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

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Structural modification of the isocoumarin moiety (A and B rings) of 1′-benzylspiro-[isocoumarin-piperidines] (**1a** and **2a**), which inhibit the compound 48/80-induced release of histamine from isolated rat peritoneal mast cells, was undertaken to clarify the structure-activity relationship. Chromanone (**3**), chroman (**4**), 1,3-benzoxazine (**5**), 1,3-benzothiazine (**6**), and 4-quinazolinone (**7**) analogs were active, although there were differences in potency.

Substituent effects on the benzene moiety (A ring) of **3** were examined.

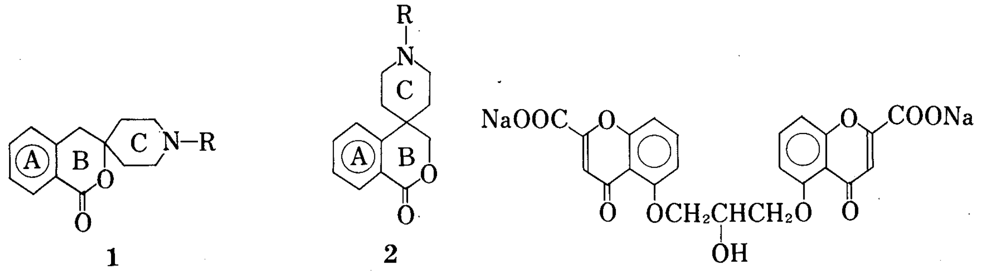
Keywords——isocoumarin; isochroman; chromanone; piperidine; spiro compound; antiallergic activity; histamine-release inhibition; structure-activity relationship

In 1967 disodium cromoglycate (DSCG) was introduced as a treatment for asthma and it was shown that it could inhibit the release of mediators of the allergic reactions.[2] However, DSCG is not active orally in man. Consequently, much chemical research has centered around chemical structures resembling the chromone molecule and possessing an acidic moiety in order to find more potent and orally active compounds.

Recently we found that spiro[isochroman-piperidines] (**1** and **2**) inhibit the compound 48/80-induced release of histamine from isolated rat peritoneal mast cells.[3] These results, suggesting that these compounds (**1** and **2**) might have antiallergic activity similar to that of DSCG, led us to study the structure-activity relationship of the inhibitory activity in this series. The effect of substituents (R) of **1** and **2** on the activity has been reported in our previous papers.[1] In this paper, we wish to report the results obtained in chemical modification studies of the A and B rings of **1a** and **2a**.

Firstly, chemical modification of the B ring of **1a** and **2a** was examined. Namely, the compounds listed in Tables I and II in which the isocoumarin ring in **1a** or **2a** was replaced by a hetero ring were synthesized as follows.

1′-Benzylspiro[chroman-2,4′-piperidin]-4-one (**3a**) was prepared by heating a mixture of 2-hydroxyacetophenone and 1-benzyl-4-piperidone in the presence of pyrrolidine. Reduction of **3a** with sodium borohydride and subsequent dehydration gave 1′-benzylspiro[2*H*-1-benzo-



1 **a**: R=CH$_2$Ph   **2** **a**: R=CH$_2$Ph   DSCG

Chart 1

pyran-2,4′-piperidine], which was converted into 1′-benzylspiro[chroman-2,4′-piperidine] (**4**) by catalytic reduction.

1′-Benzylspiro[1,3-benzoxazine-2,4′-piperidin]-4 (3*H*)-one (**5a**) and several 1′-substituted spiro[1,3-benzoxazine-2,4′-piperidin]-4(3*H*)-ones were synthesized by Nakanishi *et al.*[4] and they reported that these compounds have analgesic, depressant, and antidiabetic activities.[4] 1′-Benzyl-3-methylspiro[1,3-benzoxazine-2,4′-piperidin]-4(3*H*)-one (**5b**) was prepared by refluxing a mixture of 1-benzyl-4-piperidone, N-methylsalicylamide, and *p*-toluenesulfonic acid in xylene. 3-Acetyl-1′-benzylspiro[1,3-benzoxazine-2,4′-piperidin]-4(3*H*)-one (**5c**) was obtained by heating **5a** with acetic anhydride and pyridine.

