[Chem. Pharm. Bull. 29(3) 720—725 (1981)]

Reactivity of Isocoumarins. III.[1] Reaction of 1-Ethoxyisochroman with Benzylamines

Masatoshi Yamato,* Tadataka Ishikawa, and Toshio Kobayashi

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1, Okayama 700, Japan

(Received September 25, 1980)

As a part of our studies on the reactions of 1-ethoxyisochroman (**1**) with nucleophilic reagents, the reaction of **1** with benzylamines was examined.

Heating of **1** with benzylamine or its derivatives having an electron-releasing or -attracting group at the 4-position gave 1-benzylaminoisochroman (**2**) or the corresponding 1-(4-substituted benzylamino)isochromans (**6** and **7**).

Pyrolysis of **2**, **6**, and **7** gave 4-benzylisoquinoline (**3**) and 4-(4-substituted benzyl)-isoquinolines (**8** and **9**), respectively.

Compound **3** was also obtained by heating 2-(2-hydroxyethyl)benzaldehyde with benzylamine, or by heating 2-vinylbenzylidenebenzylamine (**4**), while the reaction of **1** with N-methylbenzylamine afforded 1-(N-methylbenzylamino)isochroman (**5**) and did not give the 4-benzylisoquinoline derivative at all.

The reaction mechanism giving 4-benzylisoquinolines is proposed to be as shown in Chart 3.

Keywords——1-ethoxyisochroman; reaction mechanism; 1-benzylaminoisochroman; 1-(4-methoxybenzylamino)isochroman; 1-(4-cyanobenzylamino)isochroman; 4-benzyl-isoquinoline; 4-(4-methoxybenzyl)isoquinoline; 4-(4-cyanobenzyl)isoquinoline

In our previous work, it was found that the reaction of 1-ethoxyisochroman (**1**) with nucleophilic compounds such as alcohols, phenols, aromatic ethers, enamines, and compounds having an active methylene group gave corresponding 1-substituted isochroman derivatives.[1]

This paper deals with the reaction of **1** with benzylamines. There has been only one previous report concerning the reactivity of **1** with amines; that is, Rieche and Schmitz prepared 2-(2-hydroxyethyl)benzaldehyde-2,4-dinitrophenylhydrazone by heating **1** with 2,4-dinitrophenylhydrazine.[2]

Heating of **1** with benzylamine at 140—150° afforded (±)-1-benzylaminoisochroman (**2**) in 63% yield, together with a small amount of by-product melting at 119—120°. This compound had a molecular formula of $C_{16}H_{13}N$ on the basis of its elemental analysis data and mass (MS) spectrum (M^+, *m/e*: 219). The proton magnetic resonance (^{1}H-NMR) spectrum of the compound in CCl_4 indicated the presence of two aromatic protons at δ: 8.19 as a singlet and δ: 8.89 as a singlet. These signals are attributable to the protons of the $C_{(1)}$ and $C_{(3)}$-positions of 4-substituted isoquinoline. These data agreed with those for an authentic sample of 4-benzylisoquinoline (**3**).[3]

Our interest in the mechanism of the formation of **3** in this reaction led us to undertake further experiments.

Since **2** was assumed to be a first intermediate of **3**, **2** was heated in an oil bath. Heating of **2** for two hours at 140—150° did not gave **3**, but heating of **2** for four hours at 200—220° afforded **3** in 24% yield, and the remaining product was a polymeric material.

2-(2-Hydroxyethyl)benzylidenebenzylamine, assumed to be a second intermediate of **3**, was prepared by treatment of 2-(2-hydroxyethyl)benzaldehyde[2] with benzylamine. The resulting 2-(2-hydroxyethyl)benzylidenebenzylamine was heated without further purification at 200—220° to give **3** in 15% yield.

