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Reactivity of Isocoumarins. IV.[1] Reaction of 1-Ethoxyisochroman with Nucleophilic Reagents

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As a part of our study on the reactions of 1-ethoxyisochroman (**1**) with nucleophilic reagents, the reactions of **1** with amines, amides, thioamides, sulfonamides, urea, thiourea, and heterocyclic compounds were examined.

Keywords——1-ethoxyisochroman; 1-substituted isochroman; 1,2,3,4-tetrahydroisoquinolines; amines; ureas; heterocyclic compounds; reactivity

We have reported that the reaction of 1-ethoxyisochroman (**1**) with benzylamines gave 4-benzylisoquinolines.[1] Subsequently, experiments on the reactivities of **1** with various nucleophilic reagents were continued, since **1** can be regarded as an intramolecular acetal of benzaldehyde.

In our previous experiment, it was found that the yield of 4-benzylisoquinoline (**2**) increased significantly on addition of Schiff base (benzylidenebenzylamine) to the reaction mixture of **1** and benzylamine, and that the Schiff base was changed into the corresponding amine (dibenzylamine).[1] This finding suggested that the Schiff base acts as a dehydrogenating agent to change 4-benzyl-3,4-dihydroisoquinoline initially formed as an intermediate into **2**. In fact, this view was supported by the result that 4-benzyl-1,2,3,4-tetrahydroisoquinoline (**3**)[2] was obtained in 10% yield accompanying **2**. The reaction of **1** with phenethylamine

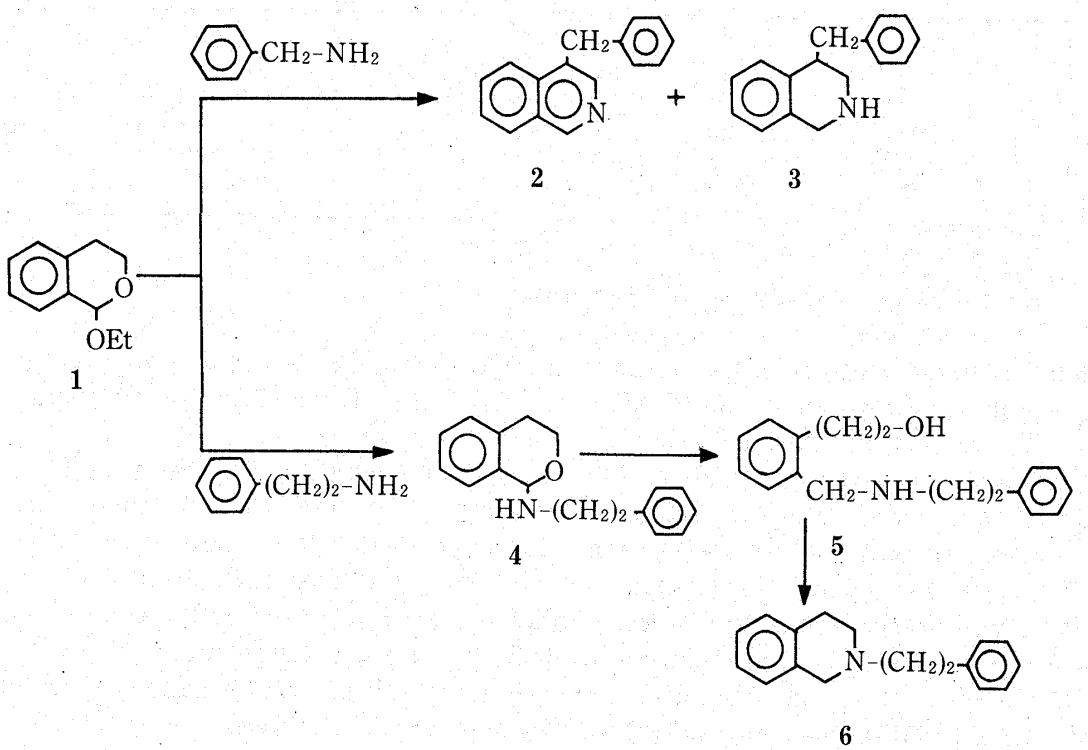
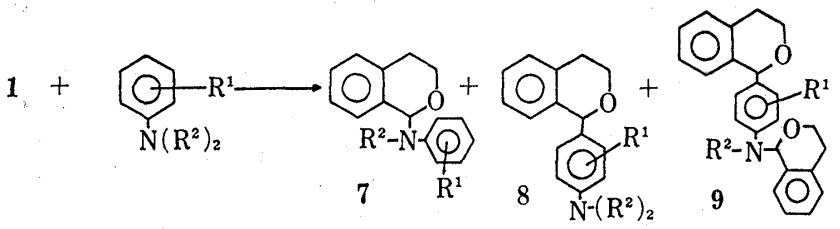


