could pass the blood–brain barrier (BBB), yet it has been shown that sufficient NCA can reach the CNS after peripheral administration to affect CNS dopamine receptors,[13,14] supporting the suggestion that aziridinium ion formation occurs after penetration of the BBB.

Finally, these data suggest that NCA analogues with leaving groups other than Cl^- in the β-position could have more selective properties on DA receptors. For example, a better leaving group, such as Br^- or tosylate, would lead to faster aziridinium ion formation with no change in the rate of ring opening, a situation that should result in faster receptor inactivation in vitro. However, if the drug is administered peripherally, the positively charged aziridinium ion would be poorly transported across the BBB. It is indeed possible that a poorer leaving group (e.g., F^-) would result in slower aziridinium ion formation, and, consequently, a greater percentage of administered drug would reach the CNS.

Experiments are currently underway that will test these hypotheses by the synthesis of a series of β-haloalkyl analogues of apomorphine and related structures.

Note Added in Proof: After completion of this study, Lehman, Lee, and Langer (*Eur. J. Pharmacol.* **1983**, *90*, 393) also presented evidence that NCA (**1c**) breaks down in solution into NHA (**1e**). Since NHA is more potent as a dopamine receptor agonist than NCA, it was suggested that the reversible agonistic action of NCA occurs at least partly through its hydrolysis into NHA in the perfusion medium.

Experimental Section

Materials. The aporphines NCA (**1c**) and NHA (**1e**) were synthesized as previously described.[11] HPLC-grade water and organic solvents were from Burdick and Jackson Laboratories, Inc., Muskegon, MI, J. T. Baker Chemical Co., Phillipsburg, NJ, and MCB Manufacturing Chemical Inc., Cincinnati, OH. Phenoxybenzamine (PBA) was a gift from Smith Kline & French Laboratories, Philadelphia, PA, and reagent-grade picric acid was from J. T. Baker Chemical Co. Other chemicals were reagent grade.

High-Performance Liquid Chromatography. The chromatographic system consisted of a Waters 6000A pump (Waters Associates, Inc., Milford, MA), a Rheodyne Model 7125 injector (Rheodyne, Inc., Cotati, CA), and bonded C_{18} 5 μM Hypersil silica column (150 × 4.6 mm), synthesized and packed according to a previously described method.[38] Detection was accomplished at 254 nm with an LDC Model 1203 fixed-wavelength detector (Laboratory Data Control, Riviera Beach, FL) and, occasionally, by oxidative electrochemical detection with BAS Model LC-4A detector (Bioanalytical Systems, West Lafayette, IN) using a glassy carbon electrode operating at a potential of +0.60 V.

Various phosphate mobile phases were used with Na^+ or triethylammonium as the counterion. A typical system consisted of 50 mM NaH_2PO_4 adjusted to pH 3.25 with H_3PO_4 containing 20–25% acetonitrile. Specific conditions are given in the figure captions. The flow rate was 1.5 mL/min.

Solvolysis of NCA. A 15-μL aliquot of a stock solution of NCA in methanol (2.9 mg/mL) was pipetted into 985 μL of buffer to give a 125 μM solution, and the reaction temperature was held at 25 or 37 °C in a thermostatted water bath. At measured time intervals, 20-μL aliquots were withdrawn and analyzed by HPLC. The total amount of NCA remaining was quantitated by comparing the peak height to a standard curve of NCA dissolved in mobile phase in the range 100–900 ng per injection.

The reaction buffer solution in the pH range 6.0–8.0 was a mixture of NaH_2PO_4–Na_2HPO_4. Below pH 6.0 an acetate buffer was used with 0.1 M sodium acetate titrated to the desired pH with 0.1 M acetic acid.

Identification of NCA Solvolysis Products. (1) Phosphate Buffer. NCA (1 mg/mL) was suspended in a solution of 50% methanol and 50% 0.1 M phosphate buffer, pH 7.0. After 45 min, 100 μL of this mixture was acidified with 300 μL of the HPLC mobile phase made up with 20% acetonitrile. The products were then separated by HPLC and collected in centrifuge tubes, and an aliquot of 20 mM picric acid equal to 10% the fraction volume was added to each fraction and thoroughly mixed. The resulting solution was then extracted twice with 250 μL of CH_2Cl_2, and the combined extracts were concentrated to 10–15 μL with a stream of N_2. Each fraction was then directly analyzed by electron-impact and/or chemical-ionization mass spectrometry.

(2) Acetate Buffer. A solution consisting of 1 mL of pH 5.80 acetate buffer and 200 μL of NCA in methanol (2.9 mg/mL) was allowed to stand at room temperature overnight. Under these conditions, NCA had completely reacted, and no aziridinium intermediate was present. The two remaining products were separated by HPLC in 20% acetonitrile and 80% NaH_2PO_4 buffer and then collected. Extraction and analysis by mass spectrometry were performed as described above.

Acknowledgment. This work was supported in part by NIH Grant NS-18178 (J.L.N.) and a grant from Northeastern University (S.A.C.). Also, we thank Ji-Hua Guan for the preparation of the aporphine derivatives, John C. Ford for his assistance in running the programs for the pK_a determinations, and Hamdy M. Maksoud and Michael J. Hayes for providing the mass spectra.

Registry No. **1c**, 75946-94-0.

(38) Tanaka, N.; Goodell, H.; Karger, B. L. *J. Chromatogr.* **1978**, *158*, 233.

Substituted (2-Phenoxyphenyl)acetic Acids with Antiinflammatory Activity. 1[1]

David C. Atkinson, Keith E. Godfrey, Bernard Meek, John F. Saville, and Michael R. Stillings*

Reckitt and Colman Ltd., Pharmaceutical Division, Kingston-upon-Hull, HU8 7DS, United Kingdom.
Received November 3, 1982

The synthesis and antiinflammatory activity of a series of substituted (2-phenoxyphenyl)acetic acids are described. Initial screening in the adjuvant arthritis test showed that halogen substitution in the phenoxy ring enhanced activity considerably. Ulcerogenic potential, as measured by the minimum ulcerogenic dose (MUD), was low in almost all the acids tested. [2-(2,4-Dichlorophenoxy)phenyl]acetic acid possessed the most favorable combination of potency with low toxicity, including ulcerogenicity, and this compound is now in therapeutic use.

A number of years ago we commenced a search for a nonsteroidal antiinflammatory drug (NSAID) that had reduced toxicity and a longer duration of action compared with existing drugs. In common with other workers,[2,3] we had noted the perhaps fortuitous resemblance of some NSAIDs to plant-growth regulators. For example, indomethacin,[4] ibufenac,[5] and a series of experimental com-

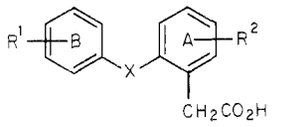
(1) Godfrey, K. E. United Kingdom Patent 1 308 327, 1973.

(2) Shen, T. Y. *Angew. Chem.* **1972**, *1*, 460.

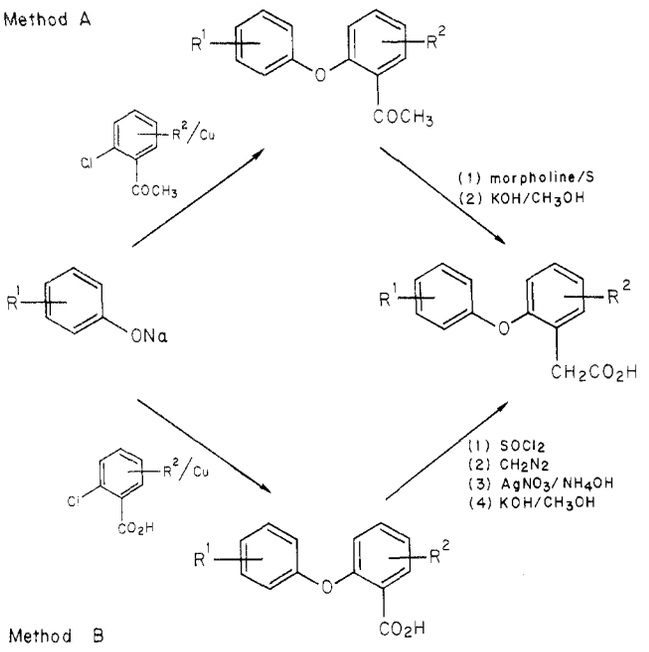
(3) Northover, B. J. *J. Pathol. Bacteriol.* **1963**, *85*, 361.

