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Synthesis and Antiulcer Activity of (Isochroman-1-yl)alkylamines.[1] II

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Numerous analogues of *N*-phenethyl-2-(isochroman-1-yl)-1-methylethylamine (**3b**), previously found to have inhibitory activity against aspirin-induced ulcer and no gastric antisecretory activity, were prepared and examined for gastric antisecretory activity and inhibitory activity against aspirin-induced ulcers in rats. It was found that a basic amine moiety is required for the antiulcer activity. Replacement of the isochroman ring of **3b** by a thioisochroman, chroman, or tetralin ring resulted in a drastic change in the antiulcer activity. Among them, the chroman analogue *N*-phenethyl-2-(chroman-4-yl)-1-methylethylamine (**32b**) was found to have the most potent antiulcer activity, comparable with that of **3b**.

Keywords——isochroman; thioisochroman; chroman; antiulcer activity; aspirin-induced ulcer; structure–activity relationship

In our previous report,[1] we showed that a series of *N*-substituted isochromanylalkylamines of general structure A have inhibitory activity against aspirin-induced ulcers in rats in spite of having no gastric antisecretory activity. Data on the effect of substituents (R^1 and R^2) of A on the antiulcer activity suggested that the steric environment around the nitrogen atom affects the antiulcer activity. *N*-Phenethyl-2-(isochroman-1-yl)-1-methylethylamine (**3b**), in which R^1 is a methyl group and R^2 is a phenethyl group, is the most active compound among the analogues previously tested.

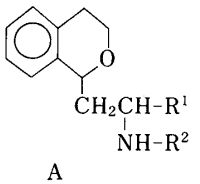
For the present work, we chose **3b** as the lead compound, and the effects of modification of its amine moiety, variation of the distance between the isochroman ring and the nitrogen atom, and change of the isochroman ring, were examined.

Chemistry

Compounds listed in Table I were synthesized as shown in Chart 1. (Isochroman-1-yl)acetone (**2**),[1,2] prepared from 1-ethoxyisochroman (**1**), was converted to the isochromanylethylamine (**3**), as previously reported.[1] Treatment of **3** with formalin and $NaBH_3CN$ gave the *N*-methylated derivative (**4**). Compound **3** was converted to the acetamide derivative (**5**) by treatment with acetic anhydride.

Reduction of **2** followed by bromination gave 1-(2-bromopropyl)isochroman (**7**), which was converted to the corresponding tertiary amine (**8**).

The isochromanylmethyl- (**13b**) and isochromanylpropyl- (**21b**) amine derivatives were



A

3b : R^1=Me, R^2=CH_2CH_2Ph

Fig. 1

prepared as shown in Chart 2. 1-Acetylisochroman (**12**) was prepared by the Grignard reaction of 1-cyanoisochroman (**11**) with methylmagnesium iodide according to the method of Samodurova *et al.*[3] The Schiff's base, prepared by the reaction of **12** with 2-phenethylamine, was reduced with $NaBH_4$ to yield the *N*-phenethylisochromanylmethylamine (**13b**). Reduction of ethyl (isochroman-1-yl)acetate (**14**)[4] followed by bromination and cyanidation gave 3-(isochroman-1-yl)propionitrile (**17**). The Grignard reaction of **17** with methylmagnesium iodide afforded a mixture of many products, and the desired 1-(isochroman-1-yl)-3-

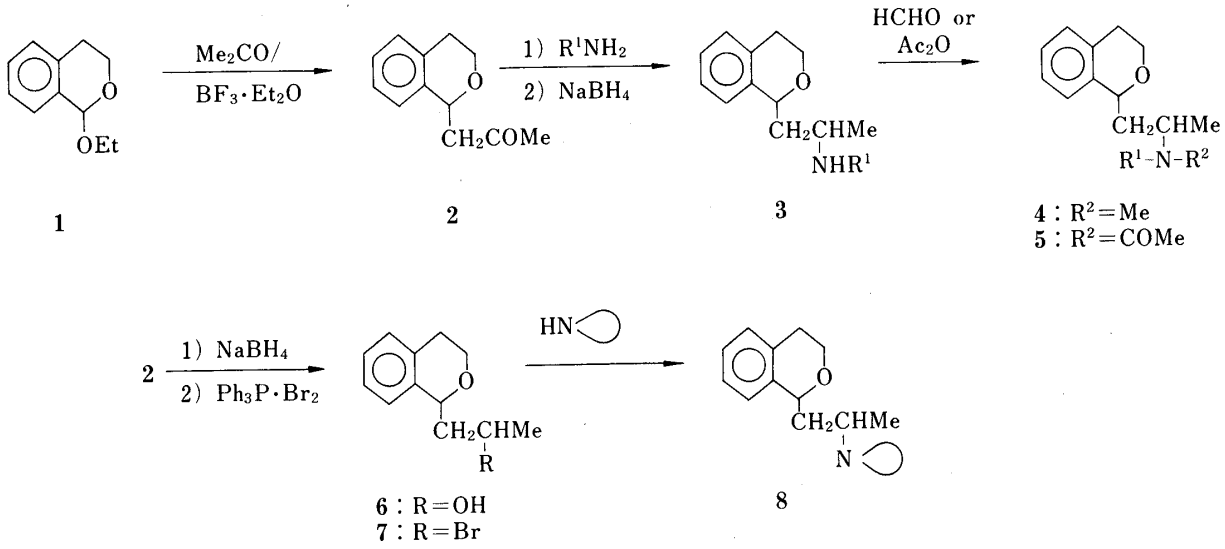
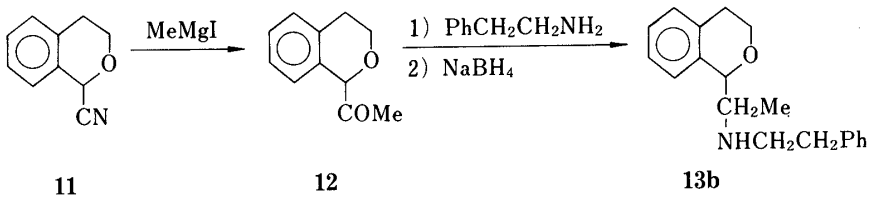