Chart 1

was undertaken in order to find whether or not a similar reaction of **1** with benzylamine takes place. 1-Phenethylaminoisochroman (**4**) was obtained in 63% yield. However, **4** was not changed into 4-phenethylisoquinoline or 4-phenethyl-1,2,3,4-tetrahydroisoquinoline under the conditions used for 1-benzylaminoisochroman[1] to give **2** and **3**. However, **4** was converted into 2-phenethyl-1,2,3,4-tetrahydroisoquinoline (**6**) as follows. Sodium borohydride reduction of **4** gave 2-(2-hydroxyethyl)-*N*-phenethylbenzylamine (**5**) in 67% yield, and this product was cyclized to **6** in 42% yield by heating with dicyclohexylcarbodiimide (DCC) in the presence of cuprous chloride (Chart 1).

The reaction of **1** with aniline gave three types of products, *N*-(1-isochromanyl)aniline (**7a**), 4-(1-isochromanyl)aniline (**8a**), and 4,*N*-di(1-isochromanyl)aniline (**9a**) in 34, 23, and 2.4% yields, respectively. Therefore, the effect of substituents on the benzene ring of aniline upon the reaction with **1** were examined, and the results are listed in Table I. Electron-attracting groups on the benzene ring act to decrease the reactivity at the C_4-position of anilines, so that the reactions gave *N*-(1-isochromanyl)anilines (**7**) selectively. On the other hand, the reaction of anilines having electron-releasing groups afforded 4-(1-isochromanyl)anilines (**8**). For example, the reaction of **1** with *N*,*N*-diethylaniline gave *N*,*N*-diethyl-4-(1-isochromanyl)-aniline (**8d**) in 62% yield and *N*,*N*-diethyl-2-(1-isochromanyl)aniline (**7d**) was not formed.

Table I. Reaction of **1** with Anilines



	Anilines R¹	Anilines R²	Temp. (°C)	Time (h)	Yield (%) 7	8	9
a	H	H	120	3	35	23	2[a]
b	*o*-COOMe	H	140—150	2	52[b]	—	—
c	*p*-COOEt	H	140—150	2	70[a]	—	—
d	H	Et	140—150	1	—	62[c]	—
e	*o*-OMe	H	140—150	1.5	61	22	3[a]
f	*p*-OMe	H	140—150	1	78[a]	—	—

a) Chromatographed on a column of alumina with petr. ether–AcOEt.
b) Recrystallized from cyclohexane.
c) Chromatographed on a column of alumina with cyclohexane.

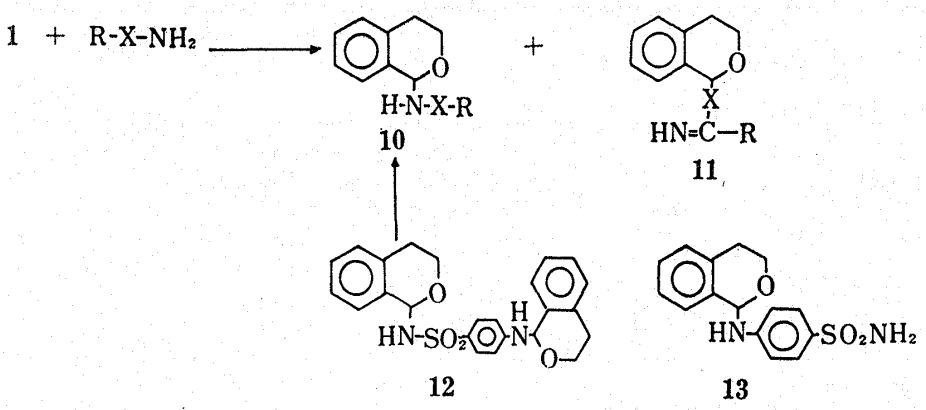
Some amides, acetamide, benzenesulfonamide, *p*-aminobenzenesulfonamide, thioamide, urea, and thiourea, were also reacted with **1** to give the corresponding 1-isochromanyl derivatives. The results are listed in Table II.