0022-2623/83/1826-1353$01.50/0

Chart I



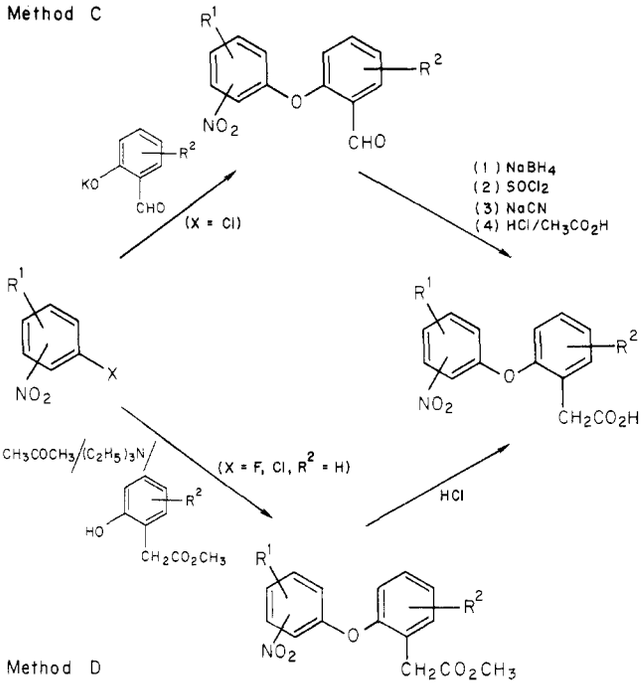
Scheme I



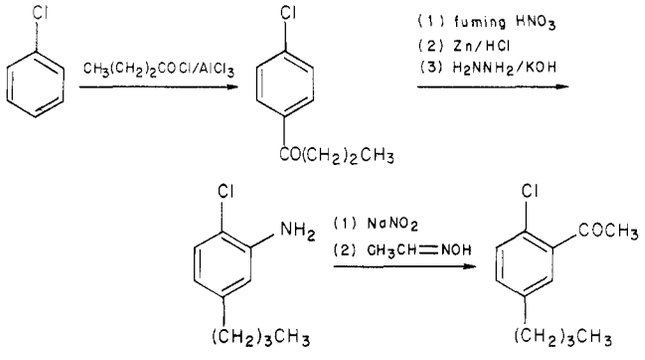
pounds investigated at Smith, Kline & French[6] are simple derivatives of the plant-growth regulators indole-3-acetic acid, phenylacetic acid, and naphthalene-1-acetic acid respectively. Bearing in mind the already well-known fenamic acid series[7] of NSAIDs, we considered that compounds of the general structure shown in Chart I, incorporating a combination of the phenylacetic acid moiety with an extension of the fenamic acid structure, would be likely to possess antiinflammatory activity. In addition, the compounds would also fit the hypothetical receptor sites described by Shen[8] and Scherrer.[9] Our own interests focused on the series in which X is oxygen and have resulted in the introduction of [2-(2,4-dichlorophenoxy)-phenyl]acetic acid (**5**, fenclofenac) as an antiinflammatory drug in a number of countries. Other workers have reported on the corresponding series of compounds in which X is imino.[10]

A brief report on the preparation and biological properties of fenclofenac has been published,[11] together with

Scheme II



Scheme III



an account of its pharmacology[12] and a general survey of both preclinical and clinical work.[13] The purpose of this paper is to present the chemistry and structure–activity relationships of the (2-phenoxyphenyl)acetic acid series.

Chemistry. The vast majority of compounds in this series were prepared by conventional routes including those using the Willgerodt–Kindler[14] (method A) and Arndt–Eistert[15] (method B) reactions (Scheme I). In addition, a smaller number were synthesized by routes involving the reaction of suitably derivatized salicylaldehydes (method C) or methyl (2-hydroxyphenyl)acetate (method D) with activated halogenobenzenes, followed by further elaboration (Scheme II). The large number of phenols (methods A and B) and acetophenones (method A) required were either commercially available or readily synthesized by standard procedures, although a small number of less easily accessible acetophenones were prepared via a route involving a little-used reaction described by Beech[16] and

(4) Shen, T. Y.; Windholz, T. B.; Rosegay, A.; Witzel, B. E.; Wilson, A. N.; Willett, J. D.; Holtz, W. J.; Ellis, R. L.; Matzuk, A. R.; Lucas, S.; Stammer, C. H.; Holly, F. W.; Sarett, L. H.; Risley, E. A.; Nuss, G. W.; Winter, C. A. *J. Am. Chem. Soc.* **1963**, *85*, 488.
(5) Adams, S. S.; Cliffe, E. E.; Lessel, B.; Nicholson, J. S. *Nature (London)* **1963**, *200*, 271.
(6) Durant, G. J.; Smith, G. M.; Spickett, R. G. W.; Szarvasi, E. *J. Med. Chem.* **1965**, *8*, 598.
(7) Winder, C. V.; Wax, J.; Scotti, L.; Scherrrer, R. A.; Jones, E. M.; Short, F. W. *J. Pharmacol. Exp. Ther.* **1962**, *138*, 405.
(8) Shen, T. Y. In "Nonsteroidal Anti-inflammatory Drugs"; Garattini, S.; Dukes, M. N. G., Eds.; Excerpta Medica Foundation: Amsterdam, 1965; pp 13–20.
(9) Scherrer, R. A.; Winder, C. B.; Short, F. W. Abstracts of the 9th National Medicinal Chemistry Symposium of the American Chemical Society, Minneapolis, MN, June 1964, pp 11a–i.
(10) Sallman, A.; Pfister R. United Kingdom Patent 1 132 318, 1968.
(11) Atkinson, D. C.; Godfrey, K. E.; Jordan, B. J.; Leach, E. C.; Meek, B.; Nichols J. D.; Saville, J. F. *J. Pharm. Pharmacol.* **1974**, *26*(5), 357.
(12) Atkinson, D. C.; Leach, E. C. *Agents Actions* **1976**, *6*(5), 657.
(13) Goldberg, A. A. J.; Godfrey, K. E. *Clin. Rheum. Dis.* **1980**, *6*(3), 647.
(14) Carmack, M.; Spielman, M. A. *Org. React.* **1946**, *3*, 83.
(15) Bachmann, W. E.; Struve, W. S. *Org. React.* **1942**, *1*, 38.
(16) Beech, W. F. *J. Chem. Soc.* **1954**, 1297.

exemplified in Scheme III. Further details are given in the Experimental Section. The synthesis of a number of simple derivatives of [2-(2,4-dichlorophenoxy)phenyl]acetic acid is also described. Compounds **1**, **3**, **32**, and **127** have been previously reported in the literature.[17-20]

