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Nonsteroidal Antiinflammatory Agents. III.[1] Synthesis of the Metabolites of 10,11-Dihydro-8,α-dimethyl-11-oxodibenz-[*b*,*f*]oxepin-2-acetic Acid (Bermoprofen)

KATSUHIKO HINO,* HIDEO NAKAMURA, SHIRO KATO, AKIRA IRIE, YASUTAKA NAGAI and HITOSHI UNO

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Enoki 33–94, Suita, Osaka 564, Japan

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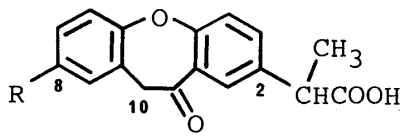
The metabolites (**3** and **4**) of 10,11-dihydro-8,α-dimethyl-11-oxodibenz[*b*,*f*]oxepin-2-acetic acid (bermoprofen, AD-1590, **1**), a promising antiinflammatory drug, were synthesized to confirm the proposed structures, and all the metabolites (**2**—**4**) were tested for activity in the carrageenin-induced edema test in rats. Metabolites **2** and **3** showed slight inhibition but **4** had no effect after intravenous administration.

Keywords——antiinflammatory agent; bermoprofen; 10,11-dihydro-8,α-dimethyl-11-oxodibenz[*b*,*f*]oxepin-2-acetic acid; metabolite

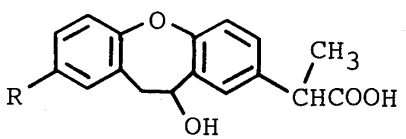
In recent years a number of nonsteroidal compounds, principally arylacetic acid derivatives, have been reported to show antiinflammatory activity in animal tests, and several of them have been clinically used. Previously we have reported the synthesis and antiinflammatory activity of 10,11-dihydrodibenz[*b*,*f*]oxepinacetic acids.[2] Among them, 10,11-dihydro-8,α-dimethyl-11-oxodibenz[*b*,*f*]oxepin-2-acetic acid (AD-1590, **1**) was found to possess antipyretic, analgesic and antiinflammatory activities comparable or superior to those of indomethacin,[3] one of the most potent antiinflammatory drugs available, and it was selected for evaluation in man as a promising drug for the treatment of various inflammatory conditions (compound **1** has been assigned the generic name "bermoprofen"). In a metabolic study, 11-hydroxy- (**2**), 8-carboxy- (**3**) and 8-carboxyl-11-hydroxy (**4**) derivatives were identified as the metabolites of **1** in the plasma and urine in rats and monkeys.[4] These metabolites were also found in human plasma.[5] Compound **2** has been dealt with in our previous paper.[2] This paper describes the synthesis of the metabolites **3** and **4**, aiming to confirm the proposed structures and to determine the effects of the metabolites (**2**—**4**) on carrageenin-induced hind paw edema in rats.

Since it seemed desirable not to subject the central oxepinone ring of **1** to drastic reaction conditions, especially alkali,[6] this ring should be formed in the final process. Therefore we



