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Synthesis and Structure–Activity Relationship of Spiro[isochroman-piperidine] Analogs for Inhibition of Histamine Release. IV¹⁾

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Various 1'-(*o*, *m*, and/or *p*-substituted benzyl) (5), 1'-(heterocyclic arylmethyl) (6), and 1'-acyl (7) analogs of spiro[isochroman-3,4'-piperidin]-1-one were prepared and tested for inhibitory activity on the compound 48/80-induced release of histamine from mast cells. The biological results suggested that the activity is mainly affected by the lipophilicity rather than by the electrostatic character of the 1'-substituent.

4-Benzylspiro[cyclohexane-1,3'-hexahydroisochroman]-1'-one (17) and 9-benzyl-1-oxa-spiro[5.5]undecan-2-one (18) were prepared and found to be inactive, implying that the benzene moiety in the isochroman ring is essential for the activity.

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

We found that *N*-alkylspiro[isochroman-piperidin]-1-ones (1 and 3) inhibited the compound 48/80-induced release of histamine from isolated rat peritoneal mast cells.²⁾ We have studied the structure–activity relationship of the activity of this series of compounds with the aim of developing new antiallergic agents.^{1–4)} This paper deals with further structural modifications of *N*-alkylspiro[isochroman-piperidines] and their consequences for the activity.

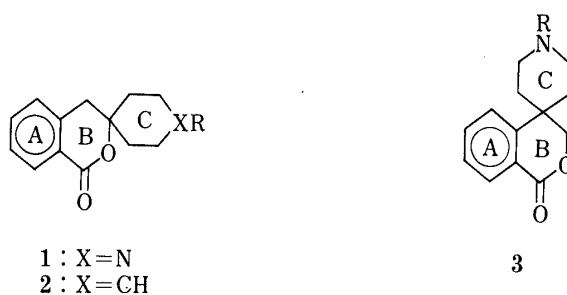


Chart 1

Modification of the Piperidine Moiety

We have investigated the effect of the substituent (R) in the piperidine ring of 1 on the activity, and the following results were obtained:²⁾ 1) *N*-alkyl analogs from butyl to heptyl showed activity, but increasing the chain length to octyl or decreasing it to propyl resulted in loss of the activity; 2) *N*-phenyl and *N*-cyclohexyl derivatives were inactive, while *N*-cyclohexylmethyl, *N*-benzyl, and *N*-phenethyl derivatives, in which an alkyl chain is present between the nitrogen atom and the cyclic groups, showed potent activity; 3) when the piperidine ring was replaced by a cyclohexyl ring, the activity was retained.

In the present work, the compounds listed in Tables I–III were prepared in order to

clarify the effect of the *N*-alkylpiperidine moiety on the activity. Various 1'-(*o*, *m*, and/or *p*-substituted benzyl)spiro[isochroman-3,4'-piperidin]-1-ones (**5**) were prepared by alkylation of spiro[isochroman-3,4'-piperidin]-1-one (**4**) using benzyl halides and potassium carbonate or by reductive alkylation of **4** using benzaldehydes and sodium cyanoborohydride (Chart 2). Various 1'-(heterocyclic arylmethyl)spiro[isochroman-3,4'-piperidin]-1-ones (**6**) were similarly prepared.

Benzyl analogs (**5**) with an electron-releasing substituent such as an alkyl, hydroxyl, methoxyl, or amino group or an electron-withdrawing substituent such as a halogen, nitro, or ethoxycarbonyl group were prepared (Table I). The biological results showed that there is no clear correlation between the activity and electrostatic character of the substituent. The benzyl group of 1'-benzylspiro[isochroman-3,4'-piperidin]-1-one (**1a**) was next replaced by a heterocyclic arylmethyl group (Table II). The furfuryl (**6a**), and 2-thienylmethyl (**6b**) analogs showed potency equal to that of **1a**, but the 4-imidazolylmethyl analog (**6c**) had remarkably low activity and the 3-pyridylmethyl analog (**6d**) was inactive. With decreasing electron density of the heterocyclic ring in **6a—d**, the potency decreased.

