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The Synthesis of Chromone-3-carboxanilides[1]

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Several chromone-3-carboxanilides (**7a**—**f**) were prepared by amidation of chromone-3-carboxylic acid (**6**), or better, by cyclization of 2-(2-hydroxybenzoyl)acetanilides (**9a**—**c**). In the latter procedure, the direct and convenient synthesis of 2-(2-benzyloxybenzoyl)-acetanilides (**8a** and **8b**) from 2-benzyloxyacetophenone (**1**) was achieved using aryl isocyanates in the presence of NaH.

Ukita and Arakawa[3] reported that 3-arylcarbamoyl-4-hydroxycoumarin shows significant antibacterial activity against both gram-positive and -negative organisms *in vitro*, however the addition of serum albumin to the test culture causes the marked decrease in the activity. With an assumption that the acidic C-4 hydroxyl group of the 4-hydroxycoumarin skeleton might be an attaching site to the albumin protein, we have investigated the synthesis and the antibacterial activity of the 3-arylcarbamoyl-4-alkoxycoumarin derivatives.[4] The modification of the C-4 hydroxyl group by the alkylation retained their activities, however the interaction with serum albumin could not be reduced. These results led us to the conclusion that the 3-arylcarbamoylcoumarin skeleton itself would be the structural factor for the interaction with the albumin. Therefore, our efforts were directed toward the synthesis of the chromone-3-carboxylic acid derivatives, which are structurally close to the 3-arylcarbamoylcoumarin and have partly an isoelectronic structure to those of the synthetic antibacterial agents: nalidixic acid[5] and oxolinic acid.[6] In addition, since some of the chromone-2-carboxylic acid derivatives are known to possess both anticoagulant[7] and analgesic[8] activities, the chromone-3-carboxylic acid derivatives may offer another possibility of being useful chemotherapeutic agents. We now report the synthesis of chromone-3-carboxylic acid (**6**) and its derivatives **7a**—**f**.

Although the Kostanecki-Robinson[9] reaction has been known as a general method for the preparation of chromones, only an application of the method to the synthesis of chromone-3-carboxylic acids has been reported so far.[10] So it is worthwhile to extend the utility of this method to the synthesis of our compounds.

Two different routs were employed for the present purpose (Chart 1). The one (procedure A) involves amidation of the acid **6**. The other (procedure B), cyclization of hydroxyanilides

1) This work was presented at the 22nd Meeting of Kinki Branch, Pharmaceutical Society of Japan, Nishinomiya, November 1972.
2) Location: *962, Kashima-cho, Higashiyodogawa-ku, Osaka.*
3) T. Ukita and K. Arakawa, *Chem. Pharm. Bull.* (Tokyo), **1**, 255 (1953).
4) Unpublished data.
5) G.Y. Lesher, E.J. Froelich, M.D. Gruett, J.H. Bailey, and R.P. Brundage, *J. Med. Pharm. Chem.*, **5**, 1063 (1962).
6) D. Kaminsky and R.I. Meltzer, *J. Med. Chem.*, **11**, 160 (1968).
7) P. Tronche, J. Couquelet, and P. Jolland, *Ann. Pharm. Franc.*, **23**, 573 (1965).
8) P. Bastide, J. Vandeleau, J. Couquelet, and P. Tronche, *Therapie*, **21**, 1361 (1966).
9) St. v. Kostanecki and A. Rozycki, *Chem. Ber.*, **34**, 102 (1901); J. Allan and R. Robinson, *J. Chem. Soc.*, **125**, 2192 (1924).
10) G.G. Badcock, F.M. Dean, A. Robertson, and W.B. Whalley, *J. Chem. Soc.*, **1950**, 903.