Chart 1



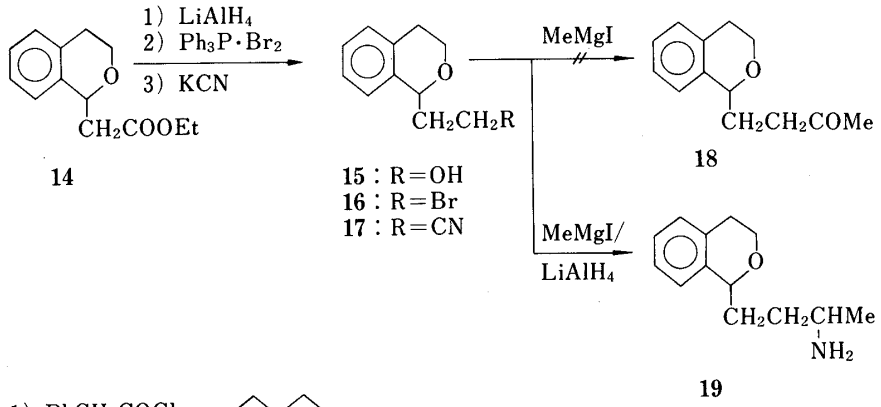
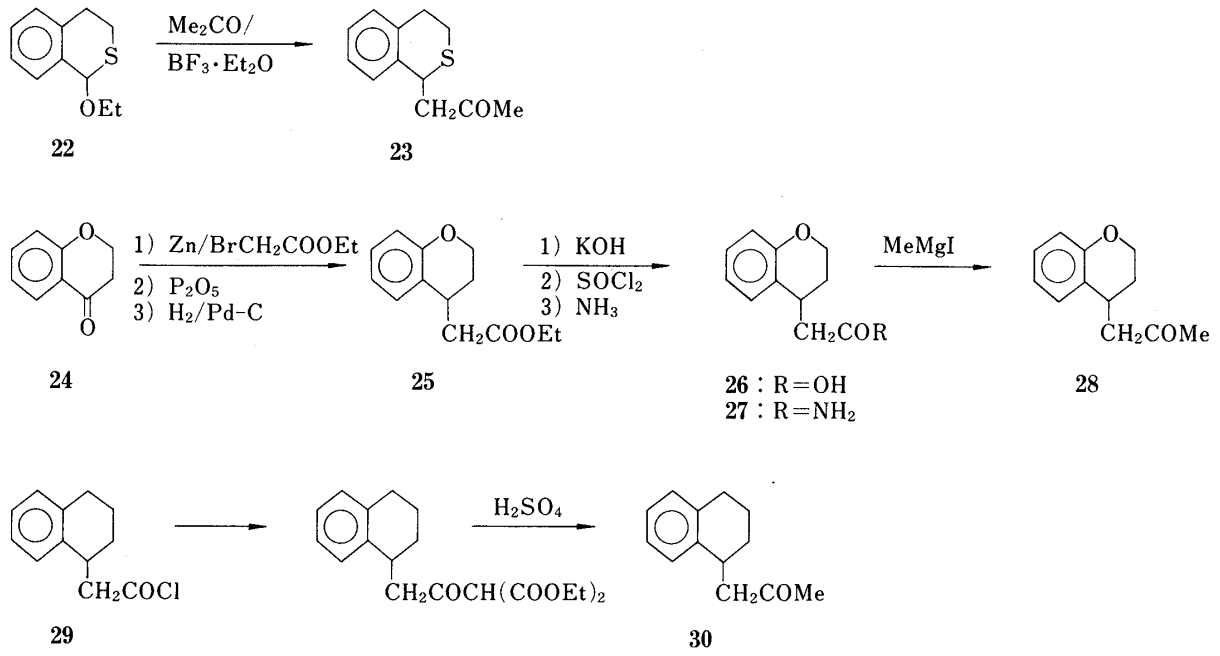
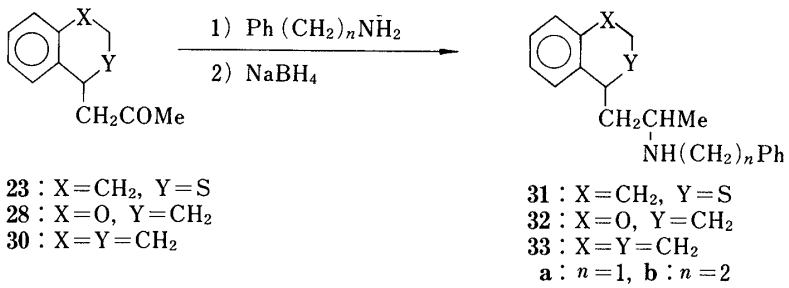


Chart 2



22 23 24 25 26 : R=OH 27 : R=NH2 28 29 30

Chart 3



23 : X=CH2, Y=S
28 : X=O, Y=CH2
30 : X=Y=CH2

31 : X=CH2, Y=S
32 : X=O, Y=CH2
33 : X=Y=CH2
a : n=1, b : n=2

Chart 4

butanone could not be isolated. On the other hand, the treatment of **17** successively with methylmagnesium iodide and $LiAlH_4$ in one flask afforded 3-(isochroman-1-yl)-1-methylpropylamine (**19**) in 48% yield. Compound **19** was treated with phenylacetyl chloride to give the amide **20**. This amide **20** was reduced with $LiAlH_4$ to yield the *N*-phenethylisochromanylpropylamine (**21b**).

