Studies on Heterocyclic Compounds. VII. Syntheses of Novel Furo[2,3-*b*]chromones [1]

Sheng-Chu Kuo*, Jiin-Sheng Wu, Li-Jiau Huang,
Chun-Hsiung Wu, Shun-Chueh Huang and Teh-Chang Chou

Graduate Institute of Medicinal and Pharmaceutical Chemistry, China Medical College,
Taichung, Taiwan 40421, Republic of China

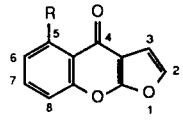
Received November 26, 1986

Furo[2,3-*b*]chromone (**1a**) was conveniently prepared by the PPE-promoted cyclization of 5-(2'-carboxyphenoxy)furan-2-carboxylic acid (**8**) which was made from methyl salicylate and ethyl 5-nitrofuran-2-carboxylate. Furo[2,3-*b*]chromon-2-acrylic acid (**13**) was obtained by a similar cyclization. Direct acylation of **1a** afforded 2-acetylfuro[2,3-*b*]chromone (**10**). Several derivatives of furo[2,3-*b*]chromone were found to display activity in the rat passive cutaneous anaphylaxis (PCA) test for antiallergic activity.

J. Heterocyclic Chem., **26**, 605 (1989).

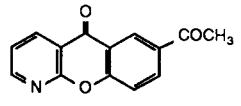
Introduction.

Furochromones are rare heterocyclic compounds found in nature. The first and perhaps the only natural furochromones reported to this time are 5-alkylfuro[2,3-*b*]chromones **1b**, **1c** isolated from *Bothriocline laxa N. E. Brown* by Bohlmann and Zdero in 1977 [2]. Since furochromones are bioisosteric to the structurally related and antiallergically active compounds, such as Y-9000 [3], Y-12141 [4], RS-7540 [5], and RU-31156 [6], it would be of interest to examine their possible biological activities. However, to our knowledge, there has not been any work directed toward the synthesis of this novel heterocyclic system. We therefore initiated a synthetic investigation with the hope of establishing a general route for the preparation of furo[2,3-*b*]chromone (**1a**) and its derivatives. We hereby describe the results of our synthetic efforts in this area.

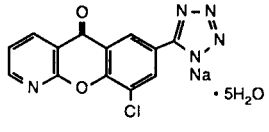


1a, R = H
1b, R = CH_3
1c, R = CH_2CH_3

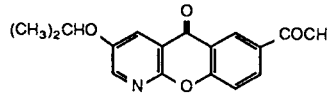
5-Alkylfuro[2,3-*b*]chromones



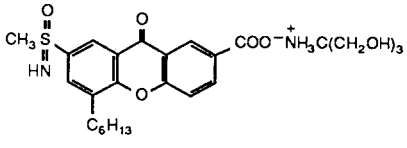
Y - 9000



Y-12141

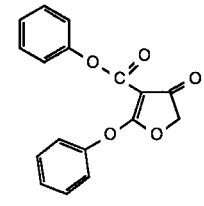


RS-7540

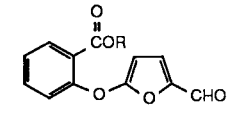


RU-31156

We initially considered phenyl 4,5-dihydro-2-phenoxy-4-oxofuran-3-carboxylate (**2**), 5-(2'-methoxycarbonylphenoxy)furan-2-carbaldyhyde (**3a**) [7], and **3b** to be the possible intermediates for elaboration of the furo[2,3-*b*]-chromone system. Ester **2** was easily prepared from the condensation of diphenyl sodium malonate with chloroacetyl chloride in THF, and **3a** was prepared by the reported method [7]. However, all compounds **2**, **3a**, and **3b**, failed to afford any desired cyclized products. The failure of **3a** to cyclize is presumably due to the strong deactivating power of the formyl group. Removing this effect by converting **3a** to the corresponding acetal did not improve matters, for compound **3a** decomposed to form methyl salicyclate and furfural under the reaction conditions (ethylene glycol/*p*-tolunesulfonic acid).