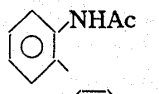
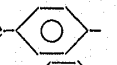
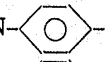
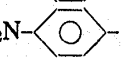
In the reaction of **1** with carboxamides such as acetamide, the 1-isochromanyl group was introduced at the N-atom of the carboxamides to give 1-(acylamino)isochromanes, *i.e.* 1-acetaminoisochroman (**10a**). This observation was in contrast to the result of the reaction of **1** with thioacetamide giving 1-iminoethyl-1-isochromanyl sulfide (**11e**). A difference similar to that between carboxamide and thioamide was observed in the reaction of **1** with urea or thiourea. Namely, *N*-(1-isochromanyl)urea (**10f**) was obtained from urea and *S*-(1-isochromanyl)isothiourea (**11g**) was obtained from thiourea. These results suggested a degree of the softness of the C_1-position of **1** in terms of the hard and soft acid and base theory.[4]

In the case of the reaction of **1** with 4-aminobenzenesulfonamide, two types of products were obtained by changing the molar ratio of **1** and 4-aminobenzenesulfonamide. Namely,

heating of a mixture of **1** and excess 4-aminobenzenesulfonamide gave 4-amino-N^1,N^4-di(1-isochromanyl)benzenesulfonamide (**12**) in 47% yield together with a small amount of 4-amino-N^4-(1-isochromanyl)benzenesulfonamide (**13**), while heating of **1** with an equimolar amount of 4-aminobenzenesulfonamide selectively gave **13d** in 49% yield. On hydrolysis of **12d** with 10% hydrochloric acid, 4-amino-N^1-(1-isochromanyl)benzenesulfonamide (**10d**) was obtained in 82% yield.

TABLE II. Reaction of **1** with Amides



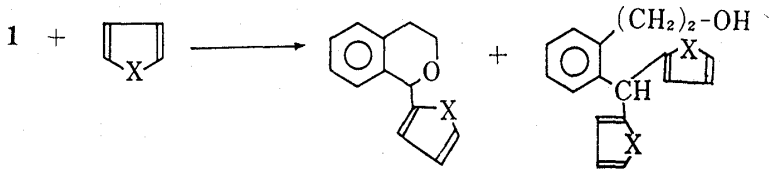
	Amides R	Amides X	Solvent	Temp. (°C)	Time (h)	Yield (%) 10	11	12	13
a	Me	CO	—	130	0.5	62	—		
b		CO	Xylene	Reflux	1.5	34	—		
c	Me- 	SO_2	Xylene	Reflux	8	59	—		
d	H_2N- 	SO_2[a]	Dioxane	Reflux	8	—	—	47	8[c]
d	H_2N- 	SO_2[b]	Dioxane	50—60	3	—	—	1	49[c]
e	Me	CS	—	120	1	—	75		
f	NH_2	CO	Xylene	Reflux	2	78	—		
g	NH_2	CS	—	100	1.5	—	51		

a) Molar ratio of **1** to *p*-aminobenzenesulfonamide was 2:1.
b) Molar ratio of **1** to *p*-aminobenzenesulfonamide was 1:1.
c) Chromatographed on a column of alumina with THF–AcOEt.

The reactions of **1** with heterocyclic compounds were examined and the results are listed in Table III. Heating of **1** with pyrrole gave 2-[di(2-pyrrolyl)methyl]phenethyl alcohol (**15a**) in 40% yield, though in the case of the heating of **1** with *N*-methylpyrrole at 120—130°C, 2-(1-isochromanyl)-*N*-methylpyrrole (**14b**) was obtained in 40% yield. When a catalytic amount of zinc chloride was added to the same reaction mixture, the reaction took place at room temperature and gave 2-[bis(*N*-methyl-2-pyrrloyl)methyl]phenethyl alcohol (**15b**) and **14b** in 15 and 9% yields, respectively. Similarly, the reaction of **1** with imidazole gave 1-(1-isochromanyl)imidazole (**14c**) in 22% yield. In the case of the reaction of **1** with furan without a catalyst, the reaction did not take place, but heating of the same mixture in the presence of a catalytic amount of boron trifluoride etherate ($BF_3 \cdot Et_2O$) at 40°C gave 1-(2-furyl)isochroman (**14d**) and [2-di(2-furyl)methyl]phenethyl alcohol (**15d**) in 10 and 15% yields, respectively. The reaction of **1** with uracil gave 5-(1-isochromanyl)uracil (**14e**) in 61% yield.

These findings on the reaction of **1** with a variety of nucleophilic reagents seemed interesting, and could be useful for the syntheses of bioactive derivatives. Work along this line will be reported in the near future.

Table III. Reaction of 1 with Heterocyclic Compounds



14 15

Hetero-cycl.	Compd. X	Method	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%) 14	Yield (%) 15
a	NH	A	—	Benezene	r.t.[a]	10	—	40
b	NMe	A	—	Xylene	Reflux	5	40	—
b	NMe	B	$ZnCl_2$	Benezene	r.t.[a]	24	9	15
c	Imidazole	A	—	—	120—130	6	59[b]	—
d	O	A	—	—	120—130	6	—	—
d	O	C	BF_3–Et_2O	—	40	10	11	15
e	Uracil	A	—	Xylene	Reflux	6.5	61[c]	—

a) r.t.=room temperature.
b) Yield of 1-(1-isochromanyl)imidazole (**14c**).
c) Yield of 5-(1-isochromanyl)uracil (**14e**).