In order to find improved conditions offering an increased yield of **3**, an equimolar mixture of **2** and benzylamine was heated at 200—220°, but the yield of **3** not improved. This result

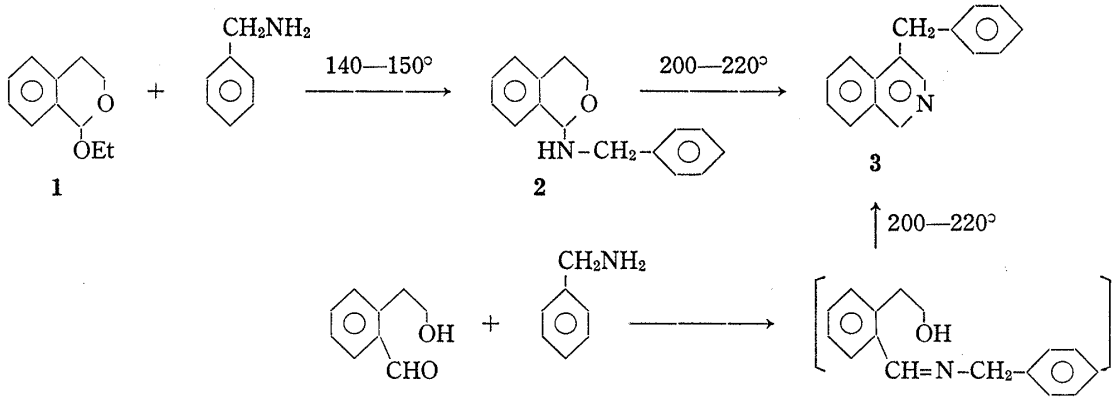


Chart 1

suggested that the benzyl group of **3** is introduced by intramolecular transformation of that of **2**.

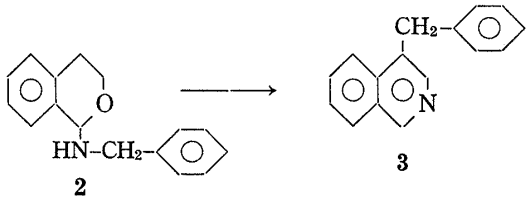
Because Maitte[4] reported the formation of 2-vinylbenzaldehyde on heating of **1** at 540°, 2-vinylbenzylidenebenzylamine (**4**), assumed to be a third intermediate of **3**, was prepared by Dale's method,[5] and heated for four hours at 200—220°. The compound **3** was obtained in 38% yield. A similar reaction was reported by Beke, *et al.*; that is, treatment of 2-methoxy-6-vinylpiperonal with benzylamine afforded 6-methoxy-4,5-methylenedioxy-2-vinylbenzylidenebenzylamine, and heating this in the presence of potassium cyanide in alcoholic alkali gave 2-benzyl-1-cyano-8-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline.[6]

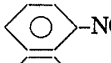
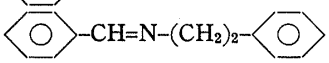
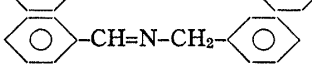
The addition of a dehydrogenating agent seemed to be effective in increasing the yield of **3**. Compound **2** was heated in the presence of nitrobenzene under usual conditions, and a slightly increased yield of **3** was obtained.

On the other hand, the effect of Schiff base on the formation of **3** was remarkable; that is, when a 1.5-fold molar excess of a Schiff base such as benzylidenebenzylamine[7] or benzylidene-β-phenethylamine[8] was used as a dehydrogenating agent for **2**, the yield of **3** increased to 80% or 57%, respectively. Dibenzylamine[9] was isolated from the products of the former reaction. The same effect of Schiff base was observed in the heating of **4**, and the yield of **3** was increased to 77%. These results are listed in Table I.

Heating of **1** with N-methylbenzylamine at 200—220° gave (±)-1-(N-methylbenzylamino)isochroman (**5**) in 49% yield, and no isoquinoline derivative. This result suggested that the formation of a 4-benzylisoquinoline derivative in the reaction of **2** with benzylamines

Table I. Effects of Dehydrogenating Agents (DH) on the Yield of **3**



Run	DH	Temp. (°C)	Time (hr)	Yield of 3 (%)
1	—	200—220	4	24
2		200—220	4	38
3		200—220	4	57
4		200—220	4	80

hangs on whether or not the corresponding 2-(2-hydroxyethyl)benzylidenebenzylamine is formed as the intermediate.