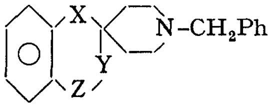
On the other hand, similar treatment of 1-benzylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (**7**) with acetic anhydride and pyridine afforded not the corresponding N-acetyl derivatives of **7** but the rearrangement product. These results were reported previously.[5]

1′-Benzylspiro[isochroman-1,4′-piperidine] (**9**) was prepared from 2-bromophenethyl bromide and 1-benzyl-4-piperidone with *n*-butyl lithium by the method of William *et al.*[6]

These compounds were tested for activity and the results are shown in Tables I and II. Although there were differences in potency, all the compounds were active and behaved as bioisosteres of **1a** or **2a**. As previously reported, 1-benzyl-4-hydroxymethyl-4-phenylpiperidine, the structure of which can be visualized as a B ring-opened form of 1′-benzylspiro-[isochroman-4,4′-piperidine] (**8**), was inactive.[1] These results suggested that the B ring moiety is not involved in interaction with the receptor site and plays a role in determining the conformation of the molecule.

In order to examine the contribution of the benzene moiety (A ring) to the activity, 1-benzyl-3′,4′,5′,6′-tetrahydrospiro[piperidine-4,2′-(2*H*-1,3-thiazin)]-4′-one (**10**), which lacks the benzene ring of **6**, was synthesized from the reaction[7] of 3-mercaptopropionamide with 1-benzyl-4-piperidone. Compound **10** was inactive, implying that the A ring moiety is essential for the appearance of activity.

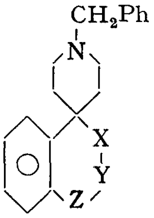
TABLE I. Inhibition of Histamine Release from Isolated Rat Peritoneal Mast Cells by Spiro[isocoumarin-3,4′-piperidines] and Related Compounds



Compd. No.	X	Y	Z	% inhibition of histamine release at various doses[a]		
				10^{-4} mol	5×10^{-4} mol	10^{-3} mol
1a·HCl	CH_2	O	CO	20.0±0.5[b]	40.0±1.6	76.0±1.2
3a·HCl	O	CH_2	CO	0	95.5±5.8	100
4·HCl	O	CH_2	CH_2	14.9±4.9	71.6±5.3	88.9±4.9
5a·HCl	O	NH	CO	8.5±2.7	51.4±5.8	66.5±4.3
5b·HCl	O	NMe	CO	18.9±2.3	88.9±1.5	88.5±4.2
5c·HCl	O	NCOMe	CO	5.1±1.7	44.2±3.8	77.1±6.0
6·HCl[c]	S	NH	CO	19.8±1.6	80.1±3.1	—
7a·AcOH	NH	NH	CO	55.8±3.8	83.3±5.4	82.5±2.2
7b·AcOH	NMe	NH	CO	5.5±1.7	21.0±2.0	63.2±5.4
7c·HCl	NH	NMe	CO	61.3±3.5	96.7±9.2	96.0±8.5
7d·HCl	NMe	NMe	CO	43.1±6.0	72.8±5.9	91.6±4.4
Disodium cromoglycate				36.0±1.3[b]	58.0±5.9	80.0±3.1

a) $p < 0.05$ using Student's *t* test.
b) Dose, 2×10^{-4} mol.
c) Nakanishi *et al.* reported that **6** has analgesic, sedative, and hypoglycemic activities. M. Nakanishi, K. Arimura, and H. Ao, Jap. patent 73 31114 [*C. A.* **80**, 27269*h* (1974)].