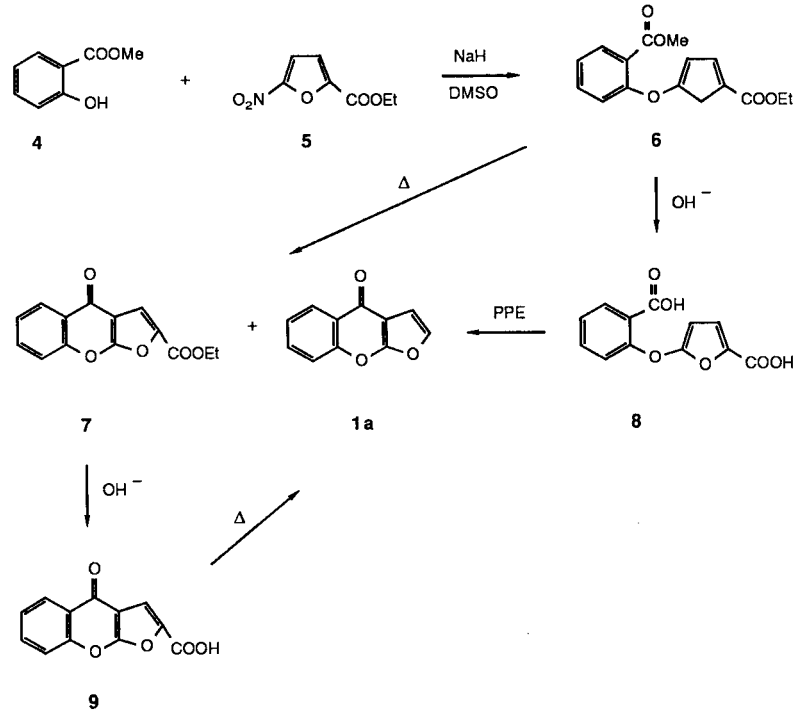
2



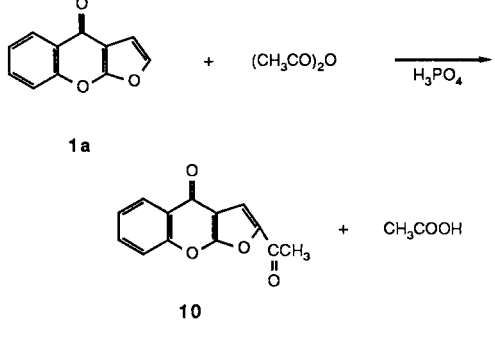
3a, R = CH_3
3b, R = H

Displacement of the formyl group in **3a** with a less electron-withdrawing carboxyl group might satisfy our purpose to effect cyclization. With this thought, we prepared the diester **6** by sodium hydride-promoted condensation of methyl salicylate (**4**) with ethyl nitrofuroate (**5**) in DMSO (Scheme I). Again heating this diester in diphenyl ether at 250° failed to give ethyl furo[2,3-*b*]chromone-2-carboxylate (**7**). Diester **6** was thus subsequently hydrolyzed to the corresponding diacid **8**. To our delight, diacid **8** could be induced to undergo cyclization by polyphosphoric ester (PPE) in toluene to afford the desired furo[2,3-*b*]chromone (**1a**) in 45% yield, along with ester **7** in about equal yield. Ester **7** could be hydrolyzed to the corresponding acid **9** which is related to RS-7540 having a carboxy functionality. Acid **9** could be decarboxylated to **1a** in 75% yield.

Scheme I



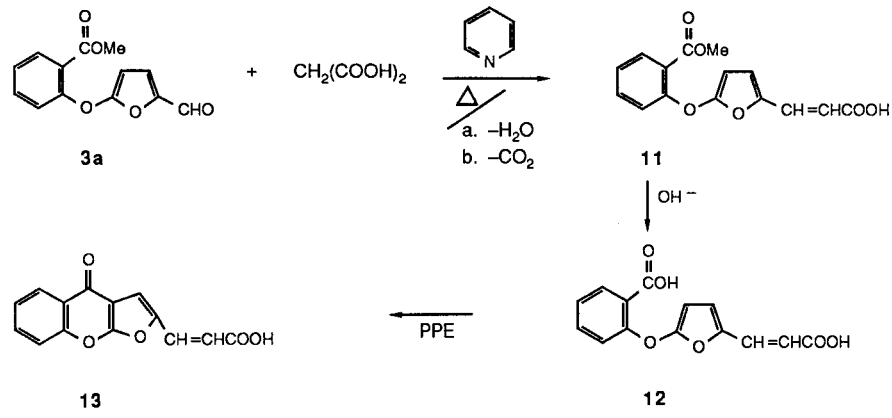
Furo[2,3-*b*]chromone (**1a**), when treated with acetic anhydride in the presence of phosphoric acid, could undergo Friedel-Crafts acylation to afford 2-acetylfuro-[2,3-*b*]chromone (**10**) in 60% yield. Compound **10** is related to Y-9000 in having an acetyl group.