Results and Discussion

Acute tests for antiinflammatory activity, such as the rat paw edema and guinea pig erythema tests rely on inflammatory situations very far removed from the chronic conditions of rheumatoid arthritis. We therefore chose to use the rat adjuvant arthritis test as our primary screen. This test has the advantage of chronicity and adaptability to therapeutic as well as prophylactic treatment, and also the lesion involved bears some resemblance to that in rheumatoid arthritis. Furthermore, it appears to be less likely to exaggerate probable clinical potencies than is the case with acute tests. The developing (prophylactic) adjuvant arthritis test was used to assess some of the early members of the series. Drug treatment and adjuvant disease initiation were commenced concurrently, and groups of three animals with nine controls were dosed daily for 14 days. Paw volume changes were assessed at day 15. This was later replaced by the established (therapeutic) version of the test in which the animals were treated with drug after the arthritis had fully developed, a test which clearly more closely reflects the clinical situation. The adjuvant disease was established in both the treated and control groups, as described by Atkinson and Leach.[12] The primary screen involved dosing groups of five arthritic animals at a single dose level for 7 days, after which their paw volumes were compared with those of a group of 20 control animals. For compounds showing interesting activity in this test, relative potency vs. a standard (compound **5**) was determined. Full experimental details of this procedure are described elsewhere.[12]

The effects of changes in substitution in ring B (Chart I) were examined in three main series of compounds in which R^2 was H, 5-Me, or 5-Cl. Most effort was devoted to that in which R^2 = 5-Me, mainly because of synthetic considerations. In general, the potencies of compounds with R^2 = 5-Me did not differ significantly from those of their analogues with R^2 = H (e.g., **5** vs. **52**, Table I). There were only three pairs in which the potency appeared to decrease with R^2 = 5-Me; however, in each case (**4** vs. **51**; **8** vs. **55**; and **17** vs. 90), results from therapeutic and prophylactic tests are involved, and the comparison is therefore questionable. Compounds with R^2 = 5-Cl, in general, appeared to have increased potencies compared with their R^2 = H analogues (e.g., **6** vs. **34**, and **16** vs. **40**).

The unsubstituted parent compound of the series, **1**, was devoid of activity, and compounds that were monosubstituted in ring B, such as **30** and **49**, were also of low activity. Further substitution led, in many cases, to active compounds, the most notable feature of the structure–activity relationship being the general requirement for a chlorine atom at the 2-position in ring B (e.g., **57** vs. its positional isomer **85** or vs. **78**). However, as already mentioned, it was important that there was further substitution in the B ring, preferably by chlorine or alkyl (compare **30** with **33**; and **49** with **52**, **53**, and **57**). Although trisubstituted and even tetrasubstituted compounds retained activity when the substituents were a mixture of chlorine and alkyl (e.g., **87** and **17**), trichloro-substituted compounds appeared to lose activity (compare **5** with **10** and **11**). Only four compounds not possessing a 2-chloro substituent showed reasonable activity, and these were the 2-methoxy compounds **20** and **82**, the 2-hydroxy compound **86**, and the dibromo compound **12**, which was only slightly less potent than its dichloro analogue **5**.

Considerable effort was devoted to the subseries in which ring B contained the 2-chloro, 4-alkyl substitution pattern. With H or Cl at position 5 in the A ring, both the 2-Cl, 4-Me compounds **13** and **36** showed only weak activity, whereas with R^2 = 5-Me (**56**) there was significant activity. The 2-Cl, 4-Et substituted compounds were more active than the 2-Cl, 4-Me compounds for both R^2 = H (**15**) and R^2 = Me (**57**), and this lead was followed up by the synthesis of a range of analogues with substituents of increasing chain length at C-4 in the B ring, varying from propyl to dodecyl (**58–70**). Potency appeared to be maximal in the *s*-Bu (**62**) and *t*-Bu (**63**) compounds but fell off rapidly as the chain length increased.

In the A ring it appeared that substitution at the 5-position by any groups other than H, Me, or Cl greatly reduced or abolished activity (e.g., **5**, **33**, and **52** vs. **96–98**; and **56** vs. **101–106**). Similarly, substitution at other positions of this ring also destroyed activity (e.g., **56** vs. **107–117**). In many of these compounds, exacerbation of paw swelling was noted. The effects of relatively minor changes in A-ring substitution indicate that very subtle electronic and steric factors are involved.

Any change in the acetic acid moiety (Table II) resulted in loss of activity, except for simple derivatives such as the ethyl ester **118**, the primary amide **119**, and the hydroxamic acid **126**. Substitution with an α-methyl group (**120**) completely abolished activity. Other variations in the length or type of acidic side chain (**121**, **122**, **124**, and **125**) also gave compounds of reduced potency. The alcohol **123** was of reasonable potency, but two of the ten animals treated had severe ulcers. Compound **127**, with the acetic acid para to the oxygen bridge, was considerably less potent than the ortho isomer **5**.

Compounds chosen for relative potency determination were also evaluated for gastric ulcerogenic activity following a single dose in rats.[12] A notable feature of these compounds was their very low level of ulcerogenicity; of the 39 compounds tested, 31 had a minimum ulcerogenic dose (MUD) greater than the cutoff point of 500 mg/kg adopted for initial ulcerogenic screening. In contrast, aspirin, ibuprofen, indomethacin, and phenylbutazone had MUD figures of 15–60, 6–13, 1.3–5, and 40–80 mg/kg, respectively, when tested under the same conditions in our laboratories.[12] Those compounds with MUD figures of less than 500 mg/kg (**33**, **56**, **59**, **61**, **72**, **76**, **87**, and **122**) were not considered for further evaluation.

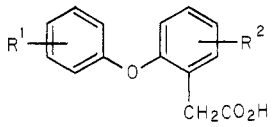
After secondary screening, a short list of compounds was prepared from which four (**5**, **57**, **62**, and **63**) were selected on the basis of a series of relative potency and MUD determinations (Table III). Short-term toxicity was also carried out and based on this, and synthetic considerations, **5** and **57** were identified as compounds suitable for further evaluation. [2-(2,4-Dichlorophenoxy)phenyl]acetic acid (**5**), for which considerably more development data were available, was subsequently chosen for progression as a therapeutic agent in man.

Experimental Section

Chemistry. Melting points were determined in a Buchi apparatus in glass capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 700 instrument and were con-

(17) Cagniant, P.; Kirsch, G. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1976**, *283*, 683.
(18) Ueda, I.; Sato, Y.; Maeno, S.; Umio, S. *Chem. Pharm. Bull.* **1975**, *23*, 2223.
(19) Gerecke, M.; Kyburz, E.; Kaplan, J. P. German Patent, 2461137, 1974.
(20) Julia, M.; Baillarge, M. *Bull. Soc. Chim. Fr.* **1953**, 640.