In order to explore the effect of substituents in the benzene ring of benzylamine on the yield of 4-benzylisoquinolines, some benzylamines having an electron-releasing or -attracting group at the $C_{(4)}$-position were heated with **1** under appropriate conditions. Heating of **1** with 4-methoxybenzylamine for eight hours at 150 —155° gave (±)-1-(4-methoxybenzylamino)isochroman (**6**) in 25% yield, and heating of **1** with 4-cyanobenzylamine for four hours at 160—170° gave (±)-1-(4-cyanobenzylamino)isochroman (**7**) in 40% yield. The resulting **6** or **7** was heated for four hours at 200—220°, and 4-(4-methoxybenzyl)isoquinoline (**8**)[10] or 4-(4-cyanobenzyl)isoquinoline (**9**) was obtained in 45% or 6% yield, respectively. Heating of **6** with benzylidene-4-methoxybenzylamine[11] gave **8** in 86% yield, while, heating of **7** with benzylidenebenzylamine gave **9** in a yield of only 10% and gave **3** in 64% yield; the latter is probably formed during the process of formation of **4** by exchange of the 4-cyanobenzylamino group of the intermediate, 2-vinylbenzylidene-4-cyanobenzylamine, with the benzylamino group of benzylidenebenzylamine. These results are shown in Chart 2. These results indicated that the effect of substituents in the benzene ring on the yield of 4-benzylisoquinolines parallels the stability of the corresponding benzyl cations.

The mechanism of formation of **3** upon heating of **1** with benzylamine is proposed to be as shown in Chart 3.

Dehydration of the second intermediate, 2-(2-hydroxyethyl)benzylidenebenzylamine, which is easily formed by prototropy, may occur to give the third intermediate (**4**) at 200—220°.