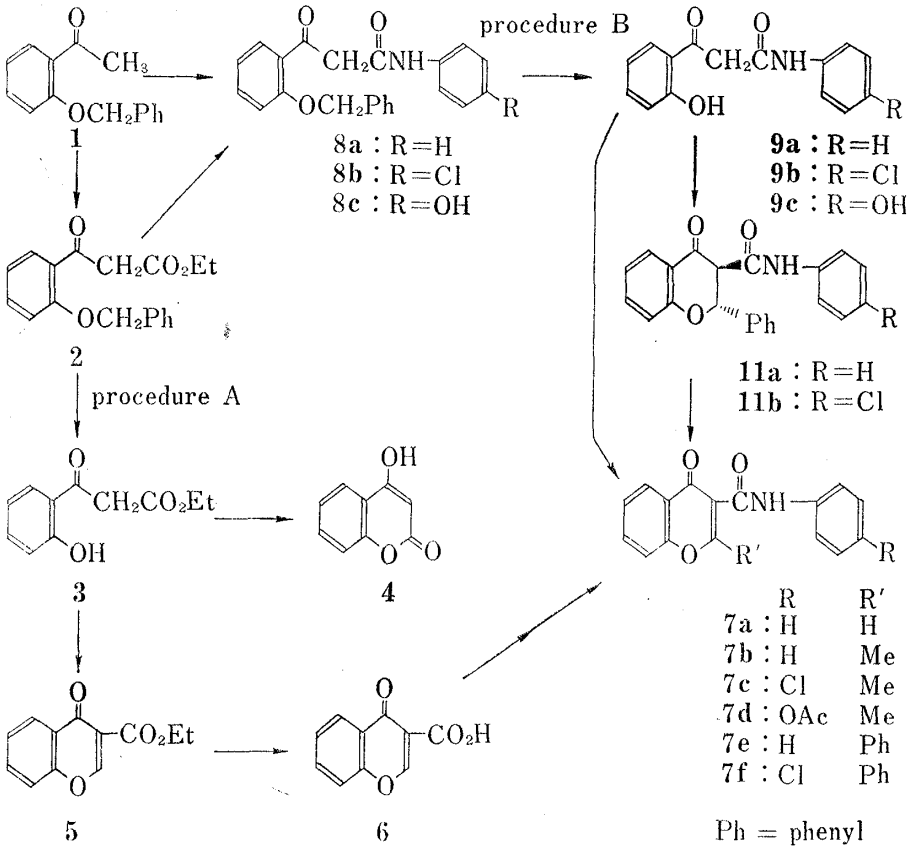

Chart 1

9a—**c**, was devised as an alternate route for the improvement on the low yield in the former and for evidence in structure assignment to the products.

Condensation of 2-benzyloxyacetophenone (**1**) with diethyl carbonate in the presence of two molar equivalents of sodium hydride afforded ethyl (2-benzyloxybenzoyl)acetate (**2**) in 41% yield. The benzyl group was then removed by the catalytic hydrogenation with 5% palladium on charcoal to give ethyl (2-hydroxybenzoyl)acetate (**3**) in an excellent yield. Cyclization of the hydroxyester **3** to ethyl chromone-3-carboxylate (**5**) was first attempted employing ethyl formate and sodium hydride in the usual manner.[11] However, the desired product **5** was not formed and 4-hydroxycoumarin (**4**), which was resulted from the intramolecular cyclization of the hydroxyester **3**, was isolated in 71% yield. Therefore, the Jones' method[12] for the preparation of 3-acylchromones was applied to the cyclization of the hydroxyester **3**. Reaction of the hydroxyester **3** with ethyl orthoformate and acetic anhydride at the reflux temperature gave **5** in the moderate yield. This step was also accomplished with more satisfactory results by the Kostanecki–Robinson reaction. Cyclization of the hydroxyester **3** with acetic formic anhydride in the presence of sodium formate at room temperature afforded **5** in 76% yield. The structure of **5** was confirmed by its elemental analysis and the spectral data (see Experimental section). Hydrolysis of **5** in the dioxane containing dilute hydrochloric acid yielded chromone-3-carboxylic acid (**6**). Treatment of **6** with oxalyl chloride gave the acid chloride, which was converted to chromone-3-carboxanilide (**7a**) by the reaction with aniline.

The alternative and more convenient synthesis of the target anilides **7a**—**f** is described below (procedure B). β-Ketoanilides **8a**—**c** were prepared by two ways: method A, one

11) C. Mentzer and P. Meunier, *Bull. Soc. Chim. France*, 11, 302 (1944).
12) G.H. Jones, J.B.D. Mackenzie, A. Robertson, and W.B. Whalley, *J. Chem. Soc.*, **1949**, 562; F. Eiden and H. Haverland, *Arch. Pharm.*, **300**, 806 (1967).

step conversion of **1** to the anilides by the reaction with the arylisocyanates in the presence of sodium hydride, and method B, the condensation of the β-ketoester **2** with the appropriate arylamine. The former was found to be more convenient and gave better result as shown in the Table.