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Proton magnetic resonance (PMR) spectra were obtained on a Hitachi R-24 spectrometer at 60 MHz, and carbon-13 magnetic resonance (^{13}C-NMR) spectra were obtained on a Hitachi R-22 FTS spectrometer at 22.6 MHz, with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 spectrometer.

Reaction of 1 with Benzylamine——A mixture of **1** (5 g) and benzylamine (4.5 g) was heated for 4 h at 200—220°C under an Ar atmosphere. The resulting mixture was chromatographed on a column of alumina with petr. ether–AcOEt (16: 1). The first eluate gave 0.4 g (9.9%) of 4-benzyl-1,2,3,4-tetrahydroisoquinoline (**3**) as a colorless oil, bp 145°C (0.05 mmHg). *Anal.* Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.12; H, 7.91; N, 6.35. PMR (CCl_4) δ: 2.72—3.01 (4H, m, C_3H_2, C_4H, and NH), 3.57 (2H, d, J=2 Hz, CH_2Ph), 3.65 (2H, s, C_1H_2), 7.02—7.35 (9H, m, Ar–H). MS *m/e*: 223 (M^+), 222 (M^+-H, base peak). The second eluate gave 1.5 g (25%) of **2**, mp 119—120°C (cyclohexane), which was identical with an authentic sample of **2** (comparison of PMR and mass spectra).

Reaction of 1 with Phenethylamine——Phenethylamine (5 g) was added to a solution of **1** (5 g) in dry xylene (80 ml) and the mixture was refluxed for 11 h. The xylene was evaporated off, and the residue was chromatographed on a column of alumina with CH_2Cl_2 to give 4.5 g (63%) of 1-phenethylaminoisochroman (**4**) as a colorless oil, bp 150°C (0.001 mmHg). *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.28; H, 7.56; N, 5.48. PMR ($CDCl_3$) δ: 2.22 (1H, s, NH), 2.62—3.25 (6H, m, C_4H_2 and NCH_2CH_2), 3.60—3.99 (2H, m, C_3H_2), 5.29 (1H, s, C_1H). MS *m/e*: 253 (M^+), 133 (C_9H_9O, base peak).

2-(2-Hydroxyethyl)benzylphenethylamine (5)——$NaBH_4$ (9.6 g) was added to a solution of **4** (10.7 g) in abs. EtOH (200 ml) and the mixture was stirred for 24 h at 40—45°C. Excess $NaBH_4$ was decomposed with dil. HCl and the EtOH was evaporated off *in vacuo*. The residue was washed with Et_2O, made basic with 10% NaOH, and extracted with Et_2O. The Et_2O layer was concentrated to give 7.2 g (67%) of **5** as a colorless oil. PMR ($CDCl_3$) δ: 2.51—3.61 (4H, m, $2\times CH_2$), 3.42—4.04 (6H, m, $3\times CH_2$), 6.92—7.52 (9H, m, Ar–H). MS *m/e*: 255 (M^+), 164 ($M^+-C_7H_7$, base peak).

The hydrochloride of **5** was formed by treatment with dry HCl in Et_2O, mp 158—159°C. *Anal.* Calcd for $C_{17}H_{22}ClNO$: C, 70.21; H, 7.28; N, 4.82. Found: C, 70.15; H, 7.30; N, 4.71.

2-Phenethyl-1,2,3,4-tetrahydroisoquinoline (6)——Compound **5** (2.8 g) was added to a mixture of Cu_2Cl_2 (0.05 g) and DCC (2.2 g) in dry xylene (20 ml) and the mixture was refluxed for 24 h. After the mixture had been cooled to 0°C, the dicyclohexylurea was removed by filtration and the xylene was evaporated off under reduced pressure. The residue was chromatographed on a column of alumina with petr. ether–AcOEt (6: 1) to give 1.1 g (42%) of **6**, as a colorless oil, bp 125°C (0.01 mmHg). *Anal.* Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.15; H, 8.25; N, 5.62. PMR ($CDCl_3$) δ: 2.50—3.17 (8H, m, C_3H_2, C_4H_2, and $2\times CH_2$), 2.76 (2H, s, C_1H_2), 7.18 (4H, s with shoulder, Ar–H), 7.35 (5H, s with shoulder, Ar–H). MS *m/e*: 237 (M^+).