That certain compounds having an acrylic group, such as cafferic acid [8], exhibit antiallergic activity, prompted us to consider introducing such a group into the furan ring of **1a**. To this end, the reaction sequence shown in Scheme I was successfully applied to prepare 2-acrylfuro-[2,3-*b*]chromone (**13**) in 45% yield as illustrated in Scheme II. Furanacrylic acid **11**, available from the condensation of **3a** with malonic acid, was hydrolyzed and subsequently cyclized to **13**.

The furo[2,3-*b*]chromones described here were evaluated for antiallergic activity in the rat passive cutaneous anaphylaxis (PCA) test. Following oral administration in a dose of 80 mg/kg, compounds **7** and **10** exhibited significant inhibition. Detailed data will be published elsewhere.

Scheme II



In summary, we have established a general synthetic approach to furo[2,3-*b*]chromone and its 2-substituted derivatives. Some of the 2-substituted furo[2,3-*b*]chromones exemplify a novel class of orally antiallergic agents with an activity profile similar to that of disodium chromoglycates (DSCG). Effort to apply the present synthetic approach to the preparation of naturally isolated 5-alkyl-substituted furo[2,3-*b*]chromones **1b**, **1c** using 5-alkylsalicylates as starting material and other furo[2,3-*b*]chromone derivatives, and to test them for antiallergic activity is still in progress.

EXPERIMENTAL

The melting points were determined in open-ended capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Meijo University (Japan) and Chung Shan Institute of Science Technology (Republic of China). The ir spectra were taken in potassium bromide using a Shimadzu-IR-440. The ^{1}H-nmr spectra were recorded on a JEOL JNM-PMX 60 spectrometer. Chemical shifts are reported in parts per million related to tetramethylsilane as an internal standard. The ^{13}C-nmr spectra were recorded in deuteriochloroform on a JEOL-FX 100 NMR spectrometer. Mass spectra were determined on a Hitachi RMU 71 mass spectrometer. The tlc were carried out on Wakogel B-5 FM plates.

Phenyl 4,5-Dihydro-2-phenoxy-4-oxofuran-3-carboxylate (**2**).

Sodium hydride (3.6 g, 1.5 moles), previously washed with dry *n*-hexane, was suspended in dry THF (250 ml) and added slowly, with shaking, to a solution of diphenyl malonate (360 g, 1.5 moles) in THF (500 ml). After the addition was completed (about 20 minutes), the reaction mixture was refluxed on a water bath for 2 minutes, then cooled to 10-12°. Chloroacetyl chloride (90.4 g, 0.8 mole) in dry THF (340 ml) was then added dropwise over 1 hour. The solution was kept at this temperature for 1 hour and at 40-50° for another hour. The solvent was partially evaporated and the concentrated residue was added with ice water. The solids that precipitated were extracted with chloroform, and the extract was washed with water and dried with magnesium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel (150 g). Elution with chloroform yielded compound **2** (300 g, 70%), mp 116-119°; ir (potassium bromide): 1750 (-COOR), 1680 (-CO-) cm^{-1}, ^{1}H-nmr (deuteriochloroform): δ 4.66 (s, 2H, -OCH$_2$-CO-), 7.0-7.5 (m, 10H, aromatic); ms: m/e 296 (M$^+$).

Anal. Calcd. for $C_{17}H_{12}O_5$: C, 68.92; H, 4.05. Found: C, 69.01; H, 4.30.

5-(2'-Hydroxycarbonylphenoxyl)furan-2-carbaldehyde (**3b**).

Compound **3a** (6.2 g, 0.025 mole) was dissolved in dioxane (50 ml). The solution was stirred at room temperature and 5% sodium hydroxide (5 ml) was added dropwise until the reaction mixture became clear. The stirring was continued for additional 30 minutes. The mixture was then poured into ice water and acidified with 10% hydrochloric acid. The solids formed were collected off and recrystallized from ethanol to give compound **3b** as pale-yellow crystalline needles (4.8 g, 82%), mp 200-201° dec; ir (potassium bromide): 1710 (COOH), 1670 (CHO) cm^{-1}; ^{1}H-nmr (d$_6$-methylsulfoxide): δ 5.40 (d, J = 3.5 Hz, 1H, 4 position of furan ring proton), 7.10-8.10 (m, 5H, 3 position of furan ring and benzene ring protons), 9.40 (s, 1H, -CHO); ms: m/e: 232 (M$^+$).