Table I. Yield (%) of **8a—c** from **1**

8	R	Method A	Method B
a	H	69	22
b	Cl	58	—
c	OH	—	28

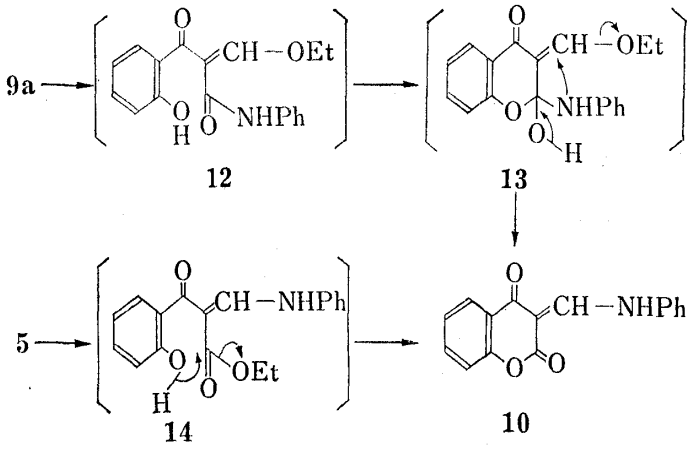

Chart 2

Reductive debenzylations of β-ketoanilides **8a—c** were carried out using palladium on charcoal as a catalyst to give the hydroxyanilides **9a—c** in good yields. An attempt was made to prepare **7a** by treatment of (2-hydroxybenzoyl)acetanilide (**9a**) with ethyl orthoformate and acetic anhydride. However, the desired product **7a** was obtained in only 4% yield, and a main product was 3-anilinomethylene-2,4-chromandione (**10**). The structure of **10** was determined from the following evidences; the infrared spectrum indicated two carbonyl absorptions assignable to the lactone and the vinylogous amide at 1690 and 1653 cm^{-1}, and NH absorption at 3180 cm^{-1}, the nuclear magnetic resonance (NMR) spectrum exhibited the methine proton (doublet) coupling with the adjacent iminoproton. In addition, the formation of the same compound **10** in the reaction of **5** with aniline strongly supported the structure for the unexpected product **10**. The most plausible mechanism for the formation of **10** would appear to be the formation of the intermediate **12** followed by a cyclization and a subsequent displacement of the ethoxyl with the anilino group (Chart 2). The anilide **9a** was converted successfully to **7a** by heating with acetic formic anhydride in the presence of sodium formate.

The Kostanecki-Robinson method also gave good results (64—69%) in the synthesis of the series of the 2-methylchromone-3-carboxanilides **7b—f**, except in the case of 2-phenylchromone-3-carboxanilide (**7e**) and 4′-chloro-2-phenylchromone-3-carboxanilide (**7f**). The syntheses of **7e** and **7f** were achieved in the following usual procedure.[13]

Condensations of **9a**, and 2-(2-hydroxybenzoyl)-4′-chloroacetanilide (**9b**) with benzaldehyde in the presence of a catalytic amount of piperidine afforded 2-phenyl-4-chromanone-3-carboxanilide (**11a**) and 4′-chloro-2-phenyl-4-chromanone-3-carboxanilide (**11b**). The NMR spectra of **11a, b** were in agreement with a flavanone structure. For example, **11a** showed an AB pattern centered at 4.38 and 5.84 ppm ($J_{2,3}$=12 Hz) for the two ring protons. The high coupling constant[14] indicated the *trans* orientation of the C-2 and C-3 substituents. Both compounds (**11a, b**) were oxidized with selenium dioxide in dioxane to afford **7e** and **7f**, respectively.

All the intermediates and the chromone-3-carboxylic acid derivatives reported herein were screened for pharmacological activity. Compound (**5**) showed antifungal activity against

13) W. Baker and F. Glockling, *J. Chem. Soc.*, **1950**, 2759.
14) K.R. Huffman, C.E. Kuhn, and A. Zweig, *J. Am. Chem. Soc.*, **92**, 599 (1970).

pricularia oryzae at 50 μg/ml (cylinder plate assay). Compound (**7d**) exhibited an antiinflammatory activity equal to that of phenylbutazone (adjuvant-induced mouse paw edema assay).