Compounds **31**—**33**, in which the isochroman ring in **3b** was replaced by another ring, were prepared as shown in Charts 3 and 4. Synthetic intermediates, the methylketones (**23**, **28**, and **30**), were synthesized as shown in Chart 3.

1-Ethoxythioisochroman[5] (**22**), in analogy with **3**, on treatment with acetone in the presence of boron trifluoride etherate afforded (thioisochroman-1-yl)acetone (**23**) in 66% yield (Chart 3). The Reformatsky reaction of chroman-4-one[6] (**24**) followed by dehydration and hydrogenation gave ethyl (chroman-4-yl)acetate (**25**), which was converted to (chroman-4-yl)acetamide (**27**). The Grignard reaction of **27** with methylmagnesium iodide gave the chromanylacetone (**28**). (1,2,3,4-Tetrahydro-1-naphthyl)acetone (**30**) was prepared from diethyl [(1,2,3,4-tetrahydro-1-naphthyl)acetyl]malonate.

The methyl ketones were converted to the amines **31**—**33** by reductive alkylation as described for **13b**.

Biological Results and Discussion

The compounds listed in Tables I—III were tested for gastric antisecretory activity in the

pylorus-ligated rat according to Shay's method.[7] Cimetidine was used as a positive control. All compounds except **10b**, **31b**, and **33b** were found to be inactive in the above test, in analogy with the previous series of *N*-substituted isochromanylalkylamines. In the cases of tetralin analogues, the *N*-benzyl analogue **33a** was inactive, while the *N*-phenethyl analogue **33b** showed potent gastric antisecretory activity.

The compounds listed in Tables I—III were also tested for inhibition of the generation of experimental ulcers in rats by aspirin, as previously reported.[1]

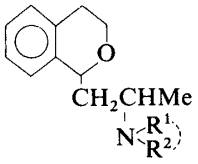
In order to examine whether the basic amine moiety is essential for the activity or not, the amide analogues (**5a**, **b** and **9b**[1]) were also synthesized (Table I). They were found to be inactive, indicating that the basic amine moiety plays an important role in the antiulcer activity.

Several tertiary amines (**4a**, **b** and **8a**, **b**) were examined (Table I). Introduction of a methyl group into the nitrogen atom in **3a**, **b** resulted in loss of the activity. Compounds **8a**, **b** with a cyclic amine were also inactive. These results showed that increase of the basicity of the amine moiety is not necessary to enhance the activity. Conversion of the amine moiety of **3a**, **b** into the tetralkyl ammonium functionality (**10a**, **b**) resulted in loss of the activity.

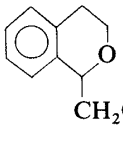
Variation of the distance between the isochroman ring and the nitrogen atom in **3b** resulted in a remarkable change of the activity (Table II). The isochromanylmethylamine **13b** with the shortened alkyl chain retained weak activity, while the isochromanylpropylamine **21b** with the extended alkyl chain was inactive.

In order to investigate the contribution of the isochroman ring to the activity, compounds **31**—**33**, in which the oxygen atom of the isochroman ring was replaced by an isoster, were synthesized (Table III). The thioisochroman analogue **31b** exhibited borderline activity. In the cases of the tetralin analogues **33a**, **b**, no activity was observed. On the other hand, the chroman analogue **32b** was found to possess potent activity similar to that of **3b**,

TABLE I. Biological Activities of **3**—**5** and **8**—**10**



3—**5**, **8**



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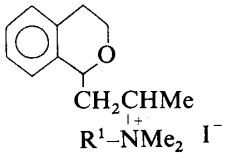

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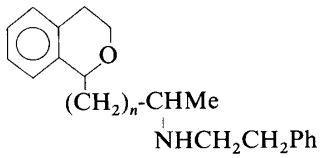
Compd. No.	R^1 and/or R^2	Antisecretory activity % inhibition of acid output in rats 20 mg/kg, i.d.	Aspirin-induced ulcer % inhibition of ulcer index in rats 20 mg/kg, *p.o.*
3a	H, CH_2Ph	30.1[a]	67.3[a]
3b	H, CH_2CH_2Ph	24.2	71.3
4a	Me, CH_2Ph	15.9	30.1
4b	Me, CH_2CH_2Ph	−32.9	27.2
5a	COMe, CH_2Ph	0.3	23.4
5b	COMe, CH_2CH_2Ph	22.5	17.3
8a	$-(CH_2)_2NH(CH_2)_2-$	−16.7	44.9
8b	$-(CH_2)_5-$	−55.6	22.4
9b	CH_2CH_2Ph	17.2	14.8
10a	CH_2Ph	−4.0	−15.5
10b	CH_2CH_2Ph	41.7	25.5
Cimetidine		51.6[b]	84.0[c]

a) Treatments in which inhibition values were more than 30% were evaluated as significantly effective. *b*) Dose: 100 mg/kg. *c*) Dose: 30 mg/kg.

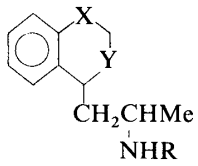
TABLE II. Biological Activities of **3b**, **13b**, and **21b**



Compd. No.	*n*	Antisecretory activity % inhibition of acid output in rats 20 mg/kg, i.d.	Aspirin-induced ulcer % inhibition of ulcer index in rats 20 mg/kg, *p.o.*
3b	0	−33.5[a)]	41.0[a)]
13b	1	24.2	71.3
21b	2	25.6	26.3

a) See the footnote to Table I.