1'-Acylspiro[isochroman-3,4'-piperidin]-1-ones (**7**) were prepared by acylation of **4** with acyl halides to examine the effect of the basicity of the piperidine moiety on the activity. *N*-Acyl analogs (**7a—c**) with a shorter acyl group than butyryl were inactive, while *N*-acyl analogs (**7d—h**) from valeryl to octanoyl, as well as the *N*-benzoyl analog (**7i**) and the *N*-phenacyl analog (**7j**), showed remarkable activity. This relationship between the activity and the length of the acyl group was in fair agreement with that between the activity and the length of the alkyl group in *N*-alkyl analogs of **1**. These results suggested that the basicity of the piperidine moiety is not essential for the activity, whereas the lipophilicity and the length of the substituent are important for the activity.

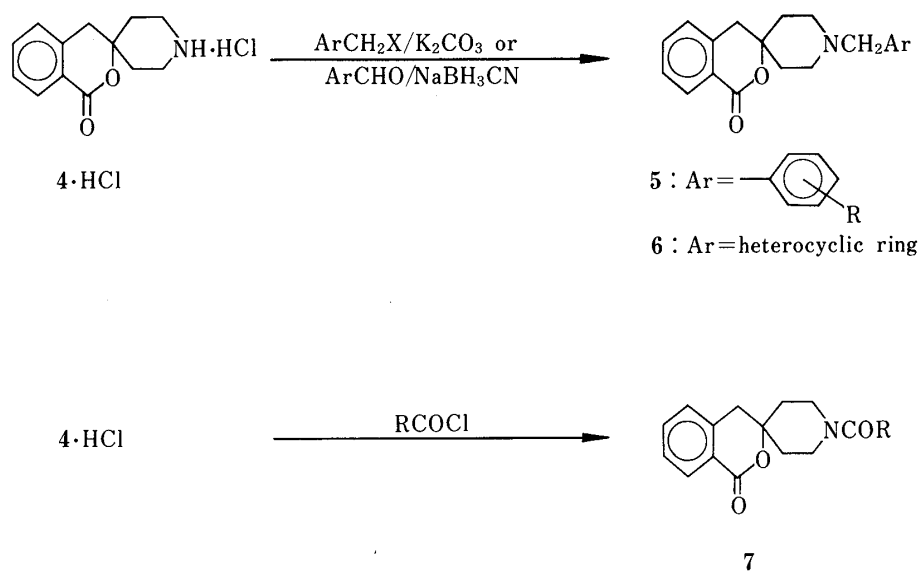


Chart 2

Modification of the Isocoumarin Moiety

We previously reported that when the isocoumarin ring was replaced by a heterocyclic ring such as chromanone, 1,3-benzoxazine, 1,3-benzthiazine, or 4-quinazolinone, the activity was retained.⁴⁾ In the present work, we prepared 1-benzylspiro[piperidine-4,1'-tetralin] (**14**), which has no hetero atom in the B ring (Chart 3). Reduction of 1,1-bis(methoxycarbonylmethyl)-2-tetralone⁵⁾ (**8**) with sodium borohydride gave 1,2,3a,4,5,9b-hexahydro-9b-(methoxycarbonylmethyl)naphtho[2,1-*b*]furan-2-one (**9**), which was converted to 9b-

(*N*-benzylcarbamoylmethyl)-1,2,3a,4,5,9b-hexahydronaphtho[2,1-*b*]furan-2-one (**11**) by hydrolysis, followed by reaction with benzylamine. Reduction of **11** with lithium aluminum hydride gave 1-benzylspiro[piperidine-4,1'-tetralin]-2'-ol (**12**). Heating of **12** in hexamethylphosphotriamide (HMPT) have 1'-benzylspiro[(1,4-dihydronaphthalene)-1,4'-piperidine] (**13**), which was converted to **14** by hydrogenation in the presence of palladium (Pd)-carbon. Compound **14** was more active than 1'-benzylspiro[isochroman-4,4'-piperidin]-1-one (**3a**), implying that the hetero atom of the B ring in **2a** or **3a** does not play a role as an active site.