Experimental

Melting points are uncorrected. IR spectra were taken with a Hitachi EPI-S2 and a Shimadzu IR-27G spectrophotometer. UV spectra were determined with a Hitachi EPS-2U recording spectrophotometer. NMR spectra were determined on a Hitachi-Parkin-Elmer R-20A at 60 MHz with tetramethylsilane as internal reference. Mass spectra were measured using a Hitachi RMS-4.

Ethyl (2-Benzyloxybenzoyl)acetate (2)——A mixture of **1**[15] (49.7 g, 0.22 mole), ethyl carbonate (250 g, 2.12 moles), and NaH (64% oil dispersion, 16.5 g, 0.44 mole) was heated with stirring at 80—100° for 15 min. The reaction mixture was concentrated to dryness *in vacuo* and the residue was triturated with ice water. After being acidified with AcOH, the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, and dried with $MgSO_4$. The dried chloroform layer was concentrated to dryness *in vacuo*, and the residual solid was recrystallized from isopropyl ether to give **2** (26.8 g, 41%), mp 49—50°. IR ν_{max}^{Nujol} cm^{-1}: 1728, 1668. NMR ($CDCl_3$) δ: 1.17 (3H, t, J=6 Hz, $-CH_2\underline{CH_3}$), 4.00 (2H, s, $-CH_2CO-$), 4.08 (2H, q, J=6 Hz, $-\underline{CH_2}-CH_3$), 5.17 (2H, s, $-CH_2-O$), 6.85—8.02 (9H, m, aromatic protons). *Anal.* Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.71; H, 6.06.

Ethyl (2-Hydroxybenzoyl)acetate (3)——A solution of **2** (7.2 g, 0.0242 mole) in EtOH (350 ml) was hydrogenated over 5% palladium on charcoal (2.8 g) at room temperature and atmospheric pressure. A total of 650 ml of hydrogen (the theoretical amount; 592 ml) was absorbed in 1 hr. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo* to give **3** (4.7 g, 94%) as a colorless oil. Distillation of this crude product afforded the pure sample, bp 102—105° (0.22 mmHg). IR ν_{max}^{neat} cm^{-1}: 2980, 1740, 1644. NMR ($CDCl_3$) δ: 1.24 (3H, t, J=6 Hz, $-CH_2\underline{CH_3}$), 3.98 (2H, s, $-CH_2-$), 4.21 (2H, q, J=6 Hz $-\underline{CH_2}-CH_3$), 6.72—7.80 (4H, m, aromatic protons), 11.80 (1H, s, OH). *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.18; H, 5.93.

4-Hydroxycoumarin (4)——To a solution of **3** (2.0 g, 9.6 mmoles) in ethyl formate (8.6 g, 0.12 mole) was added portionwise NaH (64% oil dispersion, 0.36 g, 9.6 mmoles) with stirring at 0—5°. The mixture was allowed to stand at room temperature for 24 hr. The excess reagent was evaporated *in vacuo*, and the residue was acidified with cold 10% hydrochloric acid. The resulting solid was collected by filtration, washed with H_2O, and dried to afford **4** (1.1 g, 71%), mp 204—206°. This compound was identified by IR spectrum with an authentic 4-hydroxycoumarin.

Ethyl Chromone-3-carboxylate (5). Reaction of 3 with Ethyl Orthoformate and Acetic Anhydride——A mixture of **3** (1.4 g, 6.73 mmoles), ethyl orthoformate (2.0 g, 13.5 mmoles), and acetic anhydride (2.1 g, 20.2 mmoles) was refluxed for 1 hr. The reaction mixture was concentrated *in vacuo*, and the residual oil was chromatographed on silica gel. Elution with C_6H_6–AcOEt–*n*-hexane (3: 1: 1) gave **5** (0.45 g, 31%), mp 65—68°.

This product was identical in its IR spectrum with an authentic sample obtained by the Kostanecki–Robinson reaction of **3**.