1: R=CH_3

3: R=COOH

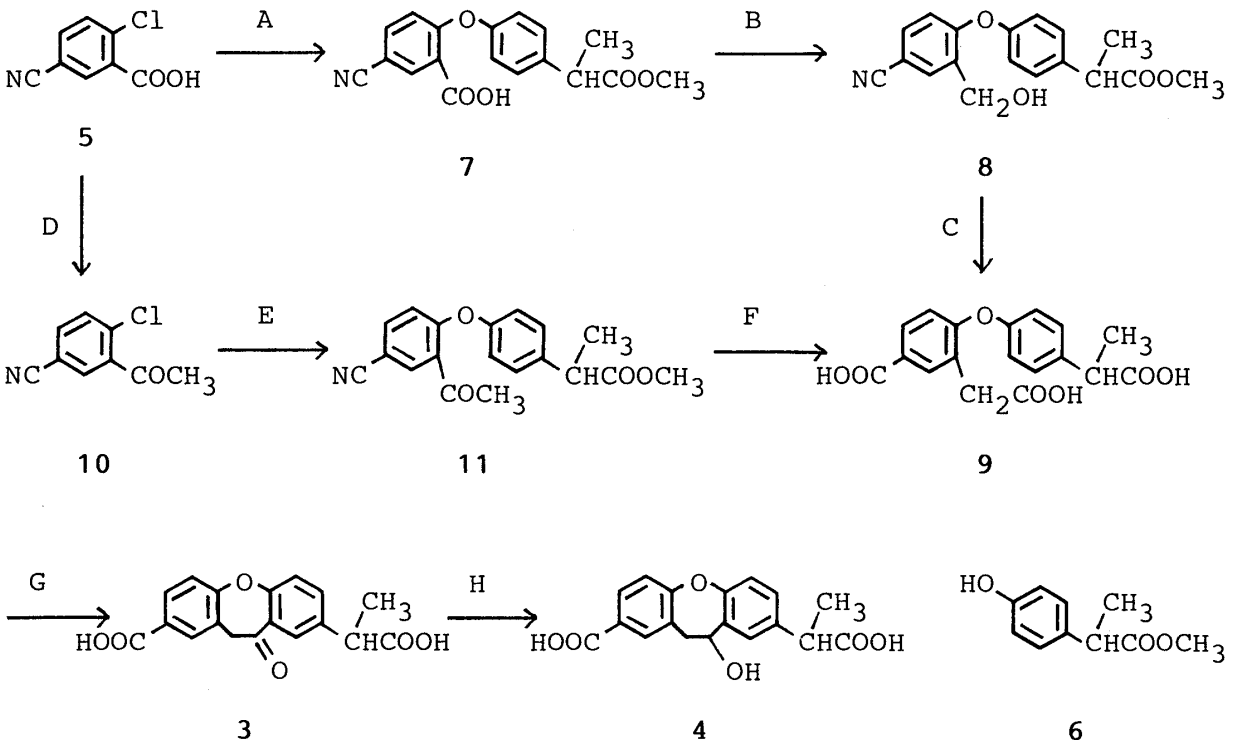


2: R=CH_3

4: R=COOH

Chart 1

regarded the tricarboxylic acid (**9**) as the key intermediate for the synthesis of **3** and **4**. The preparation of **9** was achieved by two routes as shown in Chart 2. Firstly, chlorocyanobenzoic acid (**5**) was condensed with methyl 4-hydroxyphenylpropionate (**6**) under Ullmann reaction conditions to give the ether **7** in a yield of 33%. Compound **7** exhibited the molecular ion peak (M^+) at *m/z* 325 in its mass spectrum (MS) and showed absorption bands due to nitrile and ester groups at 2230 and 1735 cm^{-1}, respectively, in its infrared (IR) spectrum. Chlorination of **7** with thionyl chloride ($SOCl_2$) gave the acid chloride, which was reduced with sodium borohydride ($NaBH_4$) to afford the alcohol (**8**) (42% yield). Compound **8** was subjected to chlorination with $SOCl_2$, followed by cyanation with potassium cyanide (KCN) and subsequent hydrolysis with potassium hydroxide (KOH), to give the desired intermediate **9**. The structure of **9** was confirmed on the basis of the M^+ at *m/z* 344 in the MS of **9** and a singlet methylene signal (δ 3.70) assignable to the 2′-carboxymethyl moiety along with a doublet methyl signal (δ 1.38) due to the 2-carboxyethyl group in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **9**. On the other hand, treatment of the acid chloride, derived from **5**, with diethyl ethoxymagnesiummalonate, followed by hydrolysis with dilute sulfuric acid (H_2SO_4), afforded the acetophenone (**10**) (80% yield), which was condensed with **6** to give **11** in 69% yield. Compound **11** exhibited absorption bands due to nitrile, ester and ketone moieties at 2220, 1730 and 1680 cm^{-1}, respectively, in its IR spectrum and two singlet methyl signals attributable to acetyl (δ 2.70) and methyl ester (δ 3.62) groups in its ^{1}H-NMR spectrum. When **11** was subjected to the Willgerodt–Kindler reaction with sulfur and morpholine, followed by hydrolysis of the resulting thiomorpholide with acid, it yielded the expected **9**, which was identical with that obtained *via* **8**. On treatment with hot polyphosphoric acid (PPA), **9** afforded the objective dibenz[*b*,*f*]oxepinone (**3**), which showed the M^+