TABLE III. Biological Activities of **3** and **31**—**33**



a: R = CH_2Ph
b: R = CH_2CH_2Ph

Compd. No.	X	Y	Antisecretory activity % inhibition of acid output in rats 20 mg/kg, i.d.	Aspirin-induced ulcer % inhibition of ulcer index in rats 20 mg/kg, *p.o.*
3a	CH_2	O	30.1[a)]	67.3[a)]
3b	CH_2	O	24.2	71.3
31b	CH_2	S	49.5	31.7
32b	O	CH_2	3.3	67.0
33a	CH_2	CH_2	23.5	−3.7
33b	CH_2	CH_2	71.3	3.2

a) See the footnote to Table I.

indicating that the presence of an oxygen atom is likely to be essential for the activity but its position is not critical.

In conclusion, many of compounds in the present study were found to lack significant gastric antisecretory activity except for **33b**. The present study indicates that the basic amine moiety has an important role in the antiulcer activity and that minor changes of steric environment around the nitrogen atom have a drastic effect on the antiulcer activity. Replacement of the isochroman ring by an another ring system or variation of the alkyl-chain length between the isochroman ring and the nitrogen atom resulted in a remarkable change in the biological 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 Me_4Si as an internal standard. Mass spectra (MS) were measured with a Shimadzu LKB-9000 spectrometer. Wako C-300 silica gel (200—300 mesh) and Wako activated alumina (300 mesh) were employed for column chromatography. Extracts were dried over $MgSO_4$.

***N*-Benzyl-*N*-methyl-2-(isochroman-1-yl)-1-methylethylamine (4a)**——A solution of *N*-benzyl-2-(isochroman-1-yl)-1-methylethylamine[1] (**3a**, 2 g, 7 mmol), 35% formalin (3.1 ml), and $NaBH_3CN$ (0.75 g, 11 mmol) in MeCN (21 ml) was stirred for 1 h at room temperature while being kept acidic by addition of AcOH. The solution was made basic with 10% KOH and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried, and concentrated. The residue was column-chromatographed on alumina (petr. ether–AcOEt, 10 : 1) to give **4a** (1.3 g, 63%) as a viscous oil. NMR (CCl_4) δ: 1.01, 1.15 (3H, each d, J=6 Hz, CHMe), 1.49—2.06 (2H, m, CH_2CH), 2.12, 2.28 (3H, each s, NMe), 2.58—2.98 (2H, m, 4′-H_2), 3.08—3.35 (1H, m, CHMe), 3.54, 3.65 (2H, each s, NCH_2), 3.68—4.24 (2H, m, 3′-H_2), 4.48—5.24 (1H, m, 1′-H), 7.04 (4H, s, ArH), 7.24 (5H, s, Ph). MS *m/z*: 295 (M^+).

***N*-Methyl-*N*-phenethyl-2-(isochroman-1-yl)-1-methylethylamine (4b)**——Compound **4b** was similarly prepared in 80% yield. Viscous oil. NMR (CCl_4) δ: 0.89, 1.04 (3H, each d, J=6 Hz, CHMe), 1.54—1.98 (2H, m, CH_2CH), 2.20, 2.26 (3H, each s, NMe), 2.57—2.71 (4H, m, NCH_2CH_2), 2.73—3.46 (3H, m, CHMe and 4′-H_2), 3.55—4.14 (2H, m, 3′-H_2), 4.50—4.90 (1H, m, 1′-H), 7.04 (4H, s, ArH), 7.15 (5H, s, Ph). MS *m/z*: 309 (M^+).

***N*-Benzyl-*N*-[2-(isochroman-1-yl)-1-methylethyl]acetamide (5a)**——A mixture of **3a** (1.21 g, 4 mmol), pyridine (0.41 g, 5 mmol), and Ac_2O (1.1 g, 11 mmol) was stirred for 1 h at room temperature, poured into ice-water, and extracted with AcOEt. The AcOEt layer was washed successively with 5% HCl, 5% $KHCO_3$, and H_2O, dried, and concentrated. Recrystallization of the residue from petr. ether–cyclohexane gave **5a** (0.6 g, 43%), mp 80—82 °C. IR ν_{max}^{Nujol} cm^{-1}: 1630. NMR ($CDCl_3$) δ: 1.26, 1.31 (3H, each d, J=7 Hz, Me), 1.78—2.18 (2H, m, CH_2CH), 2.37 (3H, s, COMe), 2.58—3.08 (2H, m, 4′-H_2), 3.68—4.36 (3H, m, CHMe and 3′-H_2), 4.61, 4.68 (2H, each s, NCH_2), 4.78—5.23 (1H, m, 1′-H), 6.68—7.36 (4H, m, ArH), 7.36—7.68 (5H, m, Ph). MS *m/z*: 323 (M^+).

***N*-Phenethyl-*N*-[2-(isochroman-1-yl)-1-methylethyl]acetamide (5b)**——Compound **5b** was similarly prepared in 75% yield. Viscous oil. IR ν_{max}^{neat} cm^{-1}: 1635. NMR ($CDCl_3$) δ: 1.31, 1.37 (2H, each d, J=7 Hz, CHMe), 1.78—2.07 (2H, m, CH_2CH), 1.91, 1.94 (3H, each s, COMe), 2.63—3.42 (6H, m, NCH_2CH_2 and 4′-H_2), 3.73—4.04 (1H, m, CHMe), 4.06—4.33 (2H, m, 3′-H_2), 4.53—4.75 (1H, m, 1′-H), 7.17 (4H, s, ArH), 7.29 (5H, s, Ph). MS *m/z*: 337 (M^+).