Anal. Calcd. for $C_{12}H_8O_5$: C, 62.07; H, 3.45. Found: C, 62.10; H, 3.32.

Ethyl 5-(2'-Methoxycarbonylphenoxy)furan-2-carboxylate (**6**).

A solution of methyl salicylate (18.2 g, 0.12 mole) in DMSO (150 ml), under stirring, was treated with sodium hydride (3.6 g, 80%, 0.24 mole). A solution of ethyl 5-nitrofuran-2-carboxylate (18.5 g, 0.1 mole) in DMSO (50 ml) was then added dropwise over 1 hour. After stirring for 8 hours at 30-32°, the reaction mixture was poured into ice water. The precipitated solid was extracted with benzene, and the extract was washed with 10% potassium hydroxide, water and dried with magnesium sulfate. The solvent was evaporated and the residue was purified by chromatography on a silica gel (150 g) column. Elution with benzene yielded a light-brown liquid of compound **6** (5.6 g, 25%); ir (potassium bromide): 1720 (-COOR) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.26 (t, 3H, -OCH$_2$CH$_3$), 3.76 (s, 3H, -OCH$_3$), 4.23 (q, 2H, -OCH$_2$CH$_3$), 5.36 (d, J = 3.5 Hz, 1H, 4 position of furan ring proton), 7.03 (d, J = 3.5 Hz, 1H, 3 position of furan ring proton), 7.16-7.9 (m, 4H, benzene ring protons); ms: m/e 280 (M$^+$). This compound was used below without additional purification.

5-(2'-Hydroxycarbonylphenoxy)furan-2-carboxylic Acid (**8**).

A mixture of compound **6** (5.6 g, 0.02 mole) and 20% sodium hydroxide (12 ml) was heated in a boiling water bath for 8 hours. The alkaline solution was cooled to room temperature and washed with a little ether and then acidified to Congo Red with diluted hydrochloric acid. The precipitate was extracted with ether, dried with magnesium sulfate and then evaporated. The resulting residue was recrystallized from acetone-water to afford pale-yellow needle crystals of compound **8** (3.8 g, 95%), mp 146-148° dec; ir (potassium bromide): 2500-2700 (OH), 1680 (>CO) cm^{-1}; ^{1}H-nmr (d$_6$-methylsulfoxide): δ 5.50 (d, J = 3.5 Hz, 1H, 4 position of furan ring proton), 7.16 (d, J = 3.5 Hz, 1H, 3 position of furan ring proton), 7.33-7.93 (m, 4H, benzene ring protons); ms: m/e 248 (M$^+$).

Anal. Calcd. for $C_{12}H_8O_6$: C, 58.06; H, 3.23. Found: C, 58.35; H, 3.01.

Cyclization of Compound **8**.

A solution of compound **8** (3.72 g, 0.015 mole) and PPE (50 g) in toluene (50 ml) was reflux for 6 hours. The reaction mixture was cooled to room temperature, poured into ice water (600 ml) and stirred for 18 hours. The toluene layer was washed with water, dried with magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (180 g). Elution with benzene yielded colorless solid of furo[2,3-*b*]chromone (**1a**) (1.3 g, 45%), mp 123-125°; uv (chloroform): λ max 243 nm; ir (potassium bromide): 1660 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 6.98 (d, J = 2.3 Hz, 1H, C$_3$-H), 7.25 (d, J = 2.3 Hz, 1H, C$_2$-H), 7.30-7.70 (m, 3H, C$_6$-H, C$_7$-H, C$_8$-H), and 8.31 (dd, J = 8.0 Hz, 2.0 Hz, 1H, C$_5$-H); ^{13}C-nmr (deuteriochloroform): δ 173.81 (C-4), 162.74 (C-9a), 153.31 (C-8a), 136.86 (C-2), 133.47 (C-7), 126.84 (C-5), 125.41 (C-6), 123.54 (C-4a), 117.79 (C-8), 106.95 (C-3), 103.27 (C-3a); ms: m/e 186 (M$^+$).

Anal. Calcd. for $C_{11}H_6O_3$: C, 70.97; H, 3.26. Found: C, 71.15; H, 3.50.