TABLB II. Inhibition of Histamine Release from Isolated Rat Peritoneal Mast Cells by Spiro[isocoumarin-4,4′-piperidines] and Related Compounds



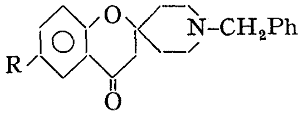
Compd. No.	X	Y	Z	% inhibition of histamine release at various doses[a)		
				10^{-4} mol	5×10^{-4} mol	10^{-3} mol
2a·HCl	CH_2	O	CO	5.0±0.7[b)	31.0±2.2	80.0±3.6
8·HCl	CH_2	O	CH_2	—	28.0±1.4	72.0±5.4
9·HCl	O	CH_2	CH_2	17.0±1.1	66.7±1.7	86.1±5.2

a) $p<0.05$ using Student's *t* test.
b) Dose, 2×10^{-4} mol.

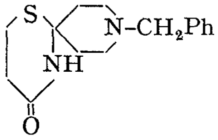
Substituent effects on the A ring were examined in a series of **3**, because the synthesis of **3** having various substituents on the benzene ring (A ring) seemed to be easier than that of the isocoumarin (**1a**) or other hetero analogs. As shown in Table III, the 6-hydroxyl (**3b**), 6-methoxyl (**3c**), 6-chloro (**3d**), and 6-bromo (**3e**) analogs were nearly equal in potency to the parent compound (**3a**). On the other hand, the introduction of a 6-phenyl group into **3a** resulted in a remarkable reduction of activity.

These results suggested that electronic effects of the substituents on the A ring do not play an important role in the activity, but the presence of bulky substituents on the A ring has an unfavorable influence on the activity owing to steric hindrance.

TABLE III. Inhibition of Histamine Release from Isolated Rat Peritoneal Mast Cells by Spiro[chromanone-2,4′-piperidines]



3



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Compd. No.	R	% inhibition of histamine release at various doses[a)		
		10^{-4} mol	5×10^{-4} mol	10^{-3} mol
10·HCl	—		Inactive	
3a·HCl	H	0	95.0±5.8	100
3b·HCl	OH	0	56.3±3.1	83.5±3.8
3c·HCl	OMe	0	55.5±1.8	83.2±2.4
3d·HCl	Cl	18.0±2.6	65.3±3.5	100
3e·HCl	Br	17.1±4.0	84.0±1.17	82.7±2.5
3f·HCl	Ph	—	23.2±1.6	46.0±6.7

a) $p<0.05$ using Student's *t* test.

Experimental

Melting points (determined on a Yanagimoto micro melting point apparatus) are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on a Hitachi 22-FTS spectrometer at 90 MHz, employing tetramethylsilane as an internal standard. Mass spectrum (MS) were recorded on a Shimadzu LKB-9000 spectrometer, and infrared (IR) spectra on a Nippon Bunko A-102 spectrometer.

1′-Benzylspiro[chroman-2,4′-piperidin]-4-ones (3)——A solution of 2-hydroxyacetophenone (5 g), 1-benzyl-4-piperidone (6.9 g), and pyrrolidine (6.9 g) in abs. MeOH (50 ml) was refluxed for 8 h under an N_2 atmosphere. The MeOH was evaporated off and the residue was chromatographed on a column of alumina with a mixture of benzene–CH_2Cl_2 to give 1′-benzylspiro[chroman-2,4′-piperidin]-4-one (**3a**) (9.3 g, 82%), which was recrystallized from benzene–cyclohexane, mp 91—93°C. *Anal.* Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.88; N, 4.55. Found: C, 77.93; H, 6.98; N, 4.52. IR ν_{max}^{Nujol} cm^{-1}: 1695 (CO). NMR (CCl_4) δ: 1.70—2.15 (4H, m, $C_{3'}$–H and $C_{5'}$–H), 2.45—2.64 (4H, m, $C_{2'}$–H and $C_{6'}$–H), 2.60 (2H, s, C_3–H), 3.45 (2H, s, $C\underline{H}_2Ph$). MS *m/e*: 307 (M^+).