1-(Isochroman-1-yl)-2-propanol (6)——A solution of $NaBH_4$ (4 g, 107 mmol) in MeOH was added dropwise to a solution of (isochroman-1-yl)acetone[1] (**2**, 16.2 g, 85 mmol) in MeOH (140 ml) with cooling and the solution was stirred for 2 h at room temperature. The solvent was evaporated off, and the residue was extracted with AcOEt. The AcOEt layer was washed with H_2O, dried, and concentrated. Distillation of the residue gave **6** (15 g, 92%) as a light-yellowish viscous oil, bp 104—106 °C (0.03 mmHg). IR ν_{max}^{neat} cm^{-1}: 3440. NMR (CCl_4) δ: 1.13, 1.17 (3H, each d, J= 6.5 Hz, CHMe), 1.25—2.07 (2H, m, CH_2CH), 2.60—3.06 (2H, m, 4′-H_2), 3.33—3.59 (1H, br, OH), 3.62—3.89 (1H, m, CHMe), 3.92—4.31 (2H, m, 3′-H_2), 4.73—5.16 (1H, m, 1′-H), 7.10 (4H, s, ArH). MS *m/z*: 192 (M^+).

1-(2-Bromopropyl)isochroman (7)——Bromine was added to a mixture of **6** (2 g, 10 mmol), Ph_3P (3.3 g, 13 mmol), K_2CO_3 (2 g, 15 mmol), and dry *N*,*N*-dimethylformamide (DMF) (20 ml) at 0 °C, until the reaction mixture showed a presistent orange color. The mixture was stirred for 1 h, poured into H_2O, and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried, and concentrated. The residue was column-chromatographed on silica gel (petr. ether–AcOEt = 10 : 1) to give **7** (1.8 g, 69%) as a light-yellowish viscous oil. NMR (CCl_4) δ: 1.74, 1.81 (3H, each d, J= 6 Hz, CHMe), 1.96—2.44 (2H, m, CH_2CH), 2.65—3.04 (2H, m, 4′-H_2), 3.49—4.43 (3H, m, CHMe and 3′-H_2), 4.94—5.14 (1H, m, 1′-H), 7.14 (4H, s, ArH). MS *m/z*: 256 (M^++2), 254 (M^+).

***N*-[2-(Isochroman-1-yl)-1-methylethyl]piperazine (8a)**——A mixture of **7** (3.5 g, 14 mmol), piperazine (5.9 g, 69 mmol), K_2CO_3 (2.8 g, 21 mmol), DMF (30 ml), and H_2O (30 ml) was stirred for 20 h at 80 °C and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried, and concentrated. The residue was column-chromatographed on alumina (CH_2Cl_2) to give **8a** (1.6 g, 43%) as a viscous oil. IR ν_{max}^{neat} cm^{-1}: 3300. NMR (CCl_4) δ: 1.08 (3H, d, J= 7 Hz, CHMe), 1.63—2.28 (2H, m, CH_2CH), 1.77 (1H, s, NH), 2.34—2.55 (4H, m, piperazine-H), 2.59—2.90 (7H, m, piperazine-H, CHMe, and 4′-H_2), 3.56—4.12 (2H, m, 3′-H_2), 4.55—4.91 (1H, m, 1′-H), 7.08 (4H, s, ArH). MS *m/z*: 260 (M^+).

***N*-[2-(Isochroman-1-yl)-1-methylethyl]piperidine (8b)**——Compound **8b** was similarly prepared in 51% yield. Viscous oil. NMR (CCl_4) δ: 1.06 (3H, d, J=6.5 Hz, Me), 1.39—1.67 (6H, m, piperidine-H), 1.74—2.08 (2H, m, CH_2CH), 2.26—2.56 (4H, m, piperidine-H), 2.59—3.32 (3H, m, CHMe and 4′-H_2), 3.66—4.24 (2H, m, 3′-H_2), 4.56—4.96 (1H, m, 1′-H), 7.08 (4H, s, ArH). MS *m/z*: 259 (M^+).

Benzyldimethyl[2-(isochroman-1-yl)-1-methylethyl]ammonium Iodide (10a)——A solution of **4a** (1.7 g, 6 mmol) and MeI (7.3 g, 48 mmol) in dry Et_2O (30 ml) was stirred for 2 d at room temperature. The resulting precipitate was filtered off, washed with dry Et_2O, and recrystallized from Me_2CO–Et_2O to give **10a** (1.7 g, 65%), mp 90—91 °C. *Anal.* Calcd for $C_{21}H_{28}INO$: C, 57.67; H, 6.41; N, 3.20. Found: C, 57.79; H, 6.50; N, 3.26. NMR ($CDCl_3$) δ: 1.41—1.91 (3H, m, CHMe), 2.01—2.48 (2H, m, CH_2CH), 2.54—3.01 (3H, m, CHMe and 4′-H_2), 3.21 (6H, s, NMe_2), 3.71—4.21 (2H, m, 3′-H_2), 4.61—5.21 (3H, m, NCH_2 and 1′-H), 6.91—8.11 (9H, m, ArH).

Dimethyl[2-(isochroman-1-yl)-1-methylethyl]phenethylammonium Iodide (10b)——Compound **10b** was similarly prepared in 92% yield, mp 109—110 °C. *Anal.* Calcd for $C_{22}H_{30}INO$: C, 58.40; H, 6.68; N, 2.98. Found: C, 58.54; H,

6.70; N, 3.10. NMR ($CDCl_3$) δ: 3.25, 3.33 (6H, each s, NMe_2), 4.65—5.01 (1H, m, 1′-H), 7.12—7.48 (9H, m, ArH).