(A) 6, K_2CO_3, Cu; (B) 1) $SOCl_2$, 2) $NaBH_4$; (C) 1) $SOCl_2$, 2)KCN, 3)KOH; (D) 1) $SOCl_2$, 2) $EtOMgCH(COOEt)_2$, 3) H_2SO_4; (E) 6, K_2CO_3, Cu; (F) 1) S, morpholine, 2) HCl, AcOH; (G) PPA; (H) $NaBH_4$

Chart 2

peak at m/z 326 in its MS. The other spectral (IR and ^{1}H-NMR) data and the analytical data for **3** were consistent with the proposed structure. Reduction of **3** with $NaBH_4$ gave the desired alcohol (**4**) (80% yield). The oxepinone ring of **3** seems to be easily conformationally interconvertible from chair to chair form,[7a] and the reduction of the ketone of **3** would occur from both α and β sides of the molecule to give **4** as two pairs of diastereomers, because of formation of a new asymmetric center at the 11-carbon. As to the oxepin ring, the 10-proton and 11-proton of the diastereomeric isomers seem to be stereochemically similar.[7b] Therefore, the difference in the chemical shifts in the ^{1}H-NMR spectra for the protons between diastereomeric isomers would be caused only by the influence of the asymmetric side chain, and may be slight. In fact, the ^{1}H-NMR spectrum of **4** exhibited a slightly separated signal at δ 5.017 and 5.027 (each dd, J=9.2, 3.3 Hz) attributable to 11-H (Table I). Compound **2**, prepared by the similar reduction of **1** with $NaBH_4$,[2] also might be obtained as two pairs of diastereomers, and its ^{1}H-NMR spectrum was reexamined. In this case, two separated signals were found for each of the protons at positions 1, 3, 4, 9 and 10, but the separation was very small. The coupling constants of 11-H observed in **2** and **4** are consistent with those reported for 11-substituted 10,11-dihydrodibenz[*b*,*f*]oxepin derivatives. Both **2** and **4** were analyzed by gas chromatography (GC) using a capillary column and showed only one peak. Compounds **3**

TABLE I. ^{1}H-NMR Data for **2** and **4** (300 MHz)[a]

	2	**4**
1-H	7.375, 7.381 (dd, J=2.2, 0.5 Hz)	7.41 (dd, J=2.1, 0.6 Hz)
3-H	7.176, 7.180 (dd, J=8.4, 2.2 Hz)	7.17 (dd, J=8.3, 2.1 Hz)
4-H	7.139, 7.142 (dd, J=8.4, 0.5 Hz)	7.15 (dd, J=8.3, 0.6 Hz)
6-H	7.04 (d, J=7.9 Hz)	7.24 (d, J=8.4 Hz)
7-H	6.98 (dd, J=7.9, 2.2 Hz)	7.77 (dd, J=8.4, 2.2 Hz)
9-H	7.03 (m)	7.82 (d, J=2.2 Hz)
10-Ha	3.118, 3.123 (dd, J=14.2, 7.5 Hz)	3.10 (dd, J=14.7, 9.2 Hz)
10-Hb	3.45 (dd, J=14.2, 3.1 Hz)	3.33 (dd, J=14.7, 3.3 Hz)
11-H	5.06 (dd, J=7.5, 3.1 Hz)	5.017, 5.027 (dd, J=9.2, 3.3 Hz)
$C\underline{H}CH_3$	3.69 (q, J=7.1 Hz)	3.66 (q, J=7.1 Hz)
$CHC\underline{H}_3$	1.465, 1.469 (d, J=7.1 Hz)	1.34 (d, J=7.1 Hz)
8-CH_3	2.30 (s)	
COOH	5.44 (br)	12.56 (2H, br s)
OH	5.44 (br)	5.74 (s)

a) The spectra were taken in $CDCl_3$ (for **2**) or DMSO-d_6 (for **4**) at 25 °C, and the chemical shifts are given as δ (ppm); s, singlet; d, doublet; dd, double doublet; q, quartet; m, multiplet; br, broad.