4-Benzylspiro[cyclohexane-1,3'-(*trans*-4a',5',6',7',8',8a'-hexahydroisochroman)]-1'-one (**17**) and 9-benzyl-1-oxaspiro[5.5]undecan-2-one (**18**) were prepared to examine whether or not the benzene moiety (A ring) in **1a** is essential for the activity. Compound **17** was obtained by the Grignard reaction of 3-benzyl-1,5-dibromopentane⁶⁾ (**16**) with *trans*-hexahydrohomophthalic anhydride⁷⁾ (**15**) according to Cannonne *et al.*⁸⁾ (Chart 3). Similarly, **18** was prepared from **16** and glutaric anhydride.

4-Benzylspiro[cyclohexane-1,3'-isochroman]-1'-one (**2a**) was previously found to have activity equal to that of **1a**. Compound **17**, the structure of which corresponds to that of **2a** with the benzene ring (A ring) hydrogenated, was inactive. In addition, **18** (lacking the ben-

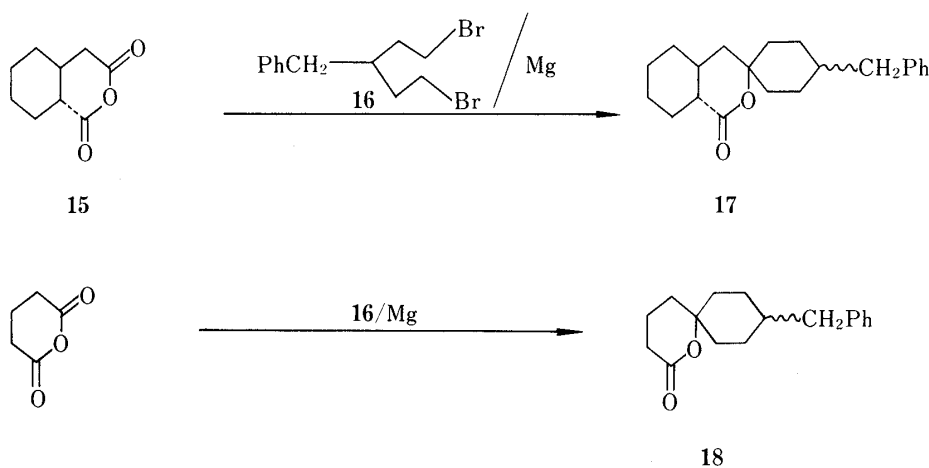
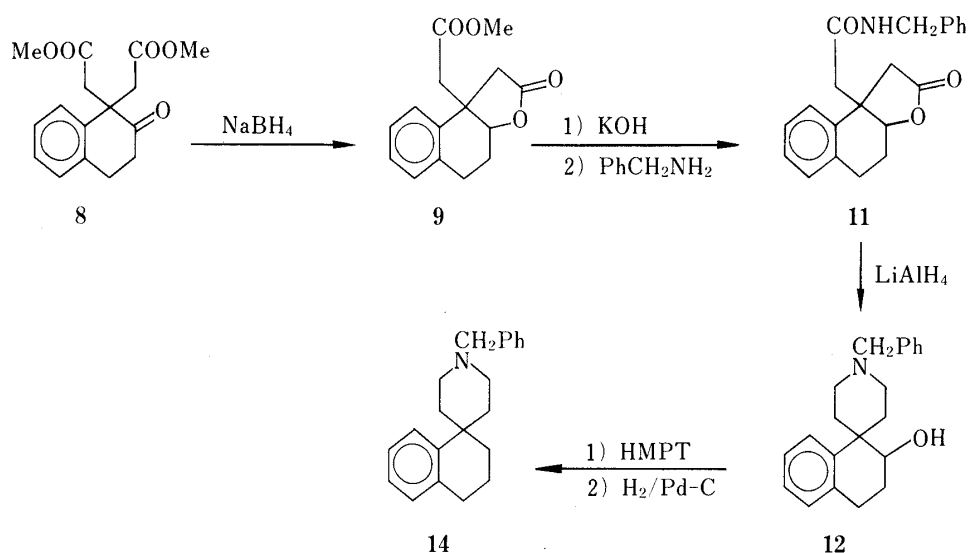


Chart 3

TABLE I. Inhibition of Histamine Release from Isolated Rat Peritoneal Mast Cells by 5a—w