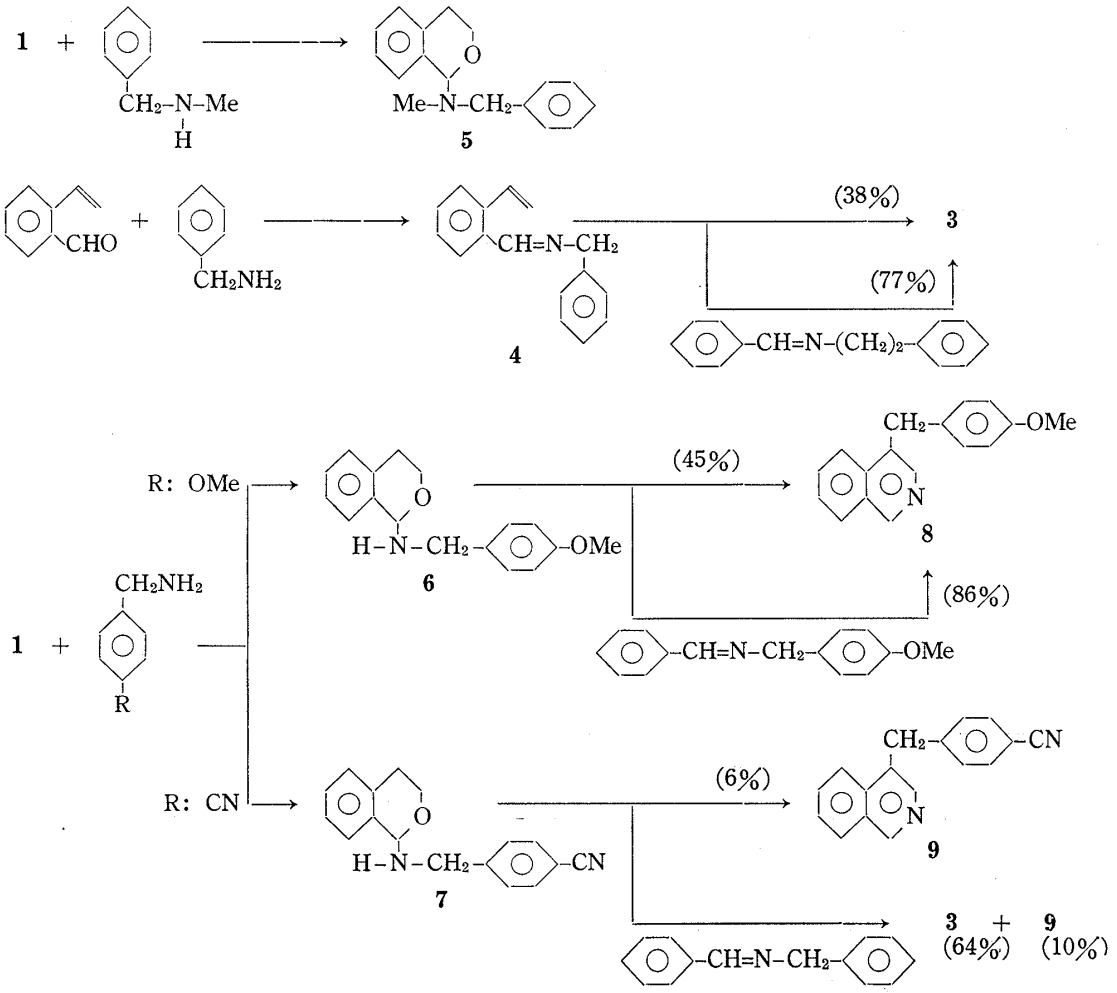


Chart 2

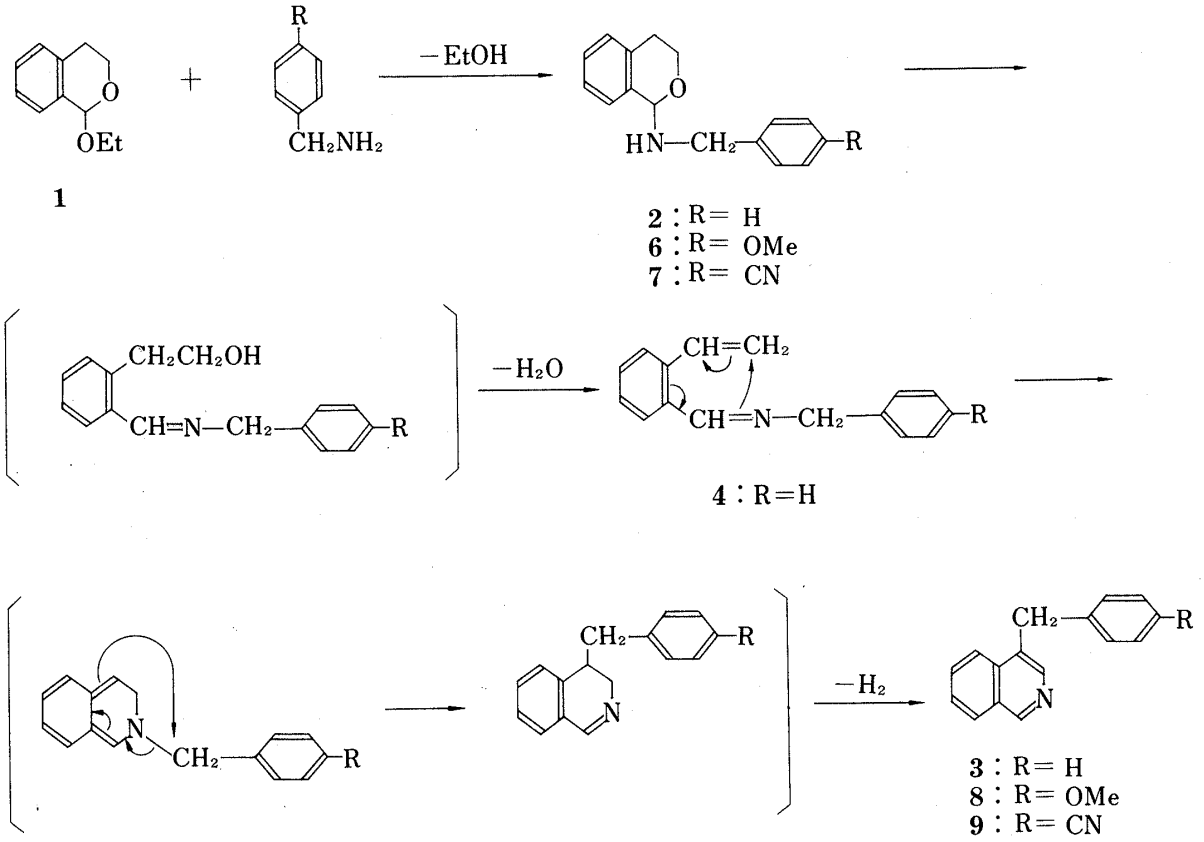


Chart 3

Subsequently, the cyclization of **4** may take place as indicated to give 4-benzyl-3,4-dihydroisoquinoline, which is readily susceptible to dehydrogenation by Schiff base (**4** formed in the course of this reaction, or added benzylidenebenzylamine) to give **3**.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. ^{1}H-NMR spectra were obtained on a Hitachi R-22 spectrometer at 90 MHz, employing tetramethylsilane as an internal standard. MS and GC–MS were measured with a Shimadzu LKB-9000 spectrometer. IR spectra were recorded on a Nihon Bunko A-102 spectrometer. Optical rotations were measured on a Nihon Bunko DIP-4 digital polarimeter.

Reaction of 1 with Benzylamine——A mixture of **1** (5 g) and benzylamine (4.5 g) was heated under an argon atmosphere at 140—150° for 4 hr. The resulting mixture was chromatographed on alumina with benzene. The first fraction gave 4.2 g (63%) of (±)-1-benzylaminoisochroman (**2**), bp 135—140° (0.007 mmHg). *Anal.* Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.59; H, 7.39; N, 5.78. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (1H, s, NH), 2.62—2.80 (2H, m, $C_{(4)}H_2$), 3.62—4.13 (2H, m, $C_{(3)}H_2$), 3.95 (2H, s, $-CH_2-C_6H_5$), 5.27 (1H, s, $C_{(1)}H$), 7.02—7.41 (9H, m, aromatic protons). MS *m/e*: 239 (M^+), 238 (M^+-H), 221 (M^+-H_2O), 220 (M^+-H-H_2O), 194 (M^+-H_2O-HCN), 133 (C_9H_9O, base peak). The second fraction gave 0.06 g (1%) of 4-benzylisoquinoline (**3**), mp 119—120° (cyclohexane) (Lit.[3] 120°). *Anal.* Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.56; H, 6.03; N, 6.21. ^{1}H-NMR (CCl_4) δ: 4.22 (2H, s, $-CH_2-C_6H_5$), 7.03 (5H, s with shoulder, aromatic protons), 7.27—7.80 (4H, m, aromatic protons), 8.19 (1H, s, $C_{(1)}H$), 8.89 (1H, s, $C_{(3)}H$). MS *m/e*: 219 (M^+, base peak), 218 (M^+-H), 191 ($M^+-H-HCN$).

Pyrolysis of (±)-1-Benzylaminoisochroman (2)——Procedure a) Compound **2** (3 g) was heated at 200—220° under an argon atmosphere for 4 hr. The resulting mixture was chromatographed on alumina with benzene to give 0.66 g (24%) of **3**, mp 119—120° (cyclohexane), which was shown to be identical with authentic **3** by comparison of ^{1}H-NMR and mass spectra.

Procedure b) A mixture of **2** (1.2 g, 5 mmol) and benzylamine (0.6 g, 5.6 mmol) was heated at 200—220° under an argon atmosphere for 4 hr. The resulting mixture was purified by the same method as in procedure a) to give 0.26 g (24%) of **3**.