TABLE II. Inhibitory Effects of the Metabolites (**2**, **3** and **4**) and **1** on Carrageenin-Induced Rat Paw Edema

Compd. No.	Dose (mg/kg, i.v.)	n[a]	Inhibition (%)	Effective[b] number	ED_{50} (mg/kg)
2	40	13	12.2[c]	2	79.1
	80	13	22.1[c]	4	(57.5—109)[d]
	120	8	44.1[c]	8	
3	80	5	15.7	1	
4	80	5	−11.9	0	
1	0.5	5	20.5[e]	2	*ca.* 0.6
	0.8	5	32.6[e]	3	

a) Number of rats used. *b*) Number of rats effective. *c*) $p<0.01$, significantly different from each control group. *d*) 95% confidence limits. *e*) $0.01<p<0.05$.

and **4**, and the previously reported **2** were confirmed to be identical with the metabolites by both thin layer chromatography (TLC) and GC-MS.[4)]

The metabolites (**2**—**4**) were tested for antiinflammatory activity using the carrageenin-induced rat paw edema method. The results obtained after intravenous administration are shown in Table II, together with those for **1**. Among the metabolites, compounds **2** and **3** exhibited weak inhibitory effect in this test, but **4** showed no effect.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a Hitachi EPI-S2 spectrometer in KBr disks unless otherwise noted and MS were taken on a JEOL JMS-D300 spectrometer. ^{1}H-NMR spectra were taken on a Varian A-60, FT-80A, A-100 or XL-300 spectrometer using tetramethylsilane as an internal standard. The chemical shifts are given as δ (ppm). Abbreviations are as follows: s, singlet; d, doublet; dd, double doublet; q, quartet. GC was carried out on a Hewlett Packard HP-5840A GC instrument with a flame ionization detector, using a capillary column (DB-5, J & W, 0.25 mm × 30 m); column temperature, 260 °C; carrier gas, He (0.66 ml/min). Organic extracts were dried over anhydrous magnesium sulfate. The following abbreviations are used: ether, diethyl ether; AcOEt, ethyl acetate; $CHCl_3$, chloroform; EtOH, ethyl alcohol; MeOH, methyl alcohol; HCl, hydrochloric acid; AcOH, acetic acid; NaOH, sodium hydroxide.

8-Carboxy-10,11-dihydro-α-methyl-11-oxodibenz[*b*,*f*]oxepin-2-acetic Acid (3)——A mixture of **9** (3 g, 0.0087 mol) and PPA (135 g) was stirred at 100 °C for 6 h and poured into ice-water. The resulting precipitates were collected and chromatographed on silica gel with $CHCl_3$–MeOH (50 : 1) to give **3** (0.92 g, 32%), mp 252 °C (MeOH–AcOEt). IR: 1690(COOH) cm^{-1}. MS *m/z*: 326 (M^+), 281 ($M^+ - COOH$). ^{1}H-NMR (100 MHz, DMSO-d_6) δ: 1.36 (3H, d, J=7 Hz, $CHC\underline{H}_3$), 3.78 (1H, q, J=7 Hz, $C\underline{H}CH_3$), 4.22 (2H, s, 10-H_2), 7.46 (1H, d, J=8 Hz, 4-H), 7.45 (1H, d, J=8.5 Hz, 6-H), 7.63 (1H, dd, J=8, 2 Hz, 3-H), 7.82 (1H, d, J=2 Hz, 9-H), 7.88 (1H, dd, J=8.5, 2 Hz, 7-H), 8.01 (1H, d, J=2 Hz, 1-H), 12.66 [2H, br s, $(COOH)_2$]. *Anal.* Calcd for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32. Found: C, 66.26; H, 4.22.

8-Carboxy-10,11-dihydro-11-hydroxy-α-methyldibenz[*b*,*f*]oxepin-2-acetic Acid (4)——$NaBH_4$ (1.45 g, 0.038 mol) was added portionwise to a solution of **3** (2.5 g, 0.038 mol) in MeOH (30 ml) and AcOEt (10 ml). The reaction mixture was stirred for 30 min, acidified with dilute HCl and extracted with AcOEt. The organic layer was washed with water, dried and concentrated. The residue was crystallized from ether to give **4** (2.0 g, 80%), mp 200—203 °C. IR: 3550 (OH), 1685(COOH) cm^{-1}. MS *m/z*: 328 (M^+), 310 ($M^+ - H_2O$), 283 ($M^+ - COOH$), 265 (*m/z* 310 − COOH). *Anal.* Calcd for $C_{18}H_{16}O_6$: C, 65.81; H, 4.91. Found: C, 65.67; H, 5.16. When **4** and **2** were analyzed by GC after treatment with diazomethane, each gave a single peak; t_R (min): 9.36 (**2**), 20.53 (**4**).