Ethyl Chromone-3-carboxylate (5). The Kostanecki-Robinson Reaction of 3——A mixture of **3** (2.1 g, 0.01 mole), acetic formic anhydride (8.8 g, 0.1 mole), and sodium formate (6.8 g, 0.1 mole) was stirred at room temperature for 15 hr. The reaction mixture was concentrated to dryness *in vacuo*, and ice water was added to the residue. This was extracted with $CHCl_3$ and the extract was dried with $MgSO_4$. The dried chloroform layer was concentrated *in vacuo* to give an oil, which was chromatographed on silica gel. The product was eluted with C_6H_6–AcOEt (4: 1), and the eluate was concentrated *in vacuo* to afford the crude product, which was recrystallized from isopropyl ether to give **5** (1.66 g, 76%), mp 66—68°. IR ν_{max}^{Nujol} cm^{-1}: 1708, 1658. NMR ($CDCl_3$) δ: 1.40 (3H, t, J=6 Hz, $-CH_2\underline{CH_3}$), 4.40 (2H, q, J=6 Hz, $-\underline{CH_2}CH_3$), 7.29—8.42 (4H, m, aromatic protons), 8.67 (1H, s, C_2-H). UV λ_{max}^{EtOH} nm (log ε): 294 (3.86), 302 (sh) (3.80). *Anal.* Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.13; H, 4.76.

Chromone-3-carboxylic Acid (6)——A mixture of **5** (100 mg, 0.459 mmole), 6N hydrochloric acid (1.5 ml), and dioxane (0.4 ml) was heated with stirring at 80—90° for 10 min. After cooling, the precipitate was collected by filtration, washed with H_2O, and dried to give **6** (83 mg, 96%), mp 195—197°. Recrystallization from EtOH gave an analytically pure sample, mp 196—198°. IR ν_{max}^{Nujol} cm^{-1}: 1743, 1718. NMR ($CDCl_3$) δ: 7.27—8.50 (4H, m, aromatic protons), 9.02 (1H, s, C_2-H), 13.39 (1H, s, CO_2H). *Anal.* Calcd. for $C_{10}H_6O_4$: C, 63.16; H, 3.18. Found: C, 62.93; H, 3.34.

Chromone-3-carboxanilide (7a)——By the Amidation of **6**: A mixture of **6** (120 mg, 0.632 mmole) and oxalyl chloride (2 ml) was refluxed for 24 hr. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was dissolved in benzene (5 ml). To this solution was added dropwise a solution of aniline (170 mg, 1.83 mmoles) in benzene (1 ml) under cooling in an ice bath. The mixture was warmed up to room temperature and stirred for 5 min. The precipitate was collected by filtration and washed with H_2O to

15) U.K. Pandit and T.C. Bruice, *J. Am. Chem. Soc.*, **82**, 3386 (1960).

give **7a** (140 mg, 84%), mp 210—212°. Recrystallization from EtOH afforded a pure sample, mp 210—212°. IR ν_{max}^{Nujol} cm^{-1}: 3180, 1676, 1621, 1550. NMR ($CDCl_3$) δ: 7.10—8.52 (9H, m, aromatic protons), 9.10 (1H, s, C_2-H), 11.40 (1H, s, -NH-). *Anal.* Calcd. for $C_{16}H_{11}O_3N$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.15; H, 4.41; N, 5.31.

2-(2-Benzyloxybenzoyl)acetanilide (8a)——Method A: A mixture of **1** (25 g, 0.11 mole), phenyl isocyanate (13 g, 0.11 mole), NaH (69% oil dispersion, 3.8 g, 0.11 mole), and anisole (125 ml) was refluxed for 25 min.[16] After evaporation of the solvent under reduced pressure, ice water was added to the residue. The mixture was acidified with AcOH, and extracted with $CHCl_3$. The combined extract was washed with H_2O, dried with $MgSO_4$, and concentrated to dryness *in vacuo*. The residue was recrystallized from EtOH to afford **8a** (26.3 g, 69%), mp 139—140°. This product was identical in its IR spectrum with an authentic sample obtained by the method B.

Method B: A mixture of **2** (1.0 g, 3.4 mmoles) and aniline (0.49 g, 5.3 mmoles) was heated at 170—180° for 10 min. After cooling, the reaction mixture was triturated with isopropyl ether, and the crystals which had formed were collected by filtration. Recrystallization from EtOH afforded **8a** (0.64 g, 53%), mp 140—141°. IR ν_{max}^{Nujol} cm^{-1}: 3260, 1670, 1640, 1544. NMR ($CDCl_3$) δ: 4.13 (2H, s, $-CH_2C=O$), 5.20 (2H, s, $-CH_2O$), 6.79—8.08 (14H, m, aromatic protons), 9.00 (1H, s, -NH-). *Anal.* Calcd. for $C_{22}H_{19}O_3N$: C, 76.50; H, 5.55; N, 4.06. Found: C, 76.79; H, 5.33; N, 3.98.