Elution with benzene-ethanol followed by recrystallization from ethanol-water afforded light yellow needle crystals of ethyl furo[2,3-*b*]-chromone-2-carboxylate **7** (1.55 g, 40%), mp 145-147°; uv (chloroform): λ max 303.5, 273, 263.8, 244.5 nm; ir (potassium bromide): 1720 (COOR), 1660 (>C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.25 (t, 3H, -CH$_2$CH$_3$), 4.30 (2H, q, -CH$_2$CH$_3$), 7.38 (s, 1H, C$_3$-H), 7.18-7.66 (m, 3H, C$_6$-H, C$_7$-H, C$_8$-H, 8.25 (dd, J = 8.0, 2.0 Hz, 1H, C$_5$-H); ms: m/e 258 (M$^+$).

Anal. Calcd. for $C_{14}H_{10}O_5$: C, 65.12; H, 3.88. Found: C, 65.00; H, 4.02.

Furo[2,3-*b*]chromone-2-carboxylic Acid (**9**).

Compound **7** (3 g, 0.01 mole) dissolved in ethanol (20 ml) was stirred at room temperature and 5% sodium hydroxide (40 ml) was added dropwise until the reaction mixture became clear. The stirring was continued for an additional 30 minutes, and the reaction mixture was then poured into ice water, and acidified with 10% hydrochloric acid. The crystals formed were collected and recrystallized from ethanol-water to give pale-yellow crystalline needles of compound **9** (1.25 g, 85%), mp 176-178°; ir (potassium bromide): 2600-2800 (OH), 1710 (COOH), 1670 (>C=O) cm^{-1}; ^{1}H-nmr (d$_6$-methylsulfoxide): δ 6.90 (s, 1H, C$_3$-H), 7.0-8.2 (m, 4H, benzene ring protons); ms: m/e 230 (M$^+$).

Anal. Calcd. for $C_{12}H_6O_5$: C, 62.61; H, 2.61. Found: C, 62.80; H, 2.45.

Decarboxylation of Compound **9**.

To a solution of compound **9** (1 g, 0.043 mole) in quinoline (6 ml) was added 0.2 g of active copper. The mixture was allowed to be heated at 200° for 30 minutes, and then cooled to room temperature. After

acidified with dil hydrochloric acid the mixture was extracted with chloroform, dried with magnesium sulfate and evaporate to dryness. The resulting residue was purified by column chromatography (benzene-silica gel) to give compound **1a** (0.6 g, 75%) which was proven to be identical with a product obtained by cyclization of compound **8**.

2-Acetylfuro[2,3-*b*]chromone (**10**).

To a suspension of compound **1a** (3.0 g, 0.016 mole) in acetic anhydride (94 ml, 1 mole) at 35°, was added crystalline orthophosphoric acid (40 g). The reaction mixture was stirred at 60° for 1.5 hours and then cooled to room temperature. Water (100 ml) was added, and the mixture was extracted with benzene. The benzene extract was washed with water, 10% sodium bicarbonate and again with water. The solution was dried with magnesium sulfate and the solvent was distilled off. The residue thus obtained was purified by chromatography over silica gel (200 g) with chloroform as eluent. The eluate was evaporated to give residue which was crystallized from chloroform-ethanol to give pale-yellow crystalline needles of **10** (2.2 g, 60%), mp 160-162°; uv (chloroform): λ max 310.5, 278 nm; ir (potassium bromide): 1650, 1670 (>C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 7.23 (s, 1H, C_3-H), 7.33-7.76 (m, 3H, C_6-H, C_7-H, C_8-H), 8.2-8.5 (m, 1H, C_5-H); ms: m/e 228 (M^+).

Anal. Calcd. for $C_{13}H_8O_4$: C, 68.42; H, 3.51. Found: C, 68.30; H, 3.71.

5-(2'-Methoxycarbonylphenoxy)furan-2-acrylic Acid (**11**).

A mixture of compound **3a** (9 g, 0.037 mole), malonic acid (3.8 g, 0.037 mole) and pyridine (1.75 ml, 0.022 mole) was heated in a boiling water bath for 2 hours. The reaction mixture was cooled to room temperature, and water (10 ml) was added. Concentrated aqueous ammonia was then added to the stirred mixture until the acid had almost dissolved. The solution was filtered and the filtrate was acidified to Congo Red with 10% hydrochloric acid and left in an ice bath for 2 hours. The precipitated product was collected and recrystallized from ethanol to afford light brown crystals of **11** (9.5 g, 95%), mp 144-146°; ir (potassium bromide): 2500-2700 (CO-OH), 1660-1700 (COOR) cm^{-1}; ^{1}H-nmr (d_6-methylsulfoxide): δ 3.80 (s, 3H, $-COOCH_3$), 5.56 (d, J = 3.5 Hz, 1H, 4 position of furan ring proton), 5.90 Hz (d, J = 8.0 Hz, 1H, -CH=C*H*-COOH), 6.86 (d, J = 3.5 Hz, 1H, 3 position of furan ring proton), 7.26 (d, J = 8.0 Hz, 1H, -C*H*=CH-COOH), 7.36-7.9 (m, 4H, benzene ring protons); ms: m/e 288 (M^+).