2-Chloro-5-cyanobenzoic Acid (5)——In the presence of platinic oxide (1 g), 2-chloro-5-nitrobenzoic acid (50 g) was hydrogenated in EtOH (200 ml) at room temperature until the theoretical volume of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate was concentrated to give crude 5-amino-2-chlorobenzoic acid (43 g, 95%) as a crystalline residue. IR: 3450 and 3350(NH_2), 1700(COOH) cm^{-1}. MS *m/z*: 171 (M^+). A solution of sodium nitrate ($NaNO_2$) (17.1 g, 0.25 mol) in water (74 ml) was added dropwise to a solution of the above crude material in 2 N HCl (310 ml) at 0 °C during 15 min. The reaction mixture was stirred for 20 min, then added dropwise to a solution of cuprous cyanide [prepared from cuprous sulfate pentahydrate (62 g, 0.25 mol), KCN (72.4 g, 1.11 mol) and water (240 ml)] at 60 °C during 40 min. The reaction mixture was diluted with AcOEt and filtered on celite. The organic layer was washed with water, dried and concentrated to give crystalline **5** (44 g, 98%), which was used for the next reaction. IR: 2225(C≡N), 1700(COOH) cm^{-1}. MS *m/z*: 181 (M^+). (lit.[8)] mp 172—174 °C).

Methyl 2-(4-Hydroxyphenyl)propionate (6)——A solution of $NaNO_2$ (13 g, 0.19 mol) in water (34 ml) was added dropwise to a solution of methyl 2-(4-aminophenyl)propionate[1)] (32.5 g, 0.18 mol) in 4 N H_2SO_4 (510 ml) at 0 °C. The resulting solution of diazonium salt was added dropwise to refluxing 2 N H_2SO_4 (500 ml) and reflux was continued for an additional 1 h. The reaction mixture was extracted with AcOEt and the organic layer was washed with brine, dried and concentrated. A mixture of the above residue, MeOH (300 ml) and H_2SO_4 (0.5 ml) was refluxed for 1 h and concentrated. The residue was dissolved in AcOEt, washed with water, dried and concentrated. The residual oil was distilled to give **6** (29 g, 90%), bp 170—175 °C (7 mmHg). IR (neat): 3390(OH), 1730 (sh) and 1705(COOH) cm^{-1}. MS *m/z*: 180 (M^+). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.46 (3H, d, J=7 Hz, $CHC\underline{H}_3$), 3.65 (3H, s, $COOCH_3$), 3.68 (1H, q, J=7 Hz, $C\underline{H}CH_3$), 6.32 (1H, s, OH), 6.74 and 7.12 (each 2H, d, J=8 Hz, Ar-4H). *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.56; H, 6.41.

Methyl 2-[4-(2-Carboxy-4-cyano)phenoxyphenyl]propionate (7)——A mixture of **5** (13.6 g, 0.075 mol), **6** (13.5 g, 0.075 mol), K_2CO_3 (20.6 g, 0.15 mol), KI (12.6 g, 0.076 mol), copper powder (Cu) (4 g) and pyridine (60 ml) was stirred under reflux for 15 h. The reaction mixture was acidified with dilute HCl and extracted with AcOEt. The organic layer was washed with water, dried and concentrated to give a residue (35 g), which was chromatographed twice on silica gel with $CHCl_3$ to give **7** (8 g, 33%), mp 103—104 °C (toluene–hexane). IR: 2230(C≡N),

1735($COOCH_3$), 1700 and 1680(COOH) cm^{-1}. MS *m/z*: 325 (M^+), 266 ($M^+ - COOCH_3$), 248 (*m/z* 266−O). ^{1}H-NMR (80 MHz, DMSO-d_6) δ: 1.35 (3H, d, J=7 Hz, $CHC\underline{H}_3$), 3.60 (3H, s, $COOCH_3$), 3.83 (1H, q, J=7 Hz, $C\underline{H}CH_3$), 7.05 (1H, d, J=8 Hz, 6′-H), 7.05 and 7.35 (each 2H, d, J=8 Hz, 2-H, 3-H, 5-H and 6-H), 7.92 (1H, dd, J=8, 2 Hz, 5′-H), 8.12 (1H, d, J=2 Hz, 3′-H), 13.03 (1H, br s, COOH). *Anal.* Calcd for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; N, 4.31. Found: C, 66.67; H, 4.69; N, 4.15.