2-(2-Benzyloxybenzoyl)-4′-chloroacetanilide (8b)——A mixture of **1** (5.0 g, 0.022 mole), *p*-chlorophenyl isocyanate (3.4 g, 0.022 mole), NaH (69% oil dispersion, 0.77 g, 0.022 mole), and anisole (30 ml) was refluxed for 15 min.[16] The solvent was evaporated *in vacuo*, and ice water was added to the residue. The resulting mixture was acidified with AcOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried with $MgSO_4$, and concentrated to dryness *in vacuo*. The residue was recrystallized from EtOH to give **8b** (4.9 g, 58%), mp 143—144°. IR ν_{max}^{Nujol} cm^{-1}: 3290, 1683, 1662, 1540. NMR ($CDCl_3$) δ: 4.12 (2H, s, $-CH_2C=O$), 5.19 (2H, s, $-CH_2O$), 6.89—7.92 (13H, m, aromatic protons). *Anal.* Calcd. for $C_{22}H_{18}O_3NCl$: C, 69.56; H, 4.77; N, 3.69. Found: C, 69.45; H, 4.87; N, 3.54.

2-(2-Benzyloxybenzoyl)-4′-hydroxyacetanilide (8c)——A mixture of **2** (2.0 g, 6.7 mmoles), *p*-aminophenol (0.76 g, 7 mmoles), and dimethyl formamide (DMF) (6 ml) was refluxed for 45 min. After evaporation of the solvent *in vacuo*, the residue was crystallized from isopropyl ether. Recrystallization from isopropyl alcohol gave **8c** (1.65 g, 68%), mp 172—174°. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3200, 1660, 1645, 1540. NMR (DMSO-d_6) δ: 4.00 (2H, s, $-CH_2C=O$), 5.27 (2H, s, $-CH_2O$), 6.57—7.90 (13H, m, aromatic protons), 9.12 (1H, s, OH), 9.77 (1H, s, -NH-). *Anal.* Calcd. for $C_{22}H_{19}O_4N$: C, 73.11; H, 5.30; N, 3.88. Found: C, 73.14; H, 5.48; N, 3.83.

2-(2-Hydroxybenzoyl)acetanilide (9a)——A solution of **8a** (2.0 g, 5.8 mmoles) in MeOH (180 ml) was hydrogenated over 5% palladium on charcoal (0.8 g) at room temperature and atmospheric pressure. Absorption of hydrogen (175 ml, the theoretical amount; 141 ml) was completed in 1 hr. After removal of the catalyst by filtration, the filtrate was concentrated to dryness *in vacuo*, and the residue was recrystallized from EtOH to afford **9a** (1.2 g, 81%), mp 149—150°. IR ν_{max}^{Nujol} cm^{-1}: 3270, 3160, 1640, 1623, 1538. NMR ($CDCl_3$) δ: 4.06 (2H, s, $-CH_2-$), 6.73—7.98 (9H, m, aromatic protons), 8.73 (1H, s, -NH-), 11.82 (1H, s, OH). *Anal.* Calcd. for $C_{15}H_{13}O_3N$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.29; H, 5.14; N, 5.39.

2-(2-Hydroxybenzoyl)-4′-chloroacetanilide (9b)——A solution of **8b** (5.0 g, 0.0132 mole) in MeOH (420 ml) was hydrogenated over 5% palladium on charcoal (1.3 g), and worked up as described for **9a**. The product was recrystallized from EtOH to give **9b** (2.3 g, 60%), mp 160—161°. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3200, 1694, 1640, 1540. NMR ($CDCl_3$) δ: 4.13 (2H, s, $-CH_2-$), 6.80—7.96 (8H, m, aromatic protons), 8.75 (1H, s, -NH-), 11.77 (1H, s, OH). *Anal.* Calcd. for $C_{15}H_{12}O_3NCl$: C, 62.18; H, 4.17; N, 4.74. Found: C, 61.87; H, 4.29; N, 4.86.