Table I. (Phenoxyphenyl)acetic Acids



no.	R^1	R^2	method of prepn	mp, °C	formula	anal.	adjuvant arthritis test: primary[a]	adjuvant arthritis test: rel to 5[b]
1	H	H	C, D	88-90	$C_{14}H_{12}O_3$	C, H	0*	
2	2-Cl	H	B	114-116	$C_{14}H_{11}ClO_3$	C, H	NT	
3	4-Cl	H	A	114-116	$C_{14}H_{11}ClO_3$	C, H	0*	
4	2,3-Cl_2	H	A	116-118	$C_{14}H_{10}Cl_2O_3$	C, H	51*	
5	2,4-Cl_2	H	A, B, D	134-136	$C_{14}H_{10}Cl_2O_3$	C, H	36	1.0
6	2,5-Cl_2	H	A	119-121	$C_{14}H_{10}Cl_2O_3$	C, H	18*	
7	2,6-Cl_2	H	A	153-154	$C_{14}H_{10}Cl_2O_3$	C, H	20*	
8	3,4-Cl_2	H	A	115-116	$C_{14}H_{10}Cl_2O_3$	C, H	20*	
9	3,5-Cl_2	H	A	121-122	$C_{14}H_{10}Cl_2O_3$	C, H	NT	
10	2,4,5-Cl_3	H	A	122-126	$C_{14}H_9Cl_3O_3$	C, H	17	
11	2,4,6-Cl_3	H	B	186-188	$C_{14}H_9Cl_3O_3$	C, H	23	
12	2,4-Br_2	H	A	147-153	$C_{14}H_{10}Br_2O_3$	C, H	29	0.8
13	2-Cl, 4-Me	H	A	149-150	$C_{15}H_{13}ClO_3$	C, H	21*	
14	4-Cl, 2-Me	H	A	104-107	$C_{15}H_{13}ClO_3$	C, H	0*	
15	2-Cl, 4-Et	H	A	117-119	$C_{16}H_{15}ClO_3$	C, H	32	0.7
16	2,4-Cl_2, 5-Me	H	A	133-134	$C_{15}H_{12}Cl_2O_3$	C, H	19*	
17	2,4-Cl_2, 3,5-Me_2	H	A	159-162	$C_{16}H_{14}Cl_2O_3$	C, H	34	1.2
18	2,4-Me_2	H	B	70-72	$C_{16}H_{16}O_3$	C, H	20*	
19	2-OH	H	A[c]	117-120	$C_{14}H_{12}O_4$	C, H	NT	
20	2-OMe	H	A	91-93	$C_{15}H_{14}O_4$	C, H[d]	38*	0.7
21	2-F	H	A	109-113	$C_{14}H_{11}FO_3$	C, H	NT	
22	2-CF_3	H	B	52-54	$C_{15}H_{11}F_3O_3$	C, H	0*	
23	2-Cl, 4-NH_2	H	C[f]	154-157	$C_{14}H_{12}ClNO_3$	C, H	+5[e]	
24	2-Cl, 4-NO_2	H	C	182-185	$C_{14}H_{10}ClNO_5$	C, H	19	
25	4-Cl, 2-NH_2	H	C, D[f]	163-165	$C_{14}H_{12}ClNO_3$	C, H	+4	
26	4-Cl, 2-NO_2	H	A	190-193	$C_{14}H_{10}ClNO_5$	C, H	+4*	
27	2,4-$(NH_2)_2$	H	D	172-174	$C_{14}H_{14}N_2O_3$	C, H	0*	
28	2,4-$(NO_2)_2$	H	D	171-174	$C_{14}H_{10}N_2O_7$	IR	0*	
29	H	5-Cl	A	124-128	$C_{14}H_{11}ClO_3$	IR	0*	
30	2-Cl	5-Cl	A	99-102	$C_{14}H_{10}Cl_2O_3$	C, H	0*	
31	3-Cl	5-Cl	A	82-84	$C_{14}H_{10}Cl_2O_3$	C, H	0*	
32	4-Cl	5-Cl	A	113-117	$C_{14}H_{10}Cl_2O_3$	C, H	21	
33	2,4-Cl_2	5-Cl	A	106-108	$C_{14}H_9Cl_3O_3$	C, H	37	1.0
34	2,5-Cl_2	5-Cl	A	139-141	$C_{14}H_9Cl_3O_3$	C, H	40*	1.0
35	2,4-Me_2	5-Cl	A	102-105	$C_{16}H_{15}ClO_3$	C, H	22*	
36	2-Cl, 4-Me	5-Cl	A	91-93	$C_{15}H_{12}Cl_2O_3$	C, H	10	
37	4-Cl, 2-Me	5-Cl	A	94-96	$C_{15}H_{12}Cl_2O_3$	C, H	7*	
38	2-Cl, 4,5-Me_2	5-Cl	A	134-136	$C_{16}H_{14}Cl_2O_3$	C, H	22*	
39	4-Cl, 3,5-Me_2	5-Cl	A	142-144	$C_{16}H_{14}Cl_2O_3$	C, H	23*	
40	2,4-Cl_2, 5-Me	5-Cl	A	145-148	$C_{15}H_{11}Cl_3O_3$	C, H	40*	0.6
41	2,4-Cl_2, 3,5-Me_2	5-Cl	A	168-169	$C_{16}H_{13}Cl_3O_3$	C, H	41*	1.0
42	2-Cl, 4-OMe	5-Cl	A	126-129	$C_{15}H_{12}Cl_2O_4$	C, H[g]	18*	
43	2-Cl, 4-OH	5-Cl	A[c]	164-167	$C_{14}H_{10}Cl_2O_4$	C, H	36*	
44	2-F	5-Cl	A	103-104	$C_{14}H_{10}ClFO_3$	C, H	21*	
45	2-F	5-Me	A	107-108	$C_{15}H_{13}FO_3$	C, H	24*	
46	2-CF_3	5-Me	A	76	$C_{16}H_{13}F_3O_3$	C, H	0	
47	3-OMe	5-Me	A	68-69	$C_{16}H_{16}O_4$	C, H	+10	
48	3-OH	5-Me	A[c]	95-97	$C_{15}H_{14}O_4$	C, H	+3	
49	2-Cl	5-Me	A	99-100	$C_{15}H_{13}ClO_3$	C, H	12	
50	4-Cl	5-Me	A	111-112	$C_{15}H_{13}ClO_3$	C, H	9	0.7
51	2,3-Cl_2	5-Me	A	120-121	$C_{15}H_{12}Cl_2O_3$	C, H	13	
52	2,4-Cl_2	5-Me	A	127-128	$C_{15}H_{12}Cl_2O_3$	C, H	29	0.8
53	2,5-Cl_2	5-Me	A	154-157	$C_{15}H_{12}Cl_2O_3$	C, H	32	0.4
54	2,6-Cl_2	5-Me	A	131-132	$C_{15}H_{12}Cl_2O_3$	C, H	16	
55	3,4-Cl_2	5-Me	A	119-120	$C_{15}H_{12}Cl_2O_3$	C, H	9	
56	2-Cl, 4-Me	5-Me	A	95-97	$C_{16}H_{15}ClO_3$	C, H	35	0.4
57	2-Cl, 4-Et	5-Me	A	106-108	$C_{17}H_{17}ClO_3$	C, H	40	1.1
58	2-Cl, 4-*n*-Pr	5-Me	A	84-85	$C_{18}H_{19}ClO_3$	C, H	27	0.6
59	2-Cl, 4-*i*-Pr	5-Me	A	100-101	$C_{18}H_{19}ClO_3$	C, H	30	1.6
60	2-Cl, 4-*n*-Bu	5-Me	A	70-72	$C_{19}H_{21}ClO_3$	C, H	25	0.9
61	2-Cl, 4-*i*-Bu	5-Me	A	85-86	$C_{19}H_{21}ClO_3$	C, H	19	0.2
62	2-Cl, 4-*s*-Bu	5-Me	A	49-50	$C_{19}H_{21}ClO_3$	C, H	42	3.0
63	2-Cl, 4-*t*-Bu	5-Me	A	133-134	$C_{19}H_{21}ClO_3$	C, H	34	1.6
64	2-Cl, 4-*n*-pent	5-Me	A	76-77	$C_{20}H_{23}ClO_3$	C, H	23	0.3
65	2-Cl, 4-*n*-hex	5-Me	A	70-73	$C_{21}H_{25}ClO_3$	C, H	5	
66	2-Cl, 4-*n*-oct	5-Me	A	61-63	$C_{23}H_{29}ClO_3$	C, H	13	
67	2-Cl, 4-*n*-non	5-Me	A	60-61	$C_{24}H_{31}ClO_3$	C, H	8	
68	2-Cl, 4-*n*-dec	5-Me	A	58-60	$C_{25}H_{33}ClO_3$	C, H	9	
69	2-Cl, 4-*n*-undec	5-Me	A	58-61	$C_{26}H_{35}ClO_3$	C, H	14	