TABLE IV. Physicochemical Properties and Spectral Data of **7**, **8**, and **9**

Compd. No.	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	MS *m/e* M^+	PMR (δ)
7a	109—111 (Petr. ether–AcOEt)	$C_{15}H_{15}NO$	79.97 (79.90	6.71 6.72	6.22 6.25)	225	4.33—4.60 (1H, br, NH), 5.99 (1H, d, J=8 Hz, $C_1'H$)[a]
8a	94—95 (Cyclohexane–benzene)	$C_{15}H_{15}NO$	79.97 (79.78	6.71 6.63	6.22 6.18)	225	3.47 (2H, s, NH_2), 5.64 (1H, s, $C_1'H$)[a]
9a	Oil					357	4.51 (1H, d, J=7 Hz, NH), 5.53 (1H, s, $C_1''H$), 5.92 (1H, d, J=7 Hz, $C_1'H$)[b]
7b	124—125 (Cyclohexane)	$C_{17}H_{17}NO_3$	72.06 (72.05	6.05 6.01	4.94 4.89)	283	3.78 (3H, s, OCH_3) 6.08 (1H, d, J=6 Hz, $C_1'H$), 8.35 (1H, br, NH)[a]
7c	116—118 (MeOH)	$C_{18}H_{19}NO_3$	72.70 (72.65	6.44 6.45	4.71 4.58)	297	6.08 (1H, d, J=8 Hz, $C_1'H$), 5.50 (1H, d, J=8 Hz, NH)[a]
8d	Oil, bp 173 (1 mmHg)	$C_{19}H_{23}NO$	81.10 (80.91	8.24 8.27	4.98 4.89)	281	5.64 (1H, s, $C_1'H$), 6.56 (2H, d, J=8 Hz, Ar–H), 7.09 (2H, d, J=8 Hz, Ar–H)[a]
7e	75—76 (MeOH)	$C_{16}H_{17}NO_2$	75.27 (75.01	6.71 6.03	5.49 5.28)	255	3.73 (3H, s, OCH_3), 5.61 (1H, d, J=8 Hz, NH), 6.06 (1H, d, J=8 Hz, $C_1'H$)[a]
8e	Oil					255	3.72 (3H, s, OCH_3), 4.32 (2H, br, NH_2), 5.88 (1H, s, $C_1'H$)[a]
9e	Oil					387	3.77 (3H, s, OCH_3), 5.18 (1H, d, J=8 Hz, NH), 5.74 (1H, s, $C_1'H$) 6.12 (1H, d, J=8 Hz, $C_1''H$)[a]
7f	70—71 (MeOH)	$C_{16}H_{17}NO_2$	75.27 (75.38	6.71 6.78	5.49 5.25)	255	3.68 (3H, s, OCH_3), 4.32 (1H, d, J=8 Hz, NH), 5.86 (1H, d, J=8 Hz, $C_1'H$)[a]

a) In $CDCl_3$ solution. *b*) In CCl_4 solution.

TABLE V. Physicochemical Properties and Spectral Data of **10**, **11**, **12**, and **13**

Compd. No.	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{Nujol} cm^{-1}	MS *m/e* M^+	PMR (δ)
10a	166—168 (Benzene)	$C_{11}H_{13}NO$	69.09 (69.14	6.85 6.73	7.33 7.22)	3290 1655	191	1.94 (3H, s, $COCH_3$), 6.34 (1H, d, J=9 Hz, C_1H), 6.85—7.45 (5H, m, Ar–H and NH)[a]
10b	231—232 (THF)	$C_{18}H_{18}N_2O_3$	69.66 (69.57	5.85 5.71	9.03 8.92)	3310 3270 1670 1650	310	2.13 (3H, s, $COCH_3$), 6.53 (1H, d, J=9.5 Hz, C_1H), 9.67 (1H, d, J=9.5 Hz, NH), 11.20 (1H, br, NH)[b]
10c	182—184 (EtOH)	$C_{16}H_{17}NO_3S$	63.36 (63.15	5.65 5.57	4.62 4.51)		303	2.45 (3H, s, CH_3), 5.98 (1H, d, J=8 Hz, C_1H), 9.13 (1H, d, J=8 Hz, NH)[b]
10f	288—290 (MeOH)	$C_{10}H_{12}N_2O_2$	62.48 (62.39	6.29 6.14	14.58 14.38)	3440 3300 3210 1650	192	5.66 (2H, br, NH_2), 6.10 (1H, d, J=10 Hz, C_1H)[b]
11e	126—128 (Benzene)	$C_{11}H_{13}NOS$	63.75 (63.62	6.32 6.19	6.76 6.71)	3260 3170	207	2.59 (3H, s, CH_3), 6.82—7.62 (5H, m, $C_1'H$ and Ar–H), 7.80—8.60 (1H, br, NH)[a]
11g	117—119 ($CHCl_3$)	$C_{10}H_{12}N_2OS$	57.68 (57.49	5.81 5.73	13.46 13.51)	3482 3350 3295	208	6.52—7.05 (2H, br, NH_2) 7.00—7.66 (5H, m, $C_1'H$ and Ar–H), 7.95—8.79 (1H, br, C=NH)[b]
12	192—194 (AcOEt)	$C_{22}H_{24}N_2O_4S$	66.04 (59.87	5.54 5.50	6.42 6.37)	3340 3270	436	3.25 (1H, br, NH), 5.82 (1H, d, J=10 Hz, C_1H), 6.02 (1H, d, J=8 Hz, $C_1'H$), 8.12 (1H, d, J=10 Hz, SO_2NH)[b]
13	191—193 (AcOEt)	$C_{15}H_{16}N_2O_3S$	59.20 (58.92	5.30 5.15	9.21 9.06)	3395 3355 3250	364	5.99 (1H, d, J=8 Hz, $C_1'H$), 6.84 (3H, s with shoulder, NH and SO_2NH_2)[b]