Anal. Calcd. for $C_{15}H_{12}O_6$: C, 62.50; H, 4.17. Found: C, 62.69; H, 4.32.

5-(2'-Hydroxycarbonylphenoxy)furan-2-acrylic Acid (**12**).

Compound **11** (1.7 g, 0.006 mole) was subjected to hydrolysis as in the preparation of compound **8** to afford compound **12** (1.4 g, 85%), mp 154-156°; ir (potassium bromide): 2500-2700 (CO-OH), 1685 (CO-OH) cm^{-1}; ^{1}H-nmr (d_6-methylsulfoxide): δ 5.56 (d, J = 3.5 Hz, 1H, 4 position of furan ring proton), 5.9 (d, J = 8.0 Hz, 1H, -CH=C*H*-COOH), 7.0 (d, J = 3.5 Hz, 1H, 3 position of furan ring proton), 7.26 (d, J = 8.0 Hz, 1H, -C*H*=CH-COOH), 7.36-7.9 (m, 4H, benzene ring protons); ms: m/e 272 (M^+).

Anal. Calcd. for $C_{14}H_{10}O_6$: C, 61.31; H, 3.65. Found: C, 61.52; H, 3.75.

Furo[2,3-*b*]chromone-2-acrylic Acid (**13**).

Compound **12** (1.2 g, 0.0043 mole) was subjected to cyclization as in the method of preparing compound **1a** and **7** to yield compound **13** (0.4 g, 45%), mp 160-162°; uv (ethanol): λ max 302.5, 234, 214.5 nm; ir (potassium bromide): 2500-2700 (CO-OH), 1650 (CO-OH) cm^{-1}; ^{1}H-nmr (d_6-dimethylsulfoxide): δ 6.67-7.00 (m, 3H, C_3-H and -CH=C*H*-COOH), 7.33-7.9 (m, 4H, benzene ring protons); ms: m/e 25 (M^+).

Anal. Calcd. for $C_{14}H_8O_5$: C, 65.63; H, 3.13. Found: C, 65.69; H, 3.40.

Acknowledgement.

The authors wish to thank the National Science Council of the Republic of China for financial support. Thanks are also due to the analytical center of Meijo University (Japan) and Chung Shan Institute of Science Technology (R.O.C.) for elemental analysis.

REFERENCES AND NOTES

[1] S. C. Kuo, T. P. Lin, S. S. Chang, C. H. Wu, B. Shieh and T. H. Chou, *J. Nat. Prod.*, **49**, 48 (1986).

[2] F. Bohlman and C. Zdero, *Phytochemistry*, **16**, 1261 (1977).

[3] Y. Maruyama, *Folia Pharmacol Japan*, **74**, 179 (1978).

[4] K. Goto, *Arch. Allergy Appl. Immunol.*, **59**, 13 (1979).

[5] J. R. Pfister, R. W. Ferraresi, I. T. Harrison, W. H. Rooks, A. P. Roszkowski, A. Van Horn and J. H. Fried, *J. Med. Chem.*, **15**, 1032 (1972).

[6] P. Miller and G. W. L. James, *Arch. Int. Pharmacodyn.*, **231**, 328 (1978).

[7] A. Tanaka, T. Usui and M. Shimadzu, *Chem. Pharm. Bull.*, **28**, 2846 (1980).

[8a] Y. Kasuko, T. Neichi, S. Murota, A. N. Lao, Y. Fujimoto and T. Tatsuno, *Biochim. Biophys. Acta.*, **792**, 92 (1984). [b] Y. Kimura, H. Okuda, T. Okuda, T. Hatano, I. Agata and S. Arichi, *Chem. Pharm. Bull.*, **33**, 690 (1985).

[9] B. B. Levine and N. M. Vaz, *Int. Arch. Allergy Appl. Immunol.*, **39**, 156 (1970).