Compd. No.	R	% inhibition at various doses (mol) ^{a)}				Synthetic method	Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%)			IR ν_{max} cm^{-1}
		10 ⁻⁴	5 × 10 ⁻⁴	10 ⁻³	C						H	N		
5a ^{b)}	H	11	40	76										
5b	2-Me	39	86	85	B	37	54—58	Cyclohexane	C ₂₁ H ₂₃ NO ₂	78.47 (78.20)	7.21 7.30	4.36 4.28)	1715	
5c	4-Me	34	90	61	B	34	52—54	Et ₂ O— cyclohexane	C ₂₁ H ₂₃ NO ₂	78.47 (78.27)	7.21 7.38	4.36 4.22)	1720	
5d	2-OH		Inactive		B	47	193—195	MeOH	C ₂₀ H ₂₁ NO ₃	74.28 (74.03)	6.55 6.24	4.33 4.08)	3410, 1715	
5e	4-OH	26	25	52	B	42	167—170	MeOH	C ₂₀ H ₂₁ NO ₃	74.28 (74.28)	6.55 6.88	4.33 4.10)	3740, 1685	
5f	2-OMe	4	11	100	B	10	Oil	—	C ₂₁ H ₂₃ NO ₃	74.75 (74.30)	6.87 6.61	4.15 4.05)	1720	
5g	4-OMe	35	80	92	B	59	107—110	Et ₂ O	C ₂₁ H ₂₃ NO ₃	74.75 (74.45)	6.87 6.88	4.15 4.02)	1710	
5h	2-NMe ₂	9	83	97	A	60	176—178	CHCl ₃ — benzene	C ₂₂ H ₂₆ N ₂ O ₂	75.30 (75.19)	7.48 7.55	7.99 7.81)	1710	
5i	4-NMe ₂	22	84	92	B	34	158—161	Benzene— cyclohexane	C ₂₂ H ₂₆ N ₂ O ₂	75.30 (75.28)	7.48 7.58	7.99 7.86)	1715	
5j	4-NEt ₂	11	96	100	B	41	63—66	Cyclohexane— petr. ether	C ₂₄ H ₃₀ N ₂ O ₂	76.15 (75.88)	7.99 8.07	7.40 7.15)	1700	
5k	4- <i>tert</i> -Bu	45	74	65	A	72	121—123	Benzene— cyclohexane	C ₂₄ H ₂₉ NO ₂	79.30 (79.12)	8.04 8.13	3.85 3.68)	1710	
5m	2-Cl	29	100	100	B	50	83—85	Et ₂ O— cyclohexane	C ₂₀ H ₂₀ ClNO ₂	70.27 (70.53)	5.89 5.93	4.10 3.94)	1705	
5n	4-Cl		Inactive		B	26	112—114	Benzene— cyclohexane	C ₂₀ H ₂₀ ClNO ₂	70.27 (70.36)	5.89 5.96	4.10 3.98)	1715	
5o	2-Br	94	97	98	A	60	Oil	—	C ₂₀ H ₂₀ BrNO ₂	62.20 (62.01)	5.21 5.04	3.63 3.57)	1710	
5p	4-Br		Inactive		A	69	129—130	Benzene— cyclohexane	C ₂₀ H ₂₀ BrNO ₂	62.20 (61.93)	5.21 5.26	3.63 3.42)	1715	
5q	2-COOMe	42	46	54	A	71	139—141	Benzene— cyclohexane	C ₂₂ H ₂₃ NO ₄	72.31 (72.23)	6.34 6.34	3.83 3.85)	1720	

5r	4-COOMe	30	37	47	B	73	220—225	MeOH	$C_{22}H_{23}NO_4$	72.31 (72.24)	6.34 6.04	3.83 3.60	1720
5s	4-NO ₂	34	58	83	B	22	130—132	Benzene- cyclohexane	$C_{20}H_{20}N_2O_4$	68.17 (68.37)	5.72 5.75	7.95 7.76	1710
5t	2,4-(OMe) ₂	1	67	100	B	24	Oil	—	$C_{22}H_{25}NO_4$	71.91 (71.80)	6.86 6.77	3.81 3.88	1720
5u	3,4-(OMe) ₂	0	0	90	B	10	123—125	Benzene- cyclohexane	$C_{22}H_{25}NO_4$	71.91 (71.71)	6.86 6.82	3.81 3.70	1710
5v	2,4-(OH) ₂	66	96	65	B	15	210—213	THF	$C_{20}H_{20}NO_4$	70.78 (70.60)	6.24 6.22	4.13 3.94	3300, 1690
5w	3-COMe, 4-OH	Inactive	Inactive		A	45	155—158	Benzene- cyclohexane	$C_{22}H_{23}NO_4$	72.31 (72.27)	6.34 6.36	3.83 3.66	3400, 1710, 1635

a) The hydrochloride derivatives of **5a—w** were tested.

b) See ref. 2.