a) In $CDCl_3$ solution. *b*) In DMSO-d_6 solution.

General Procedure for the Reaction of 1 with Anilines——Typical Example: A mixture of **1** (5 g) and aniline (5.2 g) was heated for 3 h at 120°C. Unreacted aniline was distilled off *in vacuo* and the residue was chromatographed on a column of alumina with petr. ether–AcOEt (9: 1). The first eluate gave 2.2 g (35%) of *N*-(1-isochromanyl)aniline (**7a**). The second and final eluates gave 0.24 g (2%) of *N*,4-di(1-isochromanyl)-aniline (**9a**) and 1.4 g (23%) of 4-(1-isochromanyl)aniline (**8a**), respectively.

Physicochemical properties and spectral data of **7**, **8**, and **9** are shown in Table IV.

General Procedure for the Reaction of 1 with Amides——Typical Example: A mixture of **1** (5 g) and acetamide (1.6 g) was heated for 0.5 h at 130°C under an Ar atmosphere. After cooling, the mixture was recrystallized from benzene to give 3.4 g (63%) of 1-acetaminoisochroman (**10a**).

Physicochemical properties and spectral data of **10**, **11**, **12**, and **13** are shown in Table V.

Hydrolysis of 12——A mixture of **12** (0.34 g), 10% HCl (1 ml), tetrahydrofuran (THF) (70 ml), and H_2O (16 ml) was stirred for 2 h at room temperature, then the THF was evaporated off and the residue was extracted with AcOEt. The AcOEt layer was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel with petr. ether–AcOEt (1: 1) to give 0.2 g (82%) of 4-amino-N^1-(1-isochromanyl)benzenesulfonamide (**10d**), mp 190—192.5°C (from AcOEt). *Anal.* Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.20; H, 5.30; N, 9.21. Found: C, 59.01; H, 5.22; N, 9.11. PMR (DMSO-d_6) δ: 2.46—2.86 (2H, m, C_4H_2), 3.67—3.96 (2H, m, C_3H_2), 5.79 (2H, br, NH_2), 5.89 (1H, d, J=10 Hz, C_1H), 6.75 (2H, d, J=10 Hz, $C_3'H$ and $C_5'H$), 7.28 (4H, s with shoulder, Ar–H), 7.66 (2H, d, J=10 Hz, $C_2'H$ and $C_5'H$), 8.68 (1H, d, J=10 Hz, SO_2NH). MS *m/e*: 304 (M^+).

General Procedure for the Reaction of 1 with Heterocyclic Compounds——Method A: Pyrrole (9.4 g) was added to a solution of **1** (5 g) in dry benzene (50 ml) and the mixture was stirred for 10 h at room temperature. The benzene was then evaporated off, and the residue was chromatographed on a column of silica gel with CH_2Cl_2 to give 3 g (40%) of 2-[di(2-pyrrolyl)methyl]phenethyl alcohol (**15a**).

Method B: A solution of **1** (5 g), *N*-methylpyrrole (2.7 g), and $ZnCl_2$ (0.8 g) in benzene (50 ml) was stirred overnight at room temperature. The benzene layer was washed with 5% $KHCO_3$ and H_2O, dried over $MgSO_4$, and concentrated. The residue was chromatographed on a column of silica gel with benzene–CH_2Cl_2. The first eluate gave 0.54 g (9%) of 2-(1-isochromanyl)-*N*-methylpyrrole (**14b**). The second eluate