2-(2-Hydroxybenzoyl)-4′-hydroxyacetanilide (9c)——A solution of **8c** (5.0 g, 0.0138 mole) in MeOH (250 ml) was hydrogenated over 5% palladium on charcoal (1.3 g), and worked up as above. The product was recrystallized from 50% aqueous EtOH to give **9c** (3.3 g, 92%), mp 157—158°. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3370, 1677, 1643, 1565. NMR (DMSO-d_6) δ: 4.12 (2H, s, $-CH_2-$), 6.60—8.00 (8H, m, aromatic protons), 9.17 (1H, s, C_4′-OH), 9.89 (1H, s, -NH-), 11.54 (1H, s, C_2-OH). *Anal.* Calcd. for $C_{15}H_{13}O_4N$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.22; H, 4.78; N, 5.18.

Cyclization of 9a with Ethyl Orthoformate and Acetic Anhydride——A mixture of **9a** (3.0 g, 0.0118 mole), ethyl orthoformate (1.75 g, 0.0118 mole), and acetic anhydride (3.6 g, 0.0354 mole) was heated at 100—110° for 7 min. After cooling, the reaction mixture was triturated with ether, and the resulting crystals were collected by filtration. Recrystallization from DMSO (30 ml) afforded a crude 3-anilinomethylene-2,4-chromandione (**10**, 1.6 g), mp 199—203°. Repeated recrystallization gave a pure sample (1.38 g, 44%), mp 201—202°. IR ν_{max}^{Nujol} cm^{-1}: 3180, 1690, 1653, 1605, 1572. NMR (CF_3COOH) δ: 7.10—8.23 (9H, m, aromatic protons), 9.11 (1H, d, J=14 Hz, =CHNH-), 12.95 (1H, br.s, -NH-). Mass Spectrum *m/e*: 265 (M^+). *Anal.* Calcd. for $C_{16}H_{11}O_3N$: C, 72.44; H, 4.18; N, 5.28. Found: C, 72.30; H, 4.18; N, 5.39. The mother liquor of the first recrystallization was concentrated to a volume of 10 ml *in vacuo*, and kept at room temperature.

16) A sudden exothermic reaction with violent foaming was observed when the temperature reached around 140°.

The crystals which had deposited were collected by filtration to afford **7a** (0.138 g, 4%), mp 210—213°. This sample was identified by mixed melting point test and IR spectrum with an authentic sample obtained by the procedure A.

Reaction of 5 with Aniline——To a solution of **5** (1.0 g, 4.6 mmoles) in $CHCl_3$ (10 ml) was added aniline (0.43 g, 4.6 mmoles) at room temperature. After standing at room temperature for 5 days, the solution was concentrated to the half volume, and the precipitate was collected by filtration to give **10** (1.05 g, 86%), mp 201—203°. This sample was identified by IR spectrum with the authentic sample obtained by the cyclization of **8a**.

2-Methylchromone-3-carboxanilide (7b)——A mixture of **9a** (1.7 g, 6.7 mmoles), acetic anhydride (2.04 g, 20 mmoles), and anhydrous sodium acetate (2.04 g, 25 mmoles) was heated at 110—120° for 10 min. After cooling, the mixture was poured into cold water. The precipitate was collected by filtration, washed with EtOH, and recrystallized from EtOH to afford **7b** (1.2 g, 64%), mp 127—128°. IR ν_{max}^{Nujol} cm^{-1}: 3150, 1677, 1623, 1548. NMR ($CDCl_3$) δ: 3.00 (3H, s, $-CH_3$), 6.88—8.42 (9H, m, aromatic protons), 11.79 (1H, s, -NH-). *Anal.* Calcd. for $C_{17}H_{13}O_3N$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.89; H, 4.71; N, 5.03.

4′-Chloro-2-methylchromone-3-carboxanilide (7c)——A mixture of **9b** (800 mg, 2.76 mmoles), acetic anhydride (640 mg, 6.27 mmoles), and anhydrous sodium acetate (640 mg, 7.81 mmoles) was heated at 110—120° for 10 min. After cooling, the reaction mixture was poured into cold water. The precipitate was collected by filtration, washed with EtOH, and recrystallized from EtOH to give **7c** (600 mg, 69%), mp 175—176°. IR ν_{max}^{Nujol} cm^{-1}: 3100, 1688, 1620, 1548. NMR ($CDCl_3$) δ: 2.99 (3H, s, $-CH_3$), 7.07—8.42 (8H, m, aromatic protons), 11.83 (1H, s, -NH-). *Anal.* Calcd. for $C_{17}H_{12}O_3NCl$: C, 65.07; H, 3.85; N, 4.46. Found: C, 65.06; H, 3.88; N, 4.47.