Methyl 2-[4-(4-Cyano-2-hydroxymethyl)phenoxyphenyl]propionate (8)——A mixture of **7** (6.2 g, 0.019 mol), $CHCl_3$ (10 ml), $SOCl_2$ (15 ml) and dimethylformamide (1 drop) was stirred under reflux for 30 min, and concentrated. The residue was dissolved in dioxane (150 ml), and $NaBH_4$ (2.27 g, 0.06 mol) was added in portions to this solution, followed by dropwise addition of dilute NaOH at a rate sufficient to maintain the reaction mixture at about pH 9. After excess reagent was decomposed by addition of dilute HCl, the reaction mixture was diluted with AcOEt and extracted with dilute NaOH (3 g of the unchanged starting material was recovered from the extract). The organic layer was washed with water, dried and concentrated to give **8** (2.5 g, 42%) as a residue. IR (neat): 3450(OH), 2220(C≡N), 1725($COOCH_3$) cm^{-1}.

2-[4-(4-Carboxy-2-carboxymethyl)phenoxyphenyl]propionic Acid (9)——Procedure A: A mixture of **8** (6 g, 0.019 mol), $CHCl_3$ (20 ml) and $SOCl_2$ (3 ml) was stirred under reflux for 30 min and concentrated. The residue was dissolved in AcOEt. The solution was washed with water, dried and concentrated to give a residue, which was chromatographed on silica gel with $CHCl_3$–hexane (4:1) to give the chloride (4.5 g, 71%) as an oil. IR (neat): 2220(C≡N), 1725($COOCH_3$) cm^{-1}. A mixture of the above chloride (5.1 g, 0.015 mol), KCN (2 g, 0.031 mol), dioxane (10 ml), EtOH (10 ml) and water (5 ml) was stirred under reflux for 2 h and concentrated. The residue was dissolved in AcOEt and this solution was washed with water, dried and concentrated. The residue was chromatographed on silica gel with $CHCl_3$–hexane (4:1) to give the dinitrile ester (3.6 g, 73%) as an oil. IR (neat): 2220(C≡N), 1725 ($COOCH_3$) cm^{-1}. MS *m/z*: 320 (M^+), 261 ($M^+ - COOCH_3$), 234 (*m/z* 261−HCN). A mixture of the above dinitrile (3.6 g, 0.011 mol), KOH (6.3 g), EtOH (130 ml) and water (15 ml) was stirred under reflux for 6 h and the organic solvent was removed *in vacuo*. The reaction mixture was acidified with dilute HCl and the resulting solid was collected to give **9** (3.5 g, 92%), which was crystallized from $CHCl_3$, mp 110—115 °C. IR: 1695(COOH) cm^{-1}. MS *m/z*: 344 (M^+), 299 ($M^+ - COOH$), 253 (*m/z* 299−HCOOH). ^{1}H-NMR (80 MHz, DMSO-d_6) δ: 1.38 (3H, d, J=7, $CHC\underline{H}_3$), 3.70 (2H, s, $C\underline{H}_2COOH$), 3.67 (1H, q, J=7 Hz, $C\underline{H}CH_3$), 6.80 (1H, d, J=8.5 Hz, 6′-H), 6.96 and 7.32 (each 2H, d, J=8.5 Hz, 2-H, 3-H, 5-H and 6-H), 7.80 (1H, dd, J=8.5, 2 Hz, 5′-H), 7.94 (1H, d, J=2 Hz, 6′-H), 12.40 [3H, br, $(COOH)_3$], a signal due to $CHCl_3$ was observed at δ 8.27. *Anal.* Calcd for $C_{18}H_{16}O_7 \cdot 0.44CHCl_3$: C, 55.81; H, 4.18; Cl, 11.79. Found: C, 55.68; H, 4.08; Cl, 11.85.