Table VI. Physicochemical Properties and Data of **14** and **15**

Compd. No.	mp (°C) (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	MS *m/e* M^+	PMR (δ)
14b	Oil 125—130 (0.2 mmHg)	$C_{14}H_{15}NO$	78.84 (78.68	7.09 7.29	6.57 6.39)	213	3.51 (3H, s, NCH_3), 5.88 (1H, s, $C_1'H$), 5.93—6.07 (2H, m, pyrrolyl-H)[a]
14c	49—50 (Et_2O)	$C_{12}H_{12}N_2O$	71.98 (71.80	6.04 6.15	13.99 13.79)	200	6.50 (1H, s, $C_1'H$), 6.70—7.35 (7H, m, Ar–H and imidazolyl-H)[b]
14d	Oil 115—120 (0.1 mmHg)	$C_{13}H_{12}O_2$	77.98 (77.86	6.04 6.18)		200	5.83 (1H, s, C_1H), 5.93—6.05 (1H, m, furyl-H), 6.14—6.29 (1H, m, furyl-H), 7.25—7.36 (1H, m, furyl-H)[b]
14e	303—304 (THF)	$C_{13}H_{12}N_2O_3$	63.92 (63.80	4.95 4.73	11.47 11.23)	244	5.70 (1H, s, $C_1'H$), 6.90—7.19 (5H, m, Ar–H and uracyl-H), 10.68—10.94 (1H, br, NH), 11.10—11.19 (1H, br, NH)[c]
15a	118—119 (Benzene)	$C_{17}H_{18}N_2O$	76.66 (76.42	6.81 6.75	10.52 10.30)	266	2.80 (2H, t, J=5 Hz, $C\underline{H}_2CH_2OH$), 3.40—3.80 (1H, br, OH), 3.60 (2H, t, J=5 Hz, $C\underline{H}_2OH$), 5 50—6.59 (2H, m, pyrrol-H), 5.69 (1H, s, CH), 5.79—5.93 (2H, m, pyrroly-H)) 6.50—6.59 (2H, m, pyrrolyl-H), 9.10—9.80 (2H, br, NH)[d]
15b	Oil 130—135 (0.1 mmHg)	$C_{19}H_{22}N_2O$	77.52 (77.43	7.53 7.51	9.52 9.50)	294	2.46 (1H, s, OH), 3.25 (6H, $2\times NCH_3$), 5.35—5.40 (2H, m, pyrrolyl-H), 5.56 (1H, s, CH), 5.83—5.96 (2H, m, pyrrolyl-H), 6.37—6.50 (2H, m, pyrrolyl-H)[a]
15d	Oil 135 (0.01 mmHg)	$C_{17}H_{16}O_3$	76.10 (76.35	6.01 5.82)		268	2.20—2.38 (1H, br, OH), 5.79 (1H, s, CH), 5.90—6.08 (2H, m, furyl-H), 6.25—6.40 (2H, furyl-H), 7.33—7.47 (2H, m, furyl-H)[b]

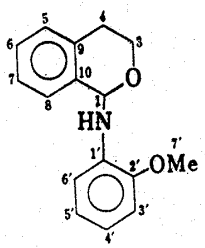
a) In $CDCl_3$ solution.
b) In CCl_4 solution.
c) In DMSO-d_6 solution.
d) In acetone-d_6 solution.

gave 1.2 g (15%) of 2-[bis(*N*-methyl-2-pyrrolyl)methyl]phenethyl alcohol (**15b**), which was purified by distillation.

Method C: A mixture of **1** (5 g), furan (5.7 g), and $BF_3 \cdot Et_2O$ (0.5 ml) was heated for 10 h at 40°C in a sealed tube, poured into ice-water, and extracted with AcOEt. The AcOEt layer was washed with 5% $KHCO_3$ and H_2O and dried over $MgSO_4$, then the solvent was evaporated off. The residue was chromatographed on a column of silica gel with petr. ether–AcOEt (2: 1). The first eluate gave 0.6 g (11%) of 1-(2-furyl)isochroman (**14d**) as a viscous oil, bp 115—120°C (0.1 mmHg). The second eluate gave 1.2 g (15%) of 2-[di(2-furyl)methyl]phenethyl alcohol (**15d**) as a viscous oil, bp 135°C (0.01 mmHg).

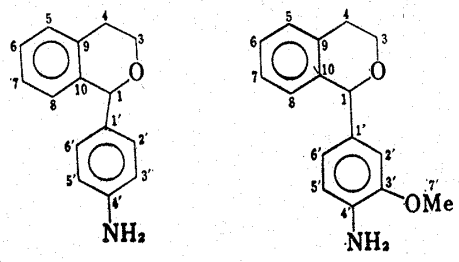
Physicochemical properties and spectral data of **14** and **15** are shown in Table VI.

^{13}C-NMR spectral data for **7b**, **8a**, **8e**, **9a**, **9e**, **14c**, and **15a** are as follows.