4′-Acetoxy-2-methylchromone-3-carboxanilide (7d)——A mixture of **9c** (1.0 g, 3.86 mmoles), acetic anhydride (2.4 g, 23.1 mmoles), and anhydrous sodium acetate (2.4 g, 29.2 mmoles) was heated at 100—120° for 30 min. After cooling, the reaction mixture was poured into cold water. The presipitate was collected by filtration, washed with MeOH, and recrystallized from dioxane to give **7d** (0.85 g, 65%), mp 181—183°. IR ν_{max}^{Nujol} cm^{-1}: 3120, 1756, 1680, 1550. NMR ($CDCl_3$) δ: 2.29 (3H, s, $-COCH_3$), 2.98 (3H, s, $-CH_3$), 6.95—8.33 (8H, m, aromatic protons), 11.78 (1H, s, -NH-). *Anal.* Calcd. for $C_{19}H_{15}O_5N$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.49; H, 4.56; N, 4.14.

2-Phenyl-4-chromanone-3-carboxanilide (11a)——A solution of **9a** (2.0 g, 7.8 mmoles), benzaldehyde (1.04 g, 9.8 mmoles), and a drop of piperidine in EtOH (40 ml) was refluxed for 2 hr. After cooling, the precipitate was collected by filtration, washed with ether to give **11a** (2.55 g, 99%), mp 216—217°. Recrystallization from EtOH afforded an analytically pure sample, mp 217—219°. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1697, 1656, 1537. NMR (DMSO-d_6) δ: 4.38 (1H, d, J=12 Hz, C_3-H), 5.84 (1H, d, J=12 Hz, C_2-H), 6.95—8.02 (14H, m, aromatic protons), 10.12 (1H, s, -NH-). *Anal.* Calcd. for $C_{22}H_{17}O_3N$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.95; H, 5.08; N, 4.09.

2-Phenylchromone-3-carboxanilide (7e)——A mixture of **11a** (1.8 g, 5.43 mmoles), selenium dioxide (1.2 g), and dioxane (70 ml) was refluxed for 5.5 hr. After cooling, the reaction mixture was filtered, and the filtrate was concentrated to dryness *in vacuo*. The residual solid was recrystallized from EtOH to afford **7e** (1.4 g, 78%), mp 196—197°. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1665, 1630, 1552. *Anal.* Calcd. for $C_{22}H_{15}O_3N$: C, 77.40; H, 4.43; N, 4.10. Found: C, 77.50; H, 4.60; N, 3.90.

4′-Chloro-2-phenyl-4-chromanone-3-carboxanilide (11b)——A solution of **9b** (1.5 g, 5.18 mmoles), benzaldehyde (0.66 g, 6.22 mmoles), and a drop of piperidine in EtOH (40 ml) was refluxed for 5 hr. After cooling, the precipitate was collected by filtration, washed with ether to give **11b** (1.8 g, 92%), mp 206—207°. Recrystallization from EtOH afforded an analytically pure sample, mp 206—207°. IR ν_{max}^{Nujol} cm^{-1}: 3230, 1680, 1643, 1539. NMR (DMSO-d_6) δ: 4.40 (1H, d, J=12 Hz, C_3-H), 5.80 (1H, d, J=12 Hz, C_2-H), 6.95—7.97 (13H, m, aromatic protons), 10.29 (1H, s, -NH-). *Anal.* Calcd. for $C_{22}H_{16}O_3NCl$: C, 69.93; H, 4.26; N, 3.70. Found: C, 69.92; H, 4.28; N, 3.77.

4′-Chloro-2-phenylchromone-3-carboxanilide (7f)——A mixture of **11b** (320 mg, 0.85 mmole), selenium dioxide (210 mg), and dioxane (15 ml) was refluxed for 14 hr. After cooling, the reaction mixture was filtered and the filtrate was concentrated to dryness *in vacuo*. The residual solid was recrystallized from EtOH to give **7f** (250 mg, 78%), mp 185—187°. IR ν_{max}^{Nujol} cm^{-1}: 3330, 1672, 1625, 1525. *Anal.* Calcd. for $C_{22}H_{14}O_3NCl$: C, 70.30; H, 3.75; N, 3.72. Found: C, 70.41; H, 3.87; N, 3.80.

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