Procedure c) A mixture of **2** (3 g, 12.5 mmol) and nitrobenzene (2.3 g, 18.6 mmol) was heated at 200—

220° under an argon atmosphere for 4 hr. The resulting mixture was purified by the same method as in procedure a) to give 1.04 g (38%) of **3**.

Procedure d) A mixture of **2** (2.45 g, 10.3 mmol) and benzylidene-β-phenethylamine[8] (3.3 g, 15.7 mmol) was heated at 200—220° under an argon atmosphere for 4 hr. The resulting mixture was purified by the same method as in procedure a) to give 1.28 g (57%) of **3**.

Procedure e) A mixture of **2** (3 g, 12.5 mmol) and benzylidenebenzylamine[7] (3.6 g, 18.4 mmol) was heated at 200—220° under an argon atmosphere for 4 hr. The resulting mixture was chromatographed on alumina with benzene. The first fraction gave 1.2 g (33%) of dibenzylamine,[9] bp 148—150° (3 mmHg). *Anal.* Calcd for $C_{14}H_{15}N$: 85.23; H, 7.66; N, 7.10. Found: C, 85.35; H, 7.68; N, 7.22. ^{1}H-NMR (CCl_4) δ: 1.50 (1H, broad s, NH), 3.65 (4H, s, $-N-CH_2\times2$), 7.17 (10H, s with shoulder, aromatic protons). MS *m/e*: 197 (M^+), 196 (M^+-H), 91 (C_7H_7, base peak). The second fraction gave 2.2 g (80%) of **3**, mp 119—120°, which was shown to be identical with authentic **3** by comparison of ^{1}H-NMR and mass spectra.

Synthesis of 3 by Heating of 2-(2-Hydroxyethyl)benzaldehyde with Benzylamine——A mixture of 2-(2-hydroxyethyl)benzaldehyde (1.7 g) and benzylamine (1.6 g) was heated at 200—220° under an argon atmosphere for 4 hr. The resulting mixture was chromatographed on alumina with benzene to give 0.37 g (15%) of **3**, mp 119—120°, which was shown to be identical with authentic **3** by comparison of ^{1}H-NMR and mass spectra.

2-Vinylbenzylidenebenzylamine (4)——Benzylamine (2.6 g) was added to a solution of o-formylstyrene[5] (3.17 g) in Et_2O (10 ml), and the mixture was stirred at room temperature under an argon atmosphere for 2 hr. The Et_2O layer was dried over $MgSO_4$ and concentrated to give 3.4 g (64%) of **4**, colorless oil. ^{1}H-NMR (CCl_4) δ: 4.70 (2H, s, $-C\underline{H}_2-C_6H_5$), 5.25 (1H, d.d, $J=1.8$ and 12 Hz, vinyl proton), 5.50 (1H, d.d, $J=1.8$ and 18 Hz, vinyl proton), 7.16 (9H, s with shoulder, vinyl and aromatic protons), 7.78—8.99 (1H, m, $C_{(3)}H$), 8.56 (1H, s, –CH=N). MS *m/e*: 221 (M^+), 220 (M^+-H, base peak), 194 (M^+-HCN), 130 ($M^+-CH_2-C_6H_5$).

Pyrolysis of 2-Vinylbenzylidenebenzylamine (4)——Procedure a) **4** (1.6 g) was heated at 200—220° under an argon atmosphere for 4 hr. The mixture was chromatographed on alumina with benzene to give 0.6 g (38%) of **3**, mp 119—120°, which was shown to be identical with authentic **3** by comparison of ^{1}H-NMR and mass spectra.

Procedure b) A mixture of **4** (1.7 g, 7.6 mmol) and benzylidenebenzylamine (2.4 g, 11.4 mmol) was heated at 200—220° under an argon atmosphere for 4 hr. The mixture was chromatographed on alumina with benzene to give 1.3 g (77%) of **3**, which was shown to be identical with authentic **3** by comparison of ^{1}H-NMR and mass spectra.