TABLE II. Inhibition of Histamine Release from Isolated Rat Peritoneal Mast Cells by **6a—d**

Compd. No.	R	% inhibition at various doses (mol) ^{a)}				Synthetic method	Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%)			IR $\nu_{\max}^{Nujol} \text{ cm}^{-1}$
		10 ⁻⁴	5 × 10 ⁻⁴	10 ⁻³							C	H	N	
6a		16	26	87	B	50	Oil	—	—	$C_{18}H_{19}NO_3$	72.70 (72.56)	6.44 6.23	4.71 4.46	1710
6b		16	29	98	B	51	84—86	Benzene- cyclohexane	—	$C_{18}H_{19}NO_2S$	68.98 (68.79)	6.11 6.11	4.47 4.32	1705
6c		9	15	35	A	44	Oil	—	—	$C_{17}H_{19}N_3O_2$	68.66 (68.51)	6.44 6.08	14.13 13.88	3350, 1710
6d		Inactive	Inactive		B	50	150—152	Benzene- cyclohexane	—	$C_{19}H_{20}N_2O_2$	74.00 (73.92)	6.54 6.54	9.09 9.14	1710

a) The hydrochloride derivatives of **6a—d** were tested.

TABLE III. Inhibition of Histamine Release from Isolated Rat Peritoneal Mast Cells by 7a-j

Compd. No.	R	% inhibition at various doses (mol) ^{a)}			Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%)			IR $\nu_{\text{max}}^{\text{Nujol}} \text{ cm}^{-1}$
									Calcd (Found)			
		10 ⁻⁴	5 × 10 ⁻⁴	10 ⁻³					C	H	N	
7a	CH ₃		Inactive		27	122—125	Benzene—cyclohexane	C ₁₅ H ₁₇ NO ₃	69.48 (69.40)	6.61 6.56	5.40 5.11	1710, 1640
7b	CH ₃ CH ₂		Inactive		56	111—113	Benzene—cyclohexane	C ₁₆ H ₁₉ NO ₃	70.21 (70.13)	7.01 7.05	5.13 4.77	1720, 1650
7c	CH ₃ (CH ₂) ₂		Inactive		70	115—117	Benzene—cyclohexane	C ₁₇ H ₂₁ NO ₃	71.05 (70.80)	7.37 7.43	4.87 4.71	1700, 1640
7d	CH ₃ (CH ₂) ₃	25	65	95	68	60—62	Benzene—cyclohexane	C ₁₈ H ₂₃ NO ₃	71.73 (71.55)	7.67 7.72	4.65 4.67	1715, 1640
7e	CH ₃ (CH ₂) ₅	35	96	96	58	55—57	CHCl ₃ —cyclohexane	C ₂₀ H ₂₇ NO ₃	73.43 (73.19)	8.51 8.56	4.08 3.88	1720, 1630
7f	CH ₃ (CH ₂) ₆	53	97	93	57	61—63	Benzene—cyclohexane	C ₂₁ H ₂₉ NO ₃	72.92 (72.69)	8.26 8.36	4.25 4.14	1720, 1615
7g	CH ₃ (CH ₂) ₇	52	76	93	79	45—47	Cyclohexane—petr. ether	C ₂₂ H ₃₁ NO ₃	73.91 (73.63)	8.74 8.72	3.92 3.99	1710, 1630
7h	cyclo-C ₆ H ₁₁	24	75	87	69	144—146	Benzene—cyclohexane	C ₂₀ H ₂₅ NO ₃	73.36 (73.10)	7.70 7.75	4.28 4.07	1715, 1630
7i	C ₆ H ₅	46	76	94	42	138—140	Benzene—cyclohexane	C ₂₀ H ₁₉ NO ₃	74.74 (74.47)	5.96 5.90	4.36 4.18	1710, 1620
7j	C ₆ H ₅ CH ₂	41	93	82	20	156—158	Benzene—cyclohexane	C ₂₁ H ₂₁ NO ₃	75.20 (74.90)	6.31 6.12	4.18 4.18	1720, 1640

a) The compounds 7a-j were tested as suspensions in carboxymethylcellulose.