Table I (*Continued*)

no.	R^1	R^2	method of prepn	mp, °C	formula	anal.	adjuvant arthritis test: primary[a]	adjuvant arthritis test: rel to 5[b]
70	2-Cl, 4-*n*-dodec	5-Me	A	56-58	$C_{27}H_{37}ClO_3$	C, H	26	0.3
71	2-Cl, 4-cyclohex	5-Me	A	139-141	$C_{21}H_{23}ClO_3$	C, H[h]	+2	
72	2-Cl, 4-Ph	5-Me	A	138-139	$C_{21}H_{17}ClO_3$	C, H	23	0.2
73	2-Cl, 5-*n*-Bu	5-Me	A	97-98	$C_{19}H_{21}ClO_3$	C, H	5	
74	2-Cl, 6-Me	5-Me	A	135-136	$C_{16}H_{15}ClO_3$	C, H	26	0.5
75	2-Cl, 5-CF_3	5-Me	A	123-124	$C_{16}H_{12}ClF_3O_3$	C, H	29	3.0
76	2-Cl, 4,5-Me_2	5-Me	A	98-100	$C_{17}H_{17}ClO_3$	C, H	46*	0.4
77	2,4-Me_2	5-Me	A	89-90	$C_{17}H_{18}O_3$	C, H	20*	
78	2,4-Et_2	5-Me	A	137-142	$C_{19}H_{22}O_3$	C, H	8	
79	3,5-$(CF_3)_2$	5-Me	A	130-131	$C_{17}H_{12}F_6O_3$	C, H	+10	
80	4-Cl, 2-Me	5-Me	A	97-98	$C_{16}H_{15}ClO_3$	C, H	17	
81	5-Cl, 2-Me	5-Me	A	158-160	$C_{16}H_{15}ClO_3$	C, H	15	0.2
82	4-Cl, 2-OMe	5-Me	A	104-106	$C_{16}H_{15}ClO_4$	C, H	23	0.7
83	4-Cl, 3-Me	5-Me	A	80-81	$C_{16}H_{15}ClO_3$	C, H	9	
84	3-Cl, 2-Me	5-Me	A	112-113	$C_{16}H_{15}ClO_3$	C, H	20	0.3
85	4-Cl, 2-Et	5-Me	A	112-115	$C_{17}H_{17}ClO_3$	C, H	17	0.4
86	4-Cl, 2-OH	5-Me	A[c]	116-117	$C_{15}H_{13}ClO_4$	C, H	26	
87	2,4-Cl_2, 5-Me	5-Me	A	147-149	$C_{16}H_{14}Cl_2O_3$	C, H	45*	0.4
88	2,4-Cl_2, 6-Me	5-Me	A	134	$C_{16}H_{14}Cl_2O_3$	C, H	23	0.3
89	4-Cl, 3,5-Me_2	5-Me	A	133-136	$C_{17}H_{17}ClO_3$	C, H	5	0.7
90	2,4-Cl_2, 3,5-Me_2	5-Me	A	153-154	$C_{17}H_{16}Cl_2O_3$	C, H	20*	
91	4-Cl, 2,6-Me_2	5-Me	A	135-136	$C_{17}H_{17}ClO_3$	C, H	14	0.3
92	4-Cl, 2,5-Me_2	5-Me	A	114-116	$C_{17}H_{17}ClO_3$	C, H	10	
93	4-Cl, 5-Me, 2-*i*-Pr	5-Me	A	105-106	$C_{19}H_{21}ClO_3$	C, H	3	
94	2,3,5-Me_3	5-Me	A	125-127	$C_{18}H_{20}O_3$	C, H	11	0.1
95	2,4-Cl_2	5-OMe	A	108-109	$C_{15}H_{12}Cl_2O_4$	C, H	3	
96	2,4-Cl_2	5-NO_2	C[i]	159-160	$C_{14}H_9Cl_2NO_5$	C, H	9	
97	2,4-Cl_2	5-NH_2	A[j]	167-168	$C_{14}H_{11}Cl_2NO_3$	C, H	0	
98	2,4-Cl_2	5-NMe_2	A[k]	212-213	$C_{16}H_{15}Cl_2NO_3$	C, H	5	
99	2,4-Cl_2	4,5-$(NO_2)_2$	A[i]	197-198	$C_{14}H_8Cl_2N_2O_7$	IR	8	
100	2,4-Cl_2, 6-NO_2	4,5-$(NO_2)_2$	A[i]	192	$C_{14}H_7Cl_2N_3O_9$	C, H	5	
101	2-Cl, 4-Me	5-Et	A	125	$C_{17}H_{17}ClO_3$	C, H	+13	
102	2-Cl, 4-Me	5-*n*-Bu	A	59-60	$C_{19}H_{21}ClO_3$	C, H	+8	
103	2-Cl, 4-Me	5-OMe	A	107-109	$C_{16}H_{15}ClO_4$	C, H	+6	
104	2-Cl, 4-Me	5-OH	A[c]	143-146	$C_{15}H_{13}ClO_4$	C, H	10	
105	2-Cl, 4-Me	5-NH_2	A	163-164	$C_{15}H_{14}ClNO_3$	C, H	3	
106	2-Cl, 4-Me	5-CF_3	A	119	$C_{16}H_{12}ClF_3O_3$	C, H	0	
107	2-Cl, 4-Me	3-Cl	A	114-116	$C_{15}H_{12}Cl_2O_3$	C, H	+23	
108	2-Cl, 4-Me	4-Me	A	122-123	$C_{16}H_{15}ClO_3$	C, H	+1	
109	2-Cl, 4-Me	4-OMe	A	109-112	$C_{16}H_{15}ClO_4$	C, H	+14	
110	2-Cl, 4-Me	4-O-*n*-Bu	A[l]	70-73	$C_{19}H_{21}ClO_4$	C, H	0	
111	2-Cl, 4-Me	4-OH	A[c]	120-122	$C_{15}H_{13}ClO_4$	C, H	+20	
112	2-Cl, 4-Me	6-OH	A[c]	165-166	$C_{15}H_{13}ClO_4$	C, H	+9	
113	2-Cl, 4-Me	4,5-Me_2	A	132-134	$C_{17}H_{17}ClO_3$	C, H	+14	
114	2-Cl, 4-Me	4-Cl, 5-Me	A	120-121	$C_{16}H_{14}Cl_2O_3$	C, H	+7	
115	2-Cl, 4-Me	4-OMe, 5-Me	A	106-108	$C_{17}H_{17}ClO_4$	C, H	+12	
116	2-Cl, 4-Me	4-OH, 5-Me	A[c]	130-131	$C_{16}H_{15}ClO_4$	C, H	12	
117	2-Cl, 4-Me	4-Me, 5-Cl	A	123-126	$C_{16}H_{14}Cl_2O_3$	C, H	+14	

[a] In rat, reduction in paw swelling at 100 mg/kg po; asterisk denotes results from the developing adjuvant arthritis test; others are from the established version of the test; ibuprofen gave a reduction of 21% at this dose level. [b] A three dose level relative potency assay using the established adjuvant arthritis test vs. compound 5; ibuprofen gave a figure of 0.12 in this test.[12] NT, not tested (these compounds were inactive in the rat paw carrageenin test at 200 mg/kg po). [c] Followed by demethylation. [d] C: calcd, 69.76; found, 68.65. [e] A plus sign denotes exacerbation of paw swelling. [f] Followed by catalytic reduction. [g] C: calcd, 55.07; found, 54.5. [h] C: calcd, 70.28; found, 70.8. [i] Followed by nitration. [j] Followed by nitration with subsequent catalytic reduction. [k] Followed by nitration, catalytic reduction, and subsequent alkylation. [l] Followed by demethylation with subsequent alkylation.

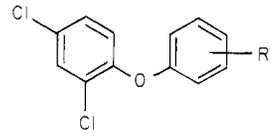
sistent with the assigned structures. Only in a small number of compounds were NMR spectra required for structure elucidation, and again these were consistent with the assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values. Ether refers to diethyl ether in all cases.