(±)-1-(N-Methylbenzylamino)isochroman (5)——A mixture of **1** (4 g) and N-methylbenzylamine (2.72 g) was heated at 200—220° under an argon atmosphere for 4 hr. The mixture was purified by distillation *in vacuo* to give 2.78 g (49%) of **5**, colorless oil, bp 167—175° (5 mmHg). *Anal.* Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.62; H, 7.45; N, 5.37. ^{1}H-NMR (CCl_4) δ: 2.22 (3H, s, $N-CH_3$), 2.80—3.22 (2H, m, $C_{(4)}H_2$), 3.30—4.22 (2H, m, $C_{(3)}H_2$), 3.73 (2H, s, $-N-C\underline{H}_2-C_6H_5$), 5.30 (1H, s, $C_{(1)}H$), 6.88—7.65 (9H, m, aromatic protons). MS *m/e*: 253 (M^+), 223 (M^+-HCHO), 133 (C_9H_9O, base peak).

Reaction of 1 with 4-Methoxybenzylamine——A mixture of **1** (5 g) and 4-methoxybenzylamine (4.6 g) was heated at 150—155° under an argon atmosphere for 8 hr. The resulting mixture was chromatographed on alumina with benzene. The first fraction gave 1.9 g (25%) of (±)-1-(4-methoxybenzylamino)isochroman (**6**), bp 150—160° (0.001 mmHg). *Anal.* Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 76.05; H, 7.23; N, 5.41. ^{1}H-NMR (CCl_4) δ: 1.96 (1H, s, NH), 2.62—2.80 (2H, m, $C_{(4)}H_2$), 3.70 (5H, s, $-CH_2-$ and CH_3), 3.64—3.85 (2H, m, $C_{(3)}H_2$), 5.20 (1H, s, $C_{(1)}H$), 6.75 (2H, d.d, $J=2$ and 8 Hz, $C_{(3')}H$ and $C_{(5')}H$), 7.10—7.55 (4H, m, aromatic protons), 7.11 (2H, d.d, $J=2$ and 8 Hz, $C_{(2')}H$ and $C_{(6')}H$). MS *m/e*: 269 (M^+), 268 (M^+-H), 251 (M^+-H_2O), 239 (M^+-HCHO), 133 (C_9H_9O, base peak). The second fraction gave 1.81 g (26%) of 4-(4-methoxybenzyl)isoquinoline (**8**), colorless oil. ^{1}H-NMR (CCl_4) δ: 3.71 (3H, s, OCH_3), 4.22 (2H, s, $-C\underline{H}_2-$  $-OMe$), 6.63—7.98 (8H, m, aromatic protons), 8.26 (1H, s, $C_{(1)}H$), 8.89 (1H, s, $C_{(3)}H$). MS *m/e*: 249 (M^+, base peak), 234 (M^+-CH_3). Picrate, mp 212—215°. *Anal.* Calcd for $C_{23}H_{18}N_4O_8$: C, 57.74; H, 3.79; N, 11.71. Found: C, 57.69; H, 3.74; N, 11.66.

Pyrolysis of (±)-1-(4-Methoxybenzylamino)isochroman (6)——Procedure a) Compound **6** (0.7 g) was heated at 200—220° under an argon atmosphere for 4 hr. The resulting mixture was chromatographed on alumina with benzene–AcOEt (3: 1) to give 0.29 g (45%) of **8**, colorless oil, which was shown to be identical with authentic **8** by comparison of ^{1}H-NMR and mass spectra.

Procedure b) A mixture of **6** (0.69 g, 2.5 mmol) and benzylidene-4-methoxybenzylamine (0.86 g, 3.8 mmol) was heated at 200—220° under an argon atmosphere for 4 hr. The resulting mixture was chromatographed on alumina with benzene–AcOEt (3: 1) to give 0.55 g (86%) of **8**, colorless oil, which was shown to be identical with authentic **8** by comparison of ^{1}H-NMR and mass spectra.