TABLE IV. Inhibition of Histamine Release from Isolated Rat Peritoneal Mast Cells

Compd. No.	% inhibition at various doses (mol)			
	5×10^{-5}	10^{-4}	5×10^{-4}	10^{-3}
14·HCl	53	72	84	94
17 ^{a)}		Inactive		
18 ^{a)}		Inactive		

a) The compound was suspended in carboxymethylcellulose.

zene moiety) was inactive. These results indicate that the benzene moiety of the isocoumarin ring is required for activity and may interact with a receptor.

In summary, it is unclear at present how these compounds inhibit the release of histamine, but it seems that the lipophilicity of these compounds is important for the existence or potency of the activity.

Experimental

Melting points (determined on a Yanagimoto micromelting point apparatus) are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on a Hitachi R-24 spectrometer at 60 MHz with tetramethylsilane as an internal standard. Mass (MS) spectra were recorded on a Shimadzu LKB-9000 spectrometer, and infrared (IR) spectra on a Nippon Bunko A-102 spectrometer.

General Procedure for 1'-(Benzylspiro[isochroman-3,4'-piperidin]-1-ones (5))—Method A (Typical Example): A mixture of spiro[isochroman-3,4'-piperidin]-1-one (4) hydrochloride²⁾ (1.0 g, 4 mmol), 4-bromobenzyl bromide (1 g, 4 mmol), anhyd. K₂CO₃ (1.1 g, 8 mmol), and dimethylformamide (DMF) (40 ml) was heated at 80 °C for 2 h, then poured into H₂O and extracted with AcOEt. The AcOEt layer was washed with H₂O, dried, and concentrated. The resulting crystals were recrystallized from benzene–cyclohexane to give 1'-(4-bromobenzyl)spiro[isochroman-3,4'-piperidin]-1-one (5p) (1.1 g, 69%), mp 129–130 °C. NMR (CDCl₃) δ : 1.30–2.20 (4H, m, piperidine H), 2.20–2.80 (4H, m, piperidine H), 3.03 (2H, s, 4-H), 3.51 (2H, s, NCH₂Ph), 6.60–7.80 (7H, m, Ar H), 8.17 (1H, dd, J = 3, 6 Hz, 8-H). MS m/z : 385 (M⁺).

Method B (Typical Example): A solution of 4·HCl (1.5 g, 5.9 mmol) and *p*-anisaldehyde (1.5 g, 12.5 mmol) in MeOH (30 ml) was stirred at room temperature for 2 h, then NaBH₃CN (1.0 g, 15.9 mmol) was added to the solution. The mixture was stirred at room temperature for 10 h and concentrated. The residue was extracted with AcOEt, then the AcOEt layer was washed with H₂O, dried, and concentrated. The resulting crystals were recrystallized from Et₂O to give 1'-(4-methoxybenzyl)spiro[isochroman-3,4'-piperidin]-1-one (5g) (1.2 g, 59%), mp 107–110 °C.

General Procedure for 1'-(Arylmethyl)spiro[isochroman-3,4'-piperidin]-1-ones (6)—Method A: The procedure described for 5p was followed, using 4·HCl (2.0 g, 7.9 mmol) and 4-(chloromethyl)imidazole hydrochloride (1.2 g, 7.9 mmol). Crude 1'-(4-imidazolylmethyl)spiro[isochroman-3,4'-piperidin]-1-one (6c) thus obtained was chromatographed on alumina with AcOEt to give pure 6c (1.0 g, 44%) as a viscous oil. NMR (CDCl₃) δ : 3.04 (2H, s, 4-H), 3.67 (2H, s, CH₂Ph), 8.22 (1H, dd, J = 2, 7 Hz, 8-H). MS m/z : 297 (M⁺).

