50 (2H, s, $NC\underline{H}_2Ph$), 4.51 (2H, s, $C_3'H_2$), 4.65 (2H, s, $C_1'H_2$), 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 $\nu_{max}^{liq.}$ 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, $C_3'H_2$), 4.58 (2H, s, $C_1'H_2$). 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, $NC\underline{H}_2Ph$), 3.65 (1H, dd, J=3.5, 13 Hz, $C_3'H$), 4.15 (1H, dd, J=2.5, 13 Hz, $C_3'H$), 4.71 (2H, s, $C_4'H_2$), 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 diphenylmethylpiperidne[4] (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, $NC\underline{H}_2Ph$), 3.48 (1H, d, J=11 Hz, $C\underline{H}Ph_2$), 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-fluorenylidenepiperidine[5] (**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,

NCH_2Ph), 3.93 (1H, d, J=2 Hz, $C_{9'}H$), 7.25 (5H, s, Ph). MS m/e: 339 (M^+). The salt was formed in Et_2O 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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4) K.W. Wheeler, J.K. Seyler, F.P. Polapoli, and F.J. Mc Cardy, U.S. Patent 2898339 (1959) [*Chem. Abstr.*, **54**, 581*c*].
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