Method A. [2-(2,4-Dichloro-5-methylphenoxy)-5-chlorophenyl]acetic Acid (40). A mixture of 2,5-dichloroacetophenone (37.8 g, 0.2 mol), sodium 2,4-dichloro-5-methylphenoxide (79.6 g, 0.4 mol), 2,4-dichloro-5-methylphenol (35.4 g, 0.2 mol), and finely divided copper[21] (0.5 g, catalytic quantity) was stirred under an atmosphere of nitrogen at an internal temperature of 120–125 °C for 24 h. The mixture was cooled, diluted with water, and extracted with ether. The organic layer was washed with 2 N sodium hydroxide and water and then dried and evaporated to give an oil. This was distilled at reduced pressure, and the 2-(2,4-dichloro-5-methylphenoxy)-5-chloroacetophenone solidified on standing: yield 30 g (45%). A portion was crystallized from methanol to give a pure sample, mp 73–75 °C. Anal. ($C_{15}H_{11}Cl_3O_2$) C, H.

A mixture of the acetophenone (18.0 g, 0.055 mol), morpholine (17.1 g, 0.197 mol), and sulfur (4.6 g, 0.143 mol) was heated under reflux for 24 h. The warm mixture was poured into methanol (85 mL) and left to cool at 0 °C. The yellow crystals that formed were removed by filtration to give [2-(2,4-dichloro-5-methylphenoxy)-5-chlorophenyl]thioacetmorpholide: yield 17.5 g (75%). A small portion was recrystallized from methanol to give a pure

(21) Brewster, R. Q.; Groening, T. In "Organic Syntheses"; Wiley: New York, 1943; Vol. II, p 446.

Table II. Simple Analogues of Fenclofenac (5)



no.	R	mp or bp (mm), °C	formula	anal.	adjuvant arthritis test: primary[a]	adjuvant arthritis test: rel to 5[b]
118	2-CH_2CO_2Et	154–155 (0.4)	$C_{16}H_{14}Cl_2O_3$	C, H	34	0.5
119	2-CH_2CONH_2	166–168	$C_{14}H_{11}Cl_2NO_2$	C, H, N	33	1.3
120	2-$CH(CH_3)CO_2H$	96–98	$C_{15}H_{12}Cl_2O_3$	C, H	0	
121	2-CO_2H	159–162	$C_{13}H_8Cl_2O_3$	C, H	18	
122	2-$COCO_2H$	109–112	$C_{14}H_8Cl_2O_4$	C, H	23	0.3
123	2-CH_2CH_2OH	168–170 (0.5)	$C_{14}H_{12}Cl_2O_2$	C, H	32	0.7
124	2-$CH_2CH_2CO_2H$	111–114	$C_{15}H_{12}Cl_2O_3$	C, H	0	
125	2-$CH{=}CH{\cdot}CO_2H$	222–224	$C_{15}H_{10}Cl_2O_3$	C, H	+8	
126	2-$CH_2CONHOH$	142–144	$C_{14}H_{11}Cl_2NO_3$	C, H, N	28	1.0
127	4-CH_2CO_2H	112–114	$C_{14}H_{10}Cl_2O_3$	C, H	2	

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I.

Table III. Further Evaluation of Selected Compounds

no.	potency rel to 5	MUD, mg/kg po (average of two determinations)	LD_{50}, mg/kg po
5	1.0	400–800	2500
57	1.1[a]	>800	2853
62	4.0[b]	400–800	1109
63	1.5[c]	>500[d]	NT[e]

[a] Average of five determinations. [b] Average of three determinations. [c] Average of four determinations. [d] Three out of ten rats had duodenal ulcers in one test. [e] NT, not tested.

sample as pale yellow needles, mp 136–137 °C. Anal. ($C_{19}H_{18}Cl_3NO_2S$) C, H, N.

The thioacetmorpholide (14.0 g, 0.032 mol) was dissolved in a solution of potassium hydroxide (14.0 g) in methanol (140 mL) and heated under reflux for 72 h. The mixture was evaporated, water was added, and the mixture was extracted with ether. The aqueous layer was acidified with concentrated HCl, and the product was extracted into ether. The ether extracts were washed with water, dried, and evaporated. The solid residue was crystallized from petroleum ether (bp 80–100 °C) to give **40**: yield 10.5 g (93%); mp 145–148 °C. Anal. ($C_{15}H_{11}Cl_3O_3$) C, H. The overall yield of acid from 2,5-dichloroacetophenone was 32%.

Method B. [2-[3-(Trifluoromethyl)phenoxy]phenyl]acetic Acid (22). 3-(Trifluoromethyl)phenol (40 g, 0.25 mol) was dissolved in sodium ethoxide solution [prepared from sodium (4.6 g, 0.2 mol) and dry ethanol (125 mL)], and the mixture was evaporated to dryness. 2-Chlorobenzoic acid (13.7 g, 0.1 mol) and copper powder (0.5 g, catalytic quantity) were added, and the stirred mixture was heated at 190 °C for 3 h under an atmosphere of nitrogen. After cooling, the mixture was partitioned between ether and water, and the aqueous layer was separated and acidified with concentrated HCl. The acid solution was then extracted with ether, which was in turn washed with saturated sodium bicarbonate solution. The basic layer was acidified, and the resultant solid was removed by filtration, dried, and crystallized from cyclohexane to give 2-[3-(trifluoromethyl)phenoxy]benzoic acid: yield 13.9 g (49%); mp 86–88 °C; IR (Nujol) ν_{max} 2750, 1690 cm^{-1}.

The acid (13.9 g, 0.049 mol) was heated at 100 °C with thionyl chloride (8.88 g, 0.075 mol) for 2 h. The mixture was then cooled and evaporated to dryness, and the crude acid chloride [yield 14.8 g (100%)] was dissolved in dry ether (50 mL) and added dropwise over 20 min to an ethereal solution of diazomethane [(6.7 g, 0.16 mol) in ether (400 mL)] at room temperature. The solution was stirred overnight and evaporated to give crude diazoketone, which was dissolved in a mixture of dry dioxane (75 mL), silver nitrate solution (22.5 mL, 10%), and 0.88 ammonia solution (37.5 mL) and heated at reflux for 16 h. The resulting mixture was filtered hot, and the filtrate was then evaporated to dryness to give a solid. Crystallization from aqueous ethanol gave 2-[2-[3-(trifluoromethyl)phenoxy]phenyl]acetamide: yield 7.2 g (50%); mp 168–172 °C. Anal. ($C_{15}H_{12}F_3NO_2$) C, H, N.

The amide (4.66 g, 0.016 mol) was hydrolyzed by heating at reflux in a mixture of sodium hydroxide (5.90 g), water (20 mL), and 2-ethoxyethanol (20 mL) for 16 h. The cooled solution was poured into water, which was washed with ether. The aqueous layer was acidified with concentrated HCl, the resulting suspension was extracted with benzene, and the organic layer was dried and evaporated to dryness to give an oil. On suspension of this in water, it crystallized, and the solid was removed by filtration, dried, and crystallized from petroleum ether (bp 40–60 °C) to give **22**: yield 3.6 g (77%); mp 52–54 °C. Anal. ($C_{15}H_{11}F_3O_3$) C, H. The overall yield from 2-chlorobenzoic acid was 19%.

Method C. [2-(2-Chloro-4-nitrophenoxy)phenyl]acetic Acid (24). 3,4-Dichloronitrobenzene (72 g, 0.38 mol) was heated to 160 °C, after which the potassium salt of salicylaldehyde (30 g, 0.19 mol) was added with stirring. The mixture was then heated at 220 °C for 2 h and allowed to cool. The solid mass was partitioned between ether, and water and the organic layer was washed with 2 N sodium hydroxide. The ether layer was dried and evaporated to give an oil, which solidified on trituration with ether to give 2-(2-chloro-4-nitrophenoxy)benzaldehyde: yield 34.3 g (65%); mp 65–67 °C. Anal. ($C_{13}H_8ClNO_4$) C, H, N.

The benzaldehyde (5.55 g, 0.02 mol) was dissolved in dry ethanol (200 mL) and cooled to 8 °C in an ice bath. Sodium borohydride (0.45 g, 0.012 mol) was added portionwise over 0.5 h. The reaction mixture was allowed to warm to room temperature, stirred for 16 h, and then poured onto ice and acidified with concentrated HCl. The resultant solid was removed by filtration, dried, and recrystallized from benzene–petroleum ether (bp 60–80 °C) to give [2-(2-chloro-4-nitrophenoxy)phenyl]methanol: yield 2.3 g (41%); mp 94–96 °C. Anal. ($C_{13}H_{10}ClNO_4$) C, H, N.