Method B (Typical Example): The procedure described for 5g was followed, using 4·HCl (1.5 g, 5.9 mmol), furfural (1.2 g, 12.5 mmol), and NaBH₃CN (1.0 g, 15.9 mmol). Crude 1'-furfurylspiro[isochroman-3,4'-piperidin]-1-one (6a) thus obtained was chromatographed on alumina with AcOEt–petr. ether (1:20, v/v) to give pure 6a (1.0 g, 50%) as a viscous oil. NMR (CDCl₃) δ : 2.99 (2H, s, 4-H), 3.57 (2H, s, NCH₂Ph), 6.16–6.41 (2H, m, furan H), 7.21–7.64 (4H, m, 5-, 6-, 7-H and furan H), 8.12 (1H, dd, J = 2, 7 Hz, 8-H). MS m/z : 297 (M⁺).

General Procedure for 1'-Acylspiro[isochroman-3,4'-piperidin]-1-ones (7)—Typical Example: Acetyl chloride (0.9 g, 12 mmol) was added dropwise to a solution of 4·HCl (2 g, 7.9 mmol) and Et₃N (4.5 g, 30 mmol) in CH₂Cl₂ (40 ml). The solution was stirred at room temperature for 1 h, washed with H₂O, dried, and concentrated. The residue was chromatographed on silica gel with AcOEt–petr. ether to give 1'-acetylspiro[isochroman-3,4'-piperidin]-1-one (7a) (0.6 g, 20%), mp 122–125 °C.

1,2,3a,4,5,9b-Hexahydro-9b-(methoxycarbonylmethyl)naphtho[2,1-*b*]furan-2-one (9)—NaBH₄ (1.3 g, 34 mmol) was added dropwise to a solution of 1,1-bis(methoxycarbonylmethyl)-2-tetralone⁵⁾ (8) (10 g, 30 mmol) at room temperature. The solution was stirred at room temperature for 3 h, concentrated, and extracted with AcOEt. The AcOEt layer was washed with H₂O, dried, and concentrated. The residue was chromatographed on silica gel with

AcOEt–petr. ether (1:20, v/v) to give **9** (7.8 g, 88%) as a viscous oil. *Anal.* Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.35; H, 6.05. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1780 (CO), 1723 (CO). NMR (CDCl_3) δ : 1.91–2.32 (2H, m, 4-H), 2.81–3.05 (6H, m, 1-, 5-H and CH_2COOMe), 3.74 (3H, s, OCH_3), 4.95–5.23 (1H, m, 3a-H), 7.32 (4H, s, Ar H). MS m/z : 260 (M^+).

9b-(N-Benzylcarbamoylmethyl)-1,2,3a,4,5,9b-hexahydronaphtho[2,1-b]furan-2-one (11)—A mixture of **9** (7.8 g, 30 mmol) and 10% KOH MeOH– H_2O solution was refluxed for 30 min, then concentrated. The residue was made acidic with 10% HCl and extracted with AcOEt. The AcOEt layer was washed with H_2O and dried. Removal of the solvent gave a residual oil, to which benzylamine (3.2 g, 30 mmol) was added. The mixture was heated at 180 °C for 4 h and the resulting precipitate was recrystallized from THF to give **11** (8.3 g, 79%), mp 204–205 °C. *Anal.* Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.03; H, 6.16; N, 4.07. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3400 (NH), 1760 (CO), 1670 (CO). NMR (dimethyl sulfoxide ($\text{DMSO}-d_6$)) δ : 1.84–2.28 (2H, m, 4-H), 2.48–2.95 (6H, m, 1-, 5-H, and CH_2CONH), 4.09–4.37 (2H, m, NHCH_2Ph), 5.04–5.39 (1H, m, 3a-H), 6.90–7.52 (9H, m, Ar H), 8.24–8.61 (1H, br, NH). MS m/z : 335 (M^+).