6-Hydroxy (**3b**), 6-methoxy (**3c**), 6-chloro (**3d**), 6-bromo (**3e**), and 6-phenyl (**3f**) derivatives of 1′-benzylspiro[chroman-2,4′-piperidin]-4-one were prepared in a similar manner.

3b: Purified by chromatography on a column of charcoal with CH_2Cl_2. Recrystallized from benzene, mp 148—151°C. Yield, 70%. *Anal.* Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.54; N, 4.33. Found: C, 73.99; H, 6.32; N, 4.40. IR ν_{max}^{Nujol} cm^{-1}: 1685 (CO). NMR ($CDCl_3$) δ: 2.64 (2H, s, C_3–H), 3.46 (2H, s, $C\underline{H}_2Ph$), 4.75—4.85 (1H, broad, OH). MS *m/e*: 323 (M^+).

3c: Purified by chromatography on a column of alumina with CH_2Cl_2. Recrystallized from CH_2Cl_2, mp 66—67°C. Yield 65%. *Anal.* Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.84; H, 6.59; N, 4.15. IR ν_{max}^{Nujol} cm^{-1}: 1695 (CO). NMR (CCl_4) δ: 2.62 (2H, s, C_3–H), 3.52 (2H, s, $C\underline{H}_2Ph$), 3.84 (3H, s, OCH_3). MS *m/e*: 337 (M^+).

3d: Purified by chromatography on a column of alumina with CH_2Cl_2. Recrystallized from MeOH, mp 83—85°C. Yield 86%. *Anal.* Calcd for $C_{20}H_{20}ClNO_2$: C, 70.29; H, 5.86; N, 4.10. Found: C, 70.48; H, 5.67; N, 4.13. IR ν_{max}^{Nujol} cm^{-1}: 1695 (CO). NMR ($CDCl_3$) δ: 2.72 (2H, s, C_3–H), 3.62 (2H, s, $C\underline{H}_2Ph$), 7.84 (1H, d, J=2 Hz, C_5–H).

3e: Purified by chromatography on a column of alumina with CH_2Cl_2. Recrystallized from MeOH, mp 80—81°C. Yield 80%. *Anal.* Calcd for $C_{20}H_{20}BrNO_2$: C, 62.18; H, 5.18; N, 3.63. Found: C, 62.35; H, 5.20; N, 3.71. IR ν_{max}^{Nujol} cm^{-1}: 1695 (CO). NMR ($CDCl_3$) δ: 2.70 (2H, s, C_3–H), 3.55 (2H, s, $C\underline{H}_2Ph$), 8.02 (1H, d, J=2 Hz, C_5–H).

3f: Recrystallized from CH_2Cl_2–cyclohexane, mp 162—164°C. Yield 45%. *Anal.* Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.66; H, 6.82; N, 3.47. IR ν_{max}^{Nujol} cm^{-1}: 1675 (CO). NMR ($CDCl_3$) δ: 2.76 (2H, s, C_3–H), 3.56 (2H, s, $C\underline{H}_2Ph$), 7.05—8.12 (13H, m, Ar–H). MS *m/e*: 283 (M^+).

1′-Benzylspiro[chroman-2,4′-piperidine] (4)——i) A mixture of **3a** (10.5 g), $NaBH_4$ (2 g), 10% NaOH (30 ml), and EtOH (50 ml) was refluxed for 2 h then concentrated *in vacuo*. The residue was extracted with AcOEt and the AcOEt layer was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated off and the residue was crystallized from CH_2Cl_2–cyclohexane to give 9.3 g (87%) of 1′-benzyl-4-hydroxyspiro[chroman-2,4′-piperidine] (**11**), mp 123—124°C. *Anal.* Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.98; H, 7.51; N, 4.60. IR ν_{max}^{Nujol} cm^{-1}: 3115 (OH). NMR ($CDCl_3$) δ: 1.50—2.10 (6H, m, C_3–H, $C_{3'}$–H, and $C_{2'}$–H), 2.20 (1H, broad, OH), 3.47 (2H, s, $C\underline{H}_2Ph$), 4.72 (1H, t, J=7 Hz, C_4–H), 6.72 (1H, dd, J=2, 7 Hz, C_8–H), 7.17 (5H, s, Ph). MS *m/e*: 309 (M^+), 291 (M^+-H_2O).