***N*-Phenethyl-1-(isochroman-1-yl)ethylamine (13b)**——A mixture of 1-acetylisochroman[3] (**12**, 2 g, 11 mmol) and 2-phenethylamine (2 g, 17 mmol) in dry benzene (20 ml) was stirred overnight at room temperature, then a solution of $NaBH_4$ (0.54 g, 14 mmol) in absolute MeOH was added portionwise at 0 °C. The mixture was stirred for 3 h at room temperature and the solvent was evaporated off. The residue was dissolved in AcOEt and the AcOEt solution was washed with H_2O, dried, and concentrated. The residue was column chromatographed on alumina (hexane–AcOEt) to give **13b** (1.3 g, 28%) as an oil. IR ν_{max}^{neat} cm^{-1}: 3340. NMR (CCl_4) δ: 1.09 (3H, d, J=7 Hz, CHMe), 1.15 (1H, s, NH), 2.43—2.79 (5H, m, CHMe and NCH_2CH_2), 2.82—3.24 (2H, m, 4′-H_2), 3.49—4.18 (2H, m, 3′-H_2), 4.55—4.71 (1H, br, 1′-H), 6.99—7.39 (9H, m, ArH). MS *m/z*: 281 (M^+).

1-(2-Bromoethyl)isochroman (16)——Compound **16** was prepared as described for **7** in 93% yield. Light-yellowish oil. NMR (CCl_4) δ: 1.96—2.42 (2H, m, 2-H_2), 2.46—2.89 (2H, m, 3′-H_2), 3.28—4.11 (4H, m, 1-H_2 and 4′-H_2), 4.61—4.93 (1H, m, 1′-H), 6.97 (4H, s, ArH). MS *m/z*: 242 (M^++2), 240 (M^+).

2-(Isochroman-1-yl)ethyl Cyanide (17)——A mixture of **16** (27.4 g, 114 mmol), KCN (14.8 g, 229 mmol), 18-crown-6-ether (2.5 g, 10 mmol), and dry MeCN (300 ml) was refluxed for 10 h and the solvent was evaporated off. The residue was poured into H_2O and extracted with benzene. The benzene layer was washed with H_2O, dried and concentrated. Distillation of the residue gave **17** (20 g, 94%), bp 105—106 °C (0.02 mmHg) as an oil. IR ν_{max}^{neat} cm^{-1}: 2250. NMR (CCl_4) δ: 1.94—2.24 (2H, m, 2-H_2), 2.26—2.47 (2H, m, CH_2CN), 2.60—2.92 (2H, m, 4′-H_2), 4.64—4.88 (1H, m, 1′-H), 7.23 (4H, s, ArH). MS *m/z*: 187 (M^+).

3-(Isochroman-1-yl)-1-methylpropylamine (19)——A solution of **17** (11.7 g, 62 mmol) in dry Et_2O (100 ml) was added dropwise to a solution of methylmagnesium iodide (75 mmol) in dry Et_2O (100 ml) under cooling with ice-water. The mixture was refluxed for 2 h, and a suspension on $LiAlH_4$ (2.8 g, 75 mmol) in dry tetrahydrofuran (THF) (100 ml) was added portionwise under cooling with ice-water. The whole was refluxed for 10 h, and the excess reactant was decomposed with H_2O. The precipitate formed was removed by filtration. The filtrate was extracted with AcOEt, and the AcOEt layer was extracted with 10% HCl. The HCl layer was made basic with 30% NaOH and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried, and concentrated. Distillation of the residue gave **19** (6.1 g, 48%) as a light-yellowish oil, bp 125—127 °C (0.02 mmHg). IR ν_{max}^{neat} cm^{-1}: 3360, 3300. NMR (CCl_4) δ: 1.00 (3H, d, J=7 Hz, Me), 1.16 (2H, s, NH_2), 1.22—1.57 (2H, m, 2-H_2), 1.59—1.92 (2H, m, 1-H_2), 2.57—3.07 (3H, m, 3-H and 4′-H_2), 3.58—4.18 (2H, m, 3′-H_2), 4.56—4.79 (1H, m, 1′-H), 7.08 (4H, s, ArH). MS *m/z*: 205 (M^+).

***N*-[3-(Isochroman-1-yl)-1-methylpropyl]phenylacetamide (20)**——A solution of phenylacetyl chloride (5.5 g, 35 mmol) in Et_2O (30 ml) was added dropwise to a solution of **19** (6.1 g, 30 mmol) and Et_3N (3 g, 30 mmol) in Et_2O (50 ml) under cooling with ice-water. The solution was stirred for 1 h at room temperature and extracted with $CHCl_3$. The $CHCl_3$ layer was washed successively with 10% HCl, 10% KOH, and H_2O, dried, and concentrated. Recrystallization of the residue from AcOEt–hexane gave **20** (8.2 g, 85%), mp 97—98 °C. *Anal.* Calcd for $C_{21}H_{25}NO_2$: C, 78.02; H, 7.74; N, 4.33. Found: C, 78.25; H, 7.91; N, 4.40. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1640. NMR ($CDCl_3$) δ: 1.09 (2H, d, J=7 Hz, Me), 3.51 (2H, s, $COCH_2$), 4.59—4.89 (1H, m, 1′-H), 5.53—5.94 (1H, br, NH), 7.13 (4H, s, ArH), 7.43 (5H, s, Ph). MS *m/z*: 323 (M^+).

***N*-Phenethyl-3-(isochroman-1-yl)-1-methylpropylamine (21b)**——A suspension of **20** (7.6 g, 24 mmol) and $LiAlH_4$ (3.6 g, 94 mmol) in THF (100 ml) was refluxed for 8 h and quenched with H_2O. The precipitate was filtered off and the filtrate was extracted with AcOEt. The AcOEt layer was washed, dried, and concentrated. The residue was column-chromatographed on alumina (hexane–AcOEt) to give **21b** (3.6 g, 49%) as a viscous oil. IR ν_{max}^{neat} cm^{-1}: 3320. NMR (CCl_4) δ: 0.97 (2H, d, J=6 Hz, Me), 1.12 (1H, s, NH), 1.14—1.53 (2H, m, 2-H_2), 1.69—1.93 (2H, m, 3-H_2), 2.39—3.33 (7H, m, CH_2CH_2Ph, 1-H and 3′-H_2), 3.61—4.13 (2H, m, 4′-H_2), 4.48—4.75 (1H, m, 1′-H), 7.00 (4H, s, ArH), 7.14 (5H, s, Ph). MS *m/z*: 309 (M^+).