1-Benzylspiro[piperidine-4,1'-tetralin]-2'-ol (12)—Compound **11** (1.1 g, 3.3 mmol) was added dropwise to a suspension of LiAlH_4 (0.25 g, 6.6 mmol) in THF. The mixture was refluxed for 6 h, then decomposed with H_2O , and extracted with AcOEt. The AcOEt layer was washed with H_2O , dried, and concentrated. The residue was crystallized from benzene–cyclohexane to give **12** (0.6 g, 59%), mp 146–148 °C. *Anal.* Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.82; H, 8.07; N, 4.34. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3150 (OH). NMR (CDCl_3) δ : 3.62 (2H, s, CH_2Ph), 4.27–4.54 (1H, m, 2'-H). MS m/z : 307 (M^+).

1'-Benzylspiro[(1,4-dihydronaphthalene)-1,4'-piperidine] (13)—A solution of **12** (1.3 g, 4.2 mmol) in HMPT (13 g) was refluxed for 30 min, then concentrated. The residue was extracted with Et_2O . The Et_2O layer was washed with H_2O , dried, and concentrated. The residue was chromatographed on alumina with AcOEt–petr. ether (1:20, v/v) to give **13** (0.25 g, 20%) as a viscous oil. *Anal.* Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 87.00; H, 8.02; N, 4.79. NMR (CDCl_3) δ : 3.26–3.45 (2H, m, 4-H), 3.57 (2H, s, CH_2Ph), 5.74–6.49 (2H, m, olefin H). MS m/z : 289 (M^+).

1-Benzylspiro[piperidine-4,1'-tetralin] (14)—Compound **13** (1.0 g, 3.5 mmol) was hydrogenated on 5% Pd–carbon in MeOH. The catalyst was removed and the filtrate was concentrated to give **14** (0.8 g, 80%) as a viscous oil. *Anal.* Calcd for $C_{21}H_{25}N$: C, 86.55; H, 8.65; N, 4.81. Found: C, 86.50; H, 8.54; N, 4.74. NMR (CDCl_3) δ : 1.39–2.50 (10H, m, 3-, 5-, 2'-, 3'-, and 4'-H), 2.62–3.01 (4H, m, 2- and 6-H), 3.50 (2H, m, CH_2Ph), 7.00–7.74 (9H, m, Ar H). MS m/z : 291 (M^+).

4-Benzylspiro[cyclohexane-1,3'-(trans-4a',5',6',7',8',8a'-hexahydroisochroman)]-1'-one (17)—A solution of 3-benzyl-1,5-dibromopentane⁶⁾ (**16**) (3.5 g, 11 mmol) in THF (15 ml) was added dropwise to a mixture of Mg (0.52 g, 22 mmol) and THF (5 ml) under an Ar atmosphere and the mixture was refluxed for 1 h, then cooled. A solution of hexahydrohomophthalic anhydride⁷⁾ (**15**) (1.8 g, 10 mmol) in THF (10 ml) was added dropwise, and the whole was stirred at room temperature overnight. After addition of 10% HCl, the reaction mixture was stirred at 40 °C for 5 h and extracted with Et_2O . The Et_2O layer was washed with H_2O , dried, and concentrated. The residue was chromatographed on silica gel with benzene–AcOEt (9:1, v/v) to give **17** (0.3 g, 10%), mp 121–122 °C (from benzene–cyclohexane). *Anal.* Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.52; H, 9.19. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1715 (CO). NMR (CDCl_3) δ : 1.15–2.11 (20H, m, 4'-, 4a'-, 5'-, 6'-, 7'-, 8'-H and cyclohexane H), 2.29–2.74 (3H, m, CH_2Ph and 1a'-H), 7.24 (5H, s, Ph). MS m/z : 312 (M^+).

9-Benzyl-1-oxaspiro[5.5]undecan-2-one (18)—The procedure described for **17** was followed, using **16** (3.0 g, 8.3 mmol), Mg (0.4 g, 17 mmol), and glutaric anhydride (0.9 g, 7.9 mmol). Crude **18** thus obtained was recrystallized from benzene–cyclohexane to give pure **18** (0.7 g, 35%), mp 114–117 °C. *Anal.* Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.76; H, 8.69. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 1715 (CO). NMR (CDCl_3) δ : 1.11–2.17 (13H, m, 4-, 5-, 7-, 8-, 9-, 10- and 11-H), 2.27–2.78 (4H, m, CH_2Ph and 3-H), 7.29 (5H, s, Ar H). MS m/z : 258 (M^+).

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

References and Notes

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