ii) A solution of **11** (2 g) in 20% H_2SO_4 (50 ml) was refluxed for 1 h, then made basic with 20% NaOH, and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried over $MgSO_4$, and concentrated to dryness *in vacuo* to give 1.7 g (90%) of 1′-benzylspiro[2*H*-1-benzopyran-2,4′-piperidine] (**12**) as a viscous oil. IR $\nu_{max}^{Liq.}$ cm^{-1}: 1638 (C=C). NMR ($CDCl_3$) δ: 1.60—2.00 (4H, m, $C_{3'}$–H, and $C_{5'}$–H), 2.40—2.75 (4H, m, $C_{2'}$–H and $C_{6'}$–H), 3.55 (2H, s, $C\underline{H}_2Ph$), 5.63 (1H, d, J=11 Hz, C_3–H), 6.43 (1H, d, J=11 Hz, C_4–H), 6.72—7.30 (4H, m, Ar–H), 7.39 (5H, s, Ph). MS *m/e*: 291 (M^+).

iii) A mixture of **12** (2.8 g), 5% palladium-charcoal (0.5 g), and EtOH (100 ml) was stirred under an H_2 atmosphere. After the theoretical amount of hydrogen had been absorbed, the catalyst was filtered off. The filtrate was concentrated to dryness *in vacuo* to give 2.7 g (96%) of **4** as a viscous oil. NMR (CCl_4) δ: 1.42—2.10 (6H, m, C_3–H, $C_{3'}$–H, and $C_{5'}$–H), 2.30—2.82 (6H, m, C_4–H, $C_{2'}$–H, and $C_{6'}$–H), 3.48 (2H, s, $C\underline{H}_2Ph$), 6.55—7.15 (4H, m, Ar–H), 7.28 (5H, s, Ph). MS *m/e*: 293 (M^+). The salt was formed in Et_2O by treatment with dry HCl and the crude hydrochloride was recrystallized from Me_2CO–MeOH to give **4**·HCl, mp 240—241°C (dec.). *Anal.* Calcd for $C_{20}H_{24}ClNO$: C, 72.82; H, 7.28; N, 4.25. Found: C, 72.91; H, 7.30; N, 4.31.

1′-Benzyl-3-methylspiro[1,3-benzoxazine-2,4′-piperidin]-4(3*H*)-one (**5b**)——A mixture of N-methylsalicylamide (3 g), 1-benzyl-4-piperidone (3.7 g), and *p*-toluenesulfonic acid (5.9 g) in xylene (150 ml) was heated for 3 h at 130°C and made basic with 20% NaOH. The xylene layer was separated and the aqueous layer was extracted with AcOEt. The AcOEt layer was combined with the xylene layer and the mixture was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on a column of alumina with CH_2Cl_2 to give 2 g (31%) of **5b**, which was recrystallized from cyclohexane, mp 80—81°C. *Anal.* Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.69; H, 6.97; N, 8.59. IR ν_{max}^{Nujol} cm^{-1}: 1670 (CO). NMR ($CDCl_3$) δ: 3.12 (2H, s, NCH_3), 3.60 (2H, s, $C\underline{H}_2Ph$), 8.09 (1H, dd, $J=1.5$, 8 Hz, C_5–H). MS *m/e*: 322 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 1670 (CO).