(Thioisochroman-1-yl)acetone (23)——A mixture of 1-ethoxythioisochroman[5] (**22**, 4 g, 21 mmol), Me_2CO (3.6 g, 63 mmol) and $BF_3 \cdot Et_2O$ (1.2 ml) was stirred for 1 h at 40 °C and extracted with Et_2O. The Et_2O layer was washed with 10% $KHCO_3$ and H_2O, dried, and concentrated. The residue was column-chromatographed on silica gel (hexane–AcOEt = 10 : 1) to give **23** (2.8 g, 66%). IR ν_{max}^{neat} cm^{-1}: 1710. NMR (CCl_4) δ: 2.07 (3H, s, Me), 2.89 (2H, d, J=6 Hz, CH_2CO), 2.68—3.10 (4H, m, 3′-H_2 and 4′-H_2), 4.39 (1H, t, J=6 Hz, 1′-H), 6.93—7.28 (4H, m, ArH). MS *m/z*: 206 (M^+).

***N*-Phenethyl-2-(thioisochroman-1-yl)-1-methylethylamine (31b)**——Compound **31b** was prepared as described for **13b** in 62% yield, using **23** (2.5 g, 12 mmol) and 2-phenethylamine (2.2 g, 18 mmol). Viscous oil. IR ν_{max}^{neat} cm^{-1}: 3320. NMR (CCl_4) δ: 0.97, 1.04 (3H, each d, J=6 Hz, Me), 1.59—2.08 (2H, m, 1-H_2), 2.45—3.07 (9H, m, 2-H, CH_2CH_2Ph, 3′-H_2, and 4′-H_2), 3.97 (1H, t, J=6 Hz, 1′-H), 7.10 (4H, s, ArH), 7.23 (5H, s, Ph). MS *m/z*: 311 (M^+).

Ethyl (Chroman-4-yl)acetate (25)——A mixture of 4-chromanone[6] (18.2 g, 123 mmol), Zn (9.1 g, 139 mmol), ethyl bromoacetate (**24**, 32 g, 192 mmol), and benzene (90 ml) was gently heated. After being refluxed for 2 h, the mixture was extracted with benzene. The benzene layer was washed with H_2O and dried, then the solvent and excess ethyl bromoacetate was removed. The residue was dissolved in dry benzene (200 ml) and P_2O_5 (21.8 g, 153 mmol) was added. After being refluxed for 1 h, the mixture was extracted with benzene. The benzene layer was washed with H_2O, dried, and concentrated. Distillation of the residue afforded a mixture (21 g, 78%) of ethyl (2*H*-chroman-4-yl)acetate and ethyl (2*H*-4-chromanylidene)acetate (67 : 34), bp 138—139 °C (1 mmHg). IR ν_{max}^{neat} cm^{-1}: 1735. NMR (CCl_4) δ:

1.22 (3H, t, J=7 Hz, Me), 1.71—2.21 (0.67H, m, 3′-H_2), 3.06—3.52 (1.33H, br, CH_2COO), 3.88—4.24 (2.67H, m, CH_2Me and 2′-H_2), 4.31—5.11 (1.33H, m, 2′-H_2), 5.41—5.86 (0.33H, br, =CH–), 6.16—6.47 (0.67H, br, chromenyl-H), 6.71—7.81 (4H, br, ArH). The mixture was used in the following reaction without further purification.

A solution of the mixture in AcOH was hydrogenated over 10% Pd–carbon (1.9 g) at room temperature. After completion of the hydrogenation, the catalyst was removed. The filtrate was concentrated. Distillation of the residue afforded **25** (14.2 g, 74%), bp 120—122 °C (1 mmHg), as an oil. IR ν_{max}^{neat} cm^{-1}: 1735. NMR (CCl_4) δ: 1.26 (3H, t, J= 7 Hz, Me), 1.96—2.16 (2H, m, 3′-H_2), 2.26—2.90 (2H, m, CH_2COO), 3.15—3.48 (1H, m, 1′-H), 3.86—4.36 (4H, m, OCH_2CH_3 and 2′-H_2), 6.71—7.36 (4H, m, ArH). MS m/z: 220 (M^+).

(Chroman-4-yl)acetic Acid (26)——A solution of **25** (14.3 g, 65 mmol) in 10% KOH–MeOH (87 ml) was refluxed for 1 h. After the MeOH was evaporated off, the residue was made acidic with 10% HCl and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried, and concentrated. Recrystallization of the residue from hexane–AcOEt gave **26** (10 g, 81%), mp 97—98 °C (lit.[8] 90 °C).

(Chroman-4-yl)acetamide (27)——$SOCl_2$ (13 g, 110 mmol) was added to a solution of **26** (7 g, 37 mmol) in dry benzene (70 ml). The solution was refluxed for 3 h, then the solvent and excess $SOCl_2$ were removed. The residue was dissolved in THF (20 ml) and the THF solution was added to 28% NH_3 aqueous solution. The mixture was stirred for 1 h and the solvent was removed. Recrystallization of the residue from hexane–Et_2O gave **27** (6.3 g, 90%) as yellowish crystals, mp 97—99 °C. *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.13; H, 6.71; N, 7.32. Found: C, 69.09; H, 6.85; N, 7.33. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3320, 1655. NMR ($CDCl_3$) δ: 5.78—6.37 (2H, br, NH_2), 6.77—7.32 (4H, m, ArH).