(±)-1-(4-Cyanobenzylamino)isochroman (7)——A mixture of **1** (3 g) and 4-cyanobenzylamine (3.7 g) was heated at 160—170° for 4 hr. The resulting mixture was chromatographed on alumina with pet. ether–benzene (1: 1) to give 1.76 g (40%) of **7**, mp 80—81° (cyclohexane). *Anal.* Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.41; H, 6.10; N, 10.53. ^{1}H-NMR (CCl_4) δ: 2.22 (1H, broad s, NH), 2.60—2.88 (2H, m, $C_{(4)}H_2$), 3.61—4.16 (2H, m, $C_{(3)}H_2$), 4.00 (2H, s, $N-CH_2$), 5.20 (1H, s, $C_{(1)}H$), 6.80—7.98 (8H, m,

aromatic protons). MS *m/e*: 264 (M^+), 263 (M^+-H), 245 (M^+-H-H_2O), 234 (M^+-HCHO), 219 (M^+-H_2O-HCN), 133 (C_9H_9O, base peak). IR ν_{max}^{Nujol} cm^{-1}: 2220 (C≡N).

Pyrolysis of (±)-1-(4-Cyanobenzylamino)isochroman (7)——Procedure a) Compound **7** (0.4 g) was heated at 200—220° under an argon atmosphere for 4 hr. The resulting mixture was chromatographed on alumina with cyclohexane–AcOEt (5: 1) to give 0.022 g (6%) of 4-(4-cyanobenzyl)isoquinoline (**9**), mp 113—114° (*n*-hexane). *Anal.* Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.75; H, 4.74; N, 11.28. ^{1}H-NMR ($CDCl_3$) δ: 4.41 (2H, s, $-C\underline{H}_2-$  $-CN$), 7.20—7.99 (8H, m, aromatic protons), 8.40 (1H, s, $C_{(1)}H$), 9.19 (1H, s, $C_{(3)}H$). MS *m/e*: 244 (M^+, base peak), 243 (M^+-H), 217 (M^+-HCN). IR ν_{max}^{Nujol} cm^{-1}: 2220 (C≡N).

Procedure b) A mixture of **7** (1 g, 3.7 mmol) and benzylidenebenzylamine[7] (1.1 g, 5.6 mmol) was heated at 200—220° under an argon atmosphere for 4 hr. The mixture was chromatographed on alumina with cyclohexane–AcOEt (5: 1). The first fraction gave 0.53 g (64%) of **3**, mp 119—120°, which was shown to be identical with authentic **3** by comparison of ^{1}H-NMR and mass spectra. The second fraction gave 0.09 g (10%) of **9**, mp 113—114°, which was identical with authentic **9** (^{1}H-NMR, mass and IR spectra).

References and Notes

1) Part II: M. Yamato, T. Ishikawa, and T. Kobayashi, *Chem. Pharm. Bull.*, **28**, 2967 (1980).
2) A. Rieche and E. Schmitz, *Chem. Ber.*, **89**, 1254 (1956).
3) J. Braun, O. Bayer, and L. Cassel, *Chem. Ber.*, **60**, 2602 (1927); M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **78**, 4096 (1956); R. Grewe, W. Krüger, and E. Vangermain, *Chem. Ber.*, **97**, 119 (1964); P. Gasside and A.C. Ritchie, *J. Chem. Soc. (C)*, **1966**, 2140.
4) P. Maitte, *Ann. Chim. (Paris)*, **9**, 431 (1954).
5) W.T. Dale, L. Starr, and C.W. Strobel, *J. Org. Chem.*, **26**, 2225 (1961).
6) D. Beke, K. Harsányi, and D. Korbonits, *Acta Chim. Acad. Sci. Hung.*, **19**, 267 (1959).
7) A.T. Mason and G.R. Winder, *J. Chem. Soc.*, **65**, 191 (1894).
8) N.A. Shepard and A.A. Ticknor, *J. Am. Chem. Soc.*, **38**, 383 (1916).
9) W. Traube and A. Engelhardt, *Chem. Ber.*, **44**, 3152 (1911).
10) L. Rügheimer and L. Schaumann, *Ann.*, **326**, 296 (1903).
11) C.K. Ingold and C.W. Shoppee, *J. Chem. Soc.*, **1929**, 1202.