The alcohol (8.4 g, 0.03 mol) was stirred at 0–5 °C in a mixture of dry pyridine (2.37 g, 0.03 mol) and dry benzene (100 mL) during the addition of a solution of thionyl chloride (5.0 g, 0.042 mol) in dry benzene (25 mL). After complete addition, the stirred mixture was heated to reflux and kept at this temperature for 16 h. After the mixture was cooled, the pyridine hydrochloride was removed by filtration, and the filtrate was evaporated to dryness. The resulting crude product was crystallized from methanol to give 2-(2-chloro-4-nitrophenoxy)benzyl chloride: yield 7.5 g (84%); mp 92–94 °C. Anal. ($C_{13}H_9Cl_2NO_3$) C, H, N.

A mixture of the benzyl chloride (6.0 g, 0.02 mol), sodium cyanide (1.0 g, 0.02 mol), water (15 mL), and ethanol (50 mL) was heated under reflux for 24 h. The mixture was cooled and partitioned between water and ether, and the organic layer was dried and evaporated to give a crude product, which was crystallized from methanol to give [2-(2-chloro-4-nitrophenoxy)phenyl]-acetonitrile: yield 2.8 g (50%); mp 111–114 °C; IR (Nujol) ν_{max} 2250, 1550 cm^{-1}.

The nitrile (1.0 g, 0.0035 mol) was hydrolyzed by heating under reflux in a solution of concentrated HCl (5 mL) and acetic acid (15 mL) for 24 h. The mixture was poured into water, and the resulting solid was removed by filtration and crystallized from

methanol to give **24**: yield 0.51 g (47%); mp 182–185 °C. Anal. ($C_{14}H_{10}ClNO_5$) C, H, N. The overall yield from salicylaldehyde was 5.3%.

Method D. [2-(2,4-Dichlorophenoxy)phenyl]acetic Acid (5). Methyl (2-hydroxyphenyl)acetate (1.66 g, 0.01 mol), 2,4-dinitrofluorobenzene (1.86 g, 0.01 mol), and triethylamine (1.02 g, 0.01 mol) were mixed in acetone (20 mL), and the solution was heated under reflux for 1 h. The acetone was then evaporated, and the residue was treated with 2 N HCl and extracted into ether. The extracts were washed with water, dried, and evaporated to give crude methyl [2-(2,4-dinitrophenoxy)phenyl]acetate, which was crystallized from methanol to give a pure sample: yield 2.64 g (80%); mp 88–89 °C. Anal. ($C_{15}H_{12}N_2O_7$) C, H, N.

The dinitro ester (2.18 g, 0.0066 mol) was hydrogenated at atmospheric pressure in ethyl acetate (75 mL) over 10% palladium on carbon. After the theoretical uptake of hydrogen was complete, the catalyst was removed by filtration, and the solution was evaporated to dryness to give a solid. Crystallization from ethyl acetate–petroleum ether (bp 60–80 °C) gave methyl [2-(2,4-diaminophenoxy)phenyl]acetate: yield 1.48 g (82%); mp 144–145 °C. Anal. ($C_{15}H_{16}N_2O_3$) C, H, N.

The diamino ester (1.36 g, 0.05 mol) in a solution of acetic acid (8 mL) was stirred and cooled to 0 °C, and a solution of sodium nitrite (0.76 g, 0.011 mol) in concentrated H_2SO_4 (5 mL) was added dropwise over 0.5 h. Freshly prepared cuprous chloride (1.2 g, 0.012 mol) was dissolved in concentrated HCl (5 mL) and stirred at 5 °C during the addition of the diazonium solution (30 min). The mixture was allowed to reach room temperature over a further 1 h and then heated at 80 °C for 30 min. The mixture was diluted with water and extracted with ether. The organic extracts were washed with saturated sodium bicarbonate solution, and the aqueous washings were acidified with concentrated HCl and then extracted with ether. The ether layer was washed with water, dried, and evaporated to give a solid residue, which was crystallized successively from petroleum ether (bp 60–80 °C), aqueous methanol (2 times), and ethyl acetate–petroleum ether (bp 60–80 °C) (2 times) to give **5**: yield 0.36 g (23%); mp 135–137 °C. Anal. ($C_{14}H_{10}Cl_2O_3$) C, H. The overall yield from methyl 2-hydroxyphenylacetate was 15%.

Simple Derivatives of [2-(2,4-Dichlorophenoxy)phenyl]acetic Acid (5). The ethyl ester **118** and primary amide **119** were prepared by conventional means from the corresponding acid **5**. The preparation of other derivatives is described in full.

2-[2-(2,4-Dichlorophenoxy)phenyl]propionic Acid (120). Sodium (0.51 g, 0.022 mol) was dissolved in ethanol (12 mL) and added to a stirred solution of ethyl [2-(2,4-dichlorophenoxy)phenyl]acetate (**118**; 6.5 g, 0.02 mol) in diethyl carbonate (50 mL) at room temperature. The solution was then heated to 140 °C, and an ethanol/diethyl carbonate mixture was allowed to distill off. When pure diethyl carbonate began distilling, the reaction was allowed to cool and poured into a mixture of concentrated HCl (100 mL) and ice (100 mL). The mixture was then partitioned between water and ether, and the organic layer was separated, dried, and evaporated to give an oil, which was distilled under reduced pressure. Ethyl 2-carbethoxy-2-[2-(2,4-dichlorophenoxy)phenyl]acetate was collected as a colorless oil: yield 2.8 g (35%); bp 177 °C (0.25 mm); IR (thin film) ν_{max} 1745 cm^{-1}.

The malonate (19.9 g, 0.05 mol) in ethanol (40 mL) was added to a solution of sodium (1.15 g, 0.5 mol) in ethanol (100 mL), and the mixture was stirred at room temperature during the addition of methyl iodide (35.5 g, 0.25 mol) over 10 min. The resulting solution was heated under reflux for 2 h. After reflux for 1 h, a further portion (10 g) of methyl iodide was added. The solution was evaporated to dryness, and the residue was partitioned between water and ether. The ether layer was washed with saturated sodium bicarbonate solution and then dried and evaporated to give crude ethyl 2-carbethoxy-2-[2-(2,4-dichlorophenoxy)phenyl]propionate (18.6 g, 91%) as an oil.

The propionate (6.6 g, 0.045 mol) was heated at reflux in a mixture of water (20 mL), ethanol (24 mL), and sodium hydroxide (3.0 g, 0.075 mol) for 3 h. The mixture was diluted with water, acidified, and extracted with ether. The ether layer was dried and evaporated to give crude 2-carboxy-2-[2-(2,4-dichlorophenoxy)phenyl]propionic acid: yield 6.4 g (40%). Decarboxylation was effected by heating the malonate at 180–200 °C for 1 h under an atmosphere of nitrogen. After cooling, the residual oily solid was triturated with hexane, and the resulting solid was removed by filtration and crystallized from hexane to give a pure sample of **120**: yield 2.1 g (37%); mp 96–98 °C. Anal. ($C_{15}H_{12}Cl_2O_3$) C, H. The overall yield from ethyl [2-(2,4-dichlorophenoxy)phenyl]acetate was 4.7%.

2-(2,4-Dichlorophenoxy)benzoic Acid (121). This was prepared via the procedure described for the synthesis of 2-[3-(trifluoromethyl)phenoxy]benzoic acid in method B: yield 30%; mp 159–162 °C. Anal. ($C_{13}H_8Cl_2O_3$) C, H.