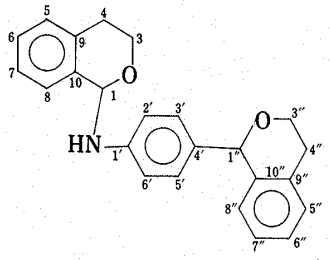
7b

Fig. 1

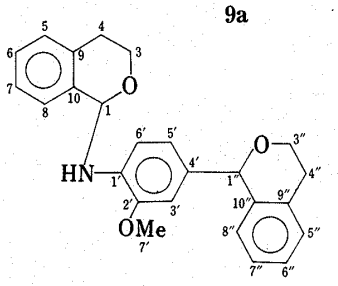


8a **8e**

Fig. 2

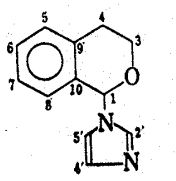


9a



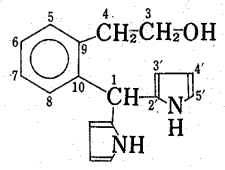
9e

Fig. 3



14c

Fig. 4



15a

Fig. 5

7b: ^{13}C-NMR ($CDCl_3$) δ: 28.27 (C_4), 55.27 (C_7'), 58.00 (C_3), 79.97 (C_1), 109.86 (C_3'), 112.05 (C_6'), 118.12 (C_4'), 121.40 (C_5'), 135.77 (C_1'), 146.87 (C_2'), 126.38, 126.93, 127.79, 128.85 (C_5, C_6, C_7, or C_8), 135.00, 135.77 (C_9 or C_{10}).

8a: ^{13}C-NMR ($CDCl_3$) δ: 28.21 (C_4), 63.29 (C_3), 79.22 (C_1), 114.70 (C_3' and C_5'), 130.02 (C_2' and C_6'), 132.00 (C_1'), 146.46 (C_4'), 125.74, 126.38, 127.02, 128.55 (C_5, C_6, C_7 or C_8), 133.89, 137.92 (C_9 or C_{10}).

8e: ^{13}C-NMR ($CDCl_3$) δ: 28.27 (C_4), 55.27 (C_7'), 58.00 (C_3), 79.97 (C_1), 109.86 (C_3'), 112.05 (C_6'), 118.12 (C_5'), 121.40 (C_4'), 135.77 (C_1'), 146.87 (C_2'), 126.38, 126.93, 127.79, 128.85 (C_5, C_6, C_7, or C_8), 135.00, 135.77 (C_9 or C_{10}).

9a: ^{13}C-NMR ($CDCl_3$) δ: 28.28, 28.89 (C_4 or C_4''), 58.26 (C_3''), 63.26 (C_3), 79.20 (C_1''), 80.31 (C_1), 113.79 (C_2' and C_6'), 130.14 (C_3' and C_5'), 132.78 (C_4'), 145.68 (C_1'), 125.83, 126.47, 126.47, 126.77, 127.16, 127.94, 128.64, 128.91 (C_5, C_5'', C_6, C_6'', C_7, C_7'', C_8, or C_8''), 134.06, 134.98, 135.50, 137.87 (C_9, C_9'', C_{10}, or C_{10}'').

9e: ^{13}C-NMR ($CDCl_3$) δ: 28.28, 28.87 (C_4 or C_4''), 55.37 (C_7'), 58.01, 63.43 (C_3 or C_3''), 79.70, 79.87 (C_1 or C_1''), 110.31 (C_3'), 111.15 (C_6'), 111.28 (C_5'), 128.61 (C_4'), 135.64 (C_1'), 146.93 (C_2'), 122.32, 125.77, 126.47, 126.91, 127.16, 127.83, 128.36, 128.83 (C_5, C_5'', C_6, C_6'', C_7, C_7'', C_8, or C_8''), 132.03, 133.95, 134.95, 137.84 (C_9, C_9'', C_{10}, or C_{10}'').

14c: ^{13}C-NMR ($CDCl_3$) δ: 27.56 (C_4), 59.93 (C_3), 81.03 (C_1), 118.85 (C_5'), 126.64, 127.06, 128.92, 129.09, 129.34 (C_4', C_5, C_6, C_7, or C_8), 130.95, 134.65 (C_9 or C_{10}), 137.46 (C_2').

15a: ^{13}C-NMR (acetone-d_6) δ: 37.28 (C_4), 41.29 (C_1), 64.28 (C_3), 108.25, 108.72 (C_3' or C_4'), 118.26 (C_5'), 127.49, 127.71, 130.13, 131.30 (C_5, C_6, C_7, or C_8), 134.66 (C_2'), 138.69, 143.31 (C_9 or C_{10}).

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