(Chroman-4-yl)acetone (28)——Compound **27** (6.3 g, 33 mmol) was added portionwise to a solution of methylmagnesium iodide (232 mmol) in dry Et_2O (130 ml). After being refluxed for 8 h, the mixture was poured into 5% H_2SO_4 and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried and concentrated. The residue was column-chromatographed on silica gel (hexane–AcOEt) to give **28** (3.5 g, 57%) as a viscous oil. IR ν_{max}^{Nujol} cm^{-1}: 1708. NMR (CCl_4) δ: 1.65—1.99 (2H, m, 3′-H_2), 2.07 (3H, s, Me), 2.49—2.87 (2H, m, CH_2CH), 3.17—3.57 (1H, m, 4′-H), 4.07 (2H, t, J=5 Hz, 2′-H_2), 6.67—7.25 (4H, m, ArH). MS m/z: 190 (M^+).

***N*-Phenethyl-2-(chroman-4-yl)-1-methylethylamine (32b)**——Compound **32b** was prepared as described for **13b** in 76% yield, using **28** (3.6 g, 18 mmol) and 2-phenethylamine (3.4 g, 28 mmol). Viscous oil. IR ν_{max}^{neat} cm^{-1}: 3330. NMR (CCl_4) δ: 1.14, 1.29 (3H, each d, J=6 Hz, Me), 1.52—2.19 (4H, m, CH_2CH and 3′-H_2), 1.60 (1H, s, NH), 2.51—2.99 (5H, m, NCH_2CH_2 and CHMe), 3.04—3.59 (1H, m, 4′-H), 4.07—4.35 (2H, m, 2′-H_2), 6.69—7.13 (4H, m, ArH), 7.34 (5H, s, Ph). MS m/z: 295 (M^+).

(1,2,3,4-Tetrahydro-1-naphthyl)acetone (30)——A solution of (1,2,3,4-tetrahydro-1-naphthyl)acetyl chloride[9] (13.4 g, 64 mmol) in dry benzene (100 ml) was added dropwise to a solution of ethoxymagnesiomalonic ester[10] (128 mmol) in dry benzene (100 ml). After being stirred for 6 h at room temperature, the mixture was decomposed with 5% H_2SO_4. The benzene layer was washed with H_2O and dried. The solvent and diethyl malonate were removed. Crude diethyl (1,2,3,4-tetrahydro-1-naphthyl)acetylmalonate was obtained as a viscous oil. IR ν_{max}^{neat} cm^{-1}: 1755, 1720. NMR (CCl_4) δ: 1.10—1.43 (6H, m, CH_2Me×2), 1.67—1.94 (4H, m, CH_2CO and 2′-H_2), 2.53—2.97 (4H, m, 3′-H_2 and 4′-H_2), 3.18—3.52 (1H, m, 1′-H), 3.96—4.48 (5H, m, CH_2Me×2 and COCH), 7.02 (4H, s, ArH).

The crude ester was added to a mixture of 40% H_2SO_4 (83 ml) and propionic acid (38 g). The mixture was refluxed for 1 h and the propionic acid was removed. The residue was neutralized with AcONa (7.1 g) and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried and concentrated. Distillation of the residue gave **30** (9.3 g, 77%), bp 90—95 °C (0.05 mmHg) [lit.[11] bp 127—129 °C (1 mmHg)].

***N*-Benzyl-2-(1,2,3,4-tetrahydro-1-naphthyl)-1-methylethylamine (33a)**——Compound **33a** was prepared as described for **13b** in 54% yield, using **30** (4 g, 21 mmol) and benzylamine (3.4 g, 32 mmol). Viscous oil. IR ν_{max}^{neat} cm^{-1}: 3320. NMR (CCl_4) δ: 1.13, 1.18 (3H, each d, J=6 Hz, Me), 1.22 (1H, s, NH), 1.50—1.99 (6H, m, CH_2CH, 2′-H_2, and 3′-H_2), 2.56—3.14 (4H, m, CHMe, 1′-H, and 4′-H_2), 3.80 (2H, s, NCH_2), 7.09 (4H, s, ArH), 7.33 (5H, s, Ph). MS m/z: 279 (M^+).

***N*-Phenethyl-2-(1,2,3,4-tetrahydro-1-naphthyl)-1-methylethylamine (33b)**——Compound **33b** was similarly prepared in 58% yield. Viscous oil. IR ν_{max}^{neat} cm^{-1}: 3320. NMR (CCl_4) δ: 0.84 (1H, s, NH), 1.01, 1.13 (3H, each d, J= 6 Hz, Me), 1.41—1.91 (6H, m, CH_2CH, 2′-H_2, and 3′-H_2), 2.56—2.96 (7H, m, CHMe, NCH_2CH_2, and 4′-H_2), 3.19—3.54 (1H, m, 1′-H), 7.00 (4H, s, ArH), 7.21 (5H, s, Ph). MS m/z: 293 (M^+).

Compounds **3**, **4**, **8**, **13**, **21**, and **31**—**33** were converted to their hydrochlorides, which were tested for biological activity.

Gastric Antisecretory Activity——Gastric antisecretory activity was evaluated using the technique of Shay,[7] as previously reported.[1] Five male SD rats, weighing 120—170 g, were used per group. The test compounds, suspended in 0.5% carboxymethylcellulose solution, were administered intraduodenally.

Aspirin-Induced Ulcer——The technique used was essentially the same as that described elsewhere.[12] Male SD rats, weighing 150—200 g, were deprived of food for 24 h. Six animals per group were used. After fasting, the pylorus was ligated, and the test compounds, suspended in 0.5% carboxymethylcellulose solution, were administered orally at a dose of 20 mg/kg. Thirty minutes later, aspirin, suspended in 1% carboxymethylcellulose solution, was given orally at a dose of 100 mg/kg. Nine hours after aspirin administration, the stomach was extirpated, and the length of lesions in the glandular portion was measured. The ulcer index (mm) was obtained by summing the length of the lesions. The

results were represented as percentage inhibition with respect to the control.

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