Procedure B: A mixture of **11** (47 g, 0.12 mol), morpholine (25.3 g, 0.29 mol), sulfur (14 g, 0.44 g·atom) and *p*-toluenesulfonic acid (0.3 g) was heated at 100 °C for 1 h. After the addition of AcOH (100 ml) and concentrated HCl (84 ml), the mixture was stirred at 100 °C for 10 h, diluted with water and extracted with AcOEt. The organic layer was extracted with dilute NaOH, and the aqueous layer was acidified with HCl and extracted with AcOEt. The organic layer was washed with water, dried and concentrated to give a residue, which was chromatographed on silica gel with $CHCl_3$–MeOH (50:1) to give **9** (13 g, 31%), identical with the product obtained in procedure A.

2-Chloro-5-cyanoacetophenone (10)——A mixture of **5** (48 g, 0.26 mol), toluene (100 ml) and $SOCl_2$ (94 g, 0.79 mol) was stirred at 70 °C for 1 h, then concentrated and diluted with ether (66 ml). The solution of this acid chloride was added dropwise to a solution of diethyl ethoxymagnesiummalonate [prepared from magnesium turnings (7.1 g, 0.29 g·atom), diethyl malonate (46.5 g, 0.29 mol), absolute EtOH (33 ml) and ether (33 ml)] at a rate sufficient to maintain continuous refluxing of the reaction mixture. The reaction mixture was refluxed for an additional 20 min, acidified with dilute H_2SO_4 and extracted with AcOEt. The extract was washed with water, dried and concentrated to give a residue (89 g). IR (neat): 2230(C≡N), 1720(ester), 1640($COCH_3$) cm^{-1}. A mixture of the above residue, AcOH (80 ml), H_2SO_4 (10 ml) and water (80 ml) was heated at 100 °C for 3 h and diluted with water. The resulting crystalline solid was collected and chromatographed on silica gel with $CHCl_3$–hexane (2:1) to give **10** (38 g, 80%), mp 60 °C (ether–hexane). IR: 2225(C≡N), 1685($COCH_3$) cm^{-1}. MS *m/z*: 179 (M^+), 164 ($M^+ - CH_3$), 136 (*m/z* 164−CO). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.70 (3H, s, $COCH_3$), 7.6—8.0 (3H, m, Ar-H).

Methyl 2-[4-(2-Acetyl-4-cyano)phenoxyphenyl]propionate (11)——A mixture of **10** (38 g, 0.21 mol), **6** (38.2 g, 0.21 mol), K_2CO_3 (29.3 g, 0.21 mol), Cu (5 g) and toluene (70 ml) was stirred under reflux for 7 h and filtered. The filtrate was concentrated to give a residue, which was chromatographed twice on silica gel with $CHCl_3$–hexane (2:1) to give **11** (47 g, 69%), mp 68 °C (ether). IR: 2220(C≡N), 1730($COOCH_3$), 1680($COCH_3$) cm^{-1}. MS *m/z*: 323 (M^+), 264 ($M^+ - COOCH_3$). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.55 (3H, J=7 Hz, $CHC\underline{H}_3$), 2.70 (3H, s, $COCH_3$), 3.62 (3H, s, $COOCH_3$), 3.82 (1H, q, J=7 Hz, $C\underline{H}CH_3$), 6.94 and 7.23 (each 2H, d, J=8 Hz, 2-H, 3-H, 5-H and 6-H), 7.46 (1H, d, J=8 Hz, 6′-H), 7.70 (1H, dd, J=8, 2 Hz, 5′-H), 8.19 (1H, d, J=2 Hz, 3′-H). *Anal.* Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.77; H, 5.36; N, 4.29.

Pharmacological Method[3a]——Male Wistar rats weighing 110—130 g were used. Hind paw edema was induced by a subcutaneous injection of carrageenin into the hind paw. Each compound was dissolved in 0.1 M NaOH and intravenously administered 1 h before carrageenin injection, and the hind paw volume was measured before and 3 h after carrageenin. An inhibitory rate of 25% or more in comparison with the vehicle control was considered to be effective. The ED_{50} and 95% confidence limits were calculated from the effective rates (number of rats effective/

number of rats tested, %), according to the method of Litchfield and Wilcoxon.[9]

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