3-Acetyl-1′-benzylspiro[1,3-benzoxazine-4,2′-piperidin]-4(3*H*)-one (**5c**)——A mixture of 1′-benzylspiro-[1,3-benzoxazin-2,4′-piperidin]-4(3*H*)-one[4] (**5a**) (3 g), acetic anhydride (30 ml), and dry pyridine (3 ml) was heated for 5 h at 120—130°C, and then concentrated *in vacuo*. The residue was dissolved in Et_2O and undissolved material (**5a**) was filtered off. The filtrate was concentrated to dryness *in vacuo* to give 2 g (88%) of **5c**, which was recrystallized from benzene–CH_2Cl_2, mp 126—127°C. *Anal.* Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00. Found: C, 72.14; H, 6.49; N, 7.95. IR ν_{max}^{Nujol} cm^{-1}: 1725 (CO), 1670 (CO). NMR ($CDCl_3$) δ: 2.51 ($COCH_3$), 3.54 ($C\underline{H}_2Ph$), 7.95 (1H, dd, $J=2$, 8 Hz, C_5–H). MS *m/e*: 350 (M^+).

1′-Benzylspiro[isochroman-1,4′-piperidine] (**9**)——A 15% *n*-butyl lithium–hexane solution (27 ml) was added dropwise to a solution of 2-bromophenethyl bromide (11 g) in dry THF (100 ml) at −70° with cooling in a dry ice–Me_2CO bath, and the solution was stirred for 5 min at −70°C. Then, 1-benzyl-4-piperidone (13 g) was added to the solution and the mixture was allowed to stand overnight in the dry ice–Me_2CO bath. It was then poured onto ice-water and extracted with Et_2O. The Et_2O layer was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on a column of alumina with cyclohexane to give 0.95 g (7.5%) of **9** as a viscous oil. NMR ($CDCl_3$) δ: 2.79 (2H, t, $J=6$ Hz, C_4–H), 3.57 (2H, s, $C\underline{H}_2Ph$), 3.90 (2H, t, $J=6$ Hz, C_3–H). MS *m/e*: 293 (M^+). The salt was formed in Et_2O by treatment with dry HCl and the crude hydrochloride was recrystallized from Me_2CO–EtOH to give **9**·HCl, mp 256—257°C (dec.). *Anal.* Calcd for $C_{20}H_{24}ClNO$: C, 72.83; H, 7.28; N, 4.25. Found: C, 73.10; H, 7.31; N, 4.16.

1-Benzyl-3′,4′,5′,6′-tetrahydrospiro[piperidine-4,2′-(2*H*-1,3-thiazin)]-4′-one (**10**)——$BF_3 \cdot Et_2O$ (8.5 ml) was added to a solution of 3-mercaptopropionamide (3.1 g), and 1-benzyl-4-piperidone (5.7 g) in dioxane (300 ml) under an Ar atmosphere and the solution was refluxed for 3 h and concentrated *in vacuo*. The residue was diluted with H_2O and extracted with AcOEt. The AcOEt layer was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated off and the residue was crystallized from CH_2Cl_2–Et_2O to give a precipitate, which was filtered off. The filtrate was concentrated to dryness and the residue was chromatographed on a column of alumina with CH_2Cl_2 to give 0.4 g (4.8%) of **10**, which was recrystallized from Et_2O–benzene, mp 155—156°C. IR ν_{max}^{Nujol} cm^{-1}: 3180 (NH), 1662 (CO). *Anal.* Calcd for $C_{15}H_{20}N_2OS$: C, 65.22; H, 7.25; N, 10.14. Found: C, 65.39; H, 7.28; N, 10.10. NMR ($CDCl_3$) δ: 1.90—2.15 (4H, m, C_3–H and C_5–H), 2.25—2.95 (8H, m, C_2–H, C_6–H, $C_5{}'$–H, and $C_{6'}$–H), 3.52 (2H, s, $C\underline{H}_2Ph$), 7.32 (5H, s, Ph). MS *m/e*: 276 (M^+).

Inhibition of Histamine Release——Assay of inhibition of histamine release was carried out as described previously.[1,3]

References and Notes

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