[2-(2,4-Dichlorophenoxy)phenyl]glyoxylic Acid (122). 2-(2,4-Dichlorophenoxy)acetophenone (110.8 g, 0.4 mol; prepared by the general procedure described in method A) was dissolved in a mixture of dioxane (300 mL) and water (300 mL) and stirred at room temperature during the addition of bromine (20 mL, 0.4 mol). After addition the solution was poured into an equal volume of water and extracted with ether. The ether layer was washed with water, dried, and evaporated to give a solid, which was crystallized from ethanol to give 2-(2,4-dichlorophenoxy)phenacyl bromide: yield 90.5 g (63%); mp 73–76 °C; IR (Nujol) ν_{max} 1715 cm^{-1}.

The bromide (18.0 g, 0.05 mol) was added quickly to a boiling solution of selenium dioxide (5.6 g, 0.05 mol) in methanol (50 mL), and the mixture was heated under reflux for 16 h and then allowed to cool. The methanol was decanted from the precipitated selenium and evaporated to dryness. The resulting oil was partitioned between water and ether, and the ether layer was washed with 2 N HCl, dried, and evaporated to give crude methyl [2-(2,4-dichlorophenoxy)phenyl]glyoxylate: yield 15.9 g (97%); IR (Nujol) ν_{max} 1710, 1670 cm^{-1}.

The glyoxylic ester (15.9 g, 0.049 mol) was heated under reflux in a mixture of aqueous sodium carbonate (100 mL, 10%) and ethanol (25 mL) for 14 h. After evaporation, the residue was partitioned between water and ether, and the aqueous layer was washed with ether and acidified. The aqueous layer was extracted with ether, which was dried and evaporated to give the required acid. Crystallization from carbon tetrachloride gave **122**: yield 7.4 g (49%); mp 109–112 °C. Anal. ($C_{14}H_8Cl_2O_4$) C, H. Overall yield from 2-(2,4-dichlorophenoxy)acetophenone was 30%.

2-[2-(2,4-Dichlorophenoxy)phenyl]ethanol (123). [2-(2,4-Dichlorophenoxy)phenyl]acetic acid (**5**; 20.0 g, 0.0675 mol) was dissolved in dry ether (200 mL) and added dropwise as fast as reflux would allow to a stirred suspension of lithium aluminium hydride (4.12 g, 0.135 mol) in dry ether (100 mL). The suspension was then stirred and heated at reflux for 2 h. After the suspension was cooled in an ice bath, water was added cautiously, and the ethereal layer was washed with 2 N NaOH and water, dried, and evaporated. The resulting oil was distilled under reduced pressure to give **123**: yield 11.7 g (61%); bp 168–170 °C (0.5 mm). Anal. ($C_{14}H_{12}Cl_2O_2$) C, H.

3-[2-(2,4-Dichlorophenoxy)phenyl]propionic Acid (124). The propionic acid **124** was synthesized via the Arndt–Eistert procedure described in method B, starting with [2-(2,4-dichlorophenoxy)phenyl]acetic acid (**5**). The overall yield from the acetic acid was 29%, mp 111–114 °C. Anal. ($C_{15}H_{12}Cl_2O_3$) C, H.

2-(2,4-Dichlorophenoxy)cinnamic Acid (125). A mixture of 2-bromobenzaldehyde (37.0 g, 0.2 mol), sodium 2,4-dichlorophenoxide (37.0 g, 0.23 mol), 2,4-dichlorophenol (32.6 g, 0.23 mol), and copper catalyst (2.0 g) was heated and stirred at 110 °C for 48 h under nitrogen. After the mixture was cooled, the resultant solid was partitioned between water and ether, and the ether layer was washed with 2 N NaOH and water, dried, and evaporated to give crude 2-(2,4-dichlorophenoxy)benzaldehyde as a solid: yield 23.3 g (44%); IR (Nujol) ν_{max} 1695 cm^{-1}.

A mixture of the aldehyde (5.34 g, 0.02 mol), malonic acid (4.16 g, 0.04 mol), pyridine (40 mL), and piperidine (0.5 mL) was heated under reflux for 5 h. After the mixture was cooled, the liquid was poured into water (200 mL), and the mixture was then acifidied with concentrated HCl. The resulting crystalline solid was removed by filtration, dried, and crystallized from ethyl methyl ketone to give **125**: yield 1.96 g (32%); mp 222–224 °C. Anal. ($C_{15}H_{10}Cl_2O_3$) C, H.

[2-(2,4-Dichlorophenoxy)phenyl]acetohydroxamic Acid (126). A mixture of hydroxylamine hydrochloride (14.1 g, 0.2025 mol) dissolved in the minimum of hot water and sodium hydroxide (8.1 g, 0.2025 mol) was stirred rapidly at room temperature while [2-(2,4-dichlorophenoxy)phenyl]acetyl chloride (21.3 g, 0.0675 mol; prepared by the general procedure described in method B) in benzene (100 mL) was added dropwise. A pink solid was pre-

cipitated, which was removed by filtration and crystallized from methanol to give **126**: yield 14.4 g (68%); mp 142–144 °C. Anal. ($C_{14}H_{11}Cl_2NO_3$) C, H.

A number of relatively inaccessible acetophenones were synthesized successfully by a route that employed a little-used reaction described by Beech;[16] the synthesis of 5-*n*-butyl-2-chloroacetophenone is described.

5-*n*-Butyl-2-chloroacetophenone (Scheme III). *n*-Butanoyl chloride (30 g, 0.28 mol) was added gradually to a stirred mixture of chlorobenzene (83 g, 0.31 mol) and freshly prepared aluminium chloride (35 g, 0.26 mol). The temperature was maintained at 40–60 °C for 4 h, after which the product was poured onto ice and extracted into diethyl ether. The ether extracts were washed with 2 N sodium hydroxide and water, dried, and evaporated to give crude 4-*n*-butanoylchlorobenzene, which was purified by distillation at reduced pressure: yield 37.2 g (73%): bp 145 °C (30 mm); IR (thin film) ν_{max} 1695 cm^{-1}. This material gradually solidified on standing.

The butanoylchlorobenzene (20.0 g, 0.11 mol) was ground up and added in portions over 20–30 min to fuming HNO_3 (110.5 g), keeping the temperature at −15 °C. After the addition, the mixture was cooled to −30 °C and poured onto ice (1 kg). The solid that precipitated was removed by filtration and washed well with water. Trituration with ice-cold petroleum ether (bp 60–80 °C) gave 4-*n*-butanoyl-2-nitrochlorobenzene: yield 14.2 g (57%); IR (Nujol) ν_{max} 1685, 1540, 1340 cm^{-1}.

The nitrochlorobenzene (92 g, 0.41 mol) was stirred and heated under reflux for 2 h with a mixture of zinc dust (197.5 g, 3.1 mol), ammonium chloride (29.3 g, 0.22 mol), ethanol (1462 mL), and water (146.2 mL). On cooling, the zinc was removed by filtration, and the filtrate was poured into water (12 L). The 2-amino-4-*n*-butanoylchlorobenzene that precipitated was removed by filtration and dried: yield 66 g (81%); IR (Nujol) ν_{max} 3450, 3300, 1700 cm^{-1}.

The amine (543 g, 2.7 mol) was heated under reflux with a mixture of potassium hydroxide (515 g, 9.2 mol), hydrazine hydrate (417 mL, 8.8 mol), and digol (3720 mL) for 1 h. Low-boiling material was allowed to distill until the temperature reached 195 °C. The reaction was maintained at this temperature for 4 h before pouring into water (30 L) and extracting with ether. The ether extracts were combined, washed with water, dried, and evaporated to give a brown oil, which was distilled under reduced pressure to give 2-amino-4-*n*-butylchlorobenzene: yield 349.6 g (70.5%); bp 81–82 °C (0.25 mm); IR (thin film) ν_{max} 3430, 3310 cm^{-1}.

A solution of sodium nitrite (27.5 g, 0.4 mol) in water (31.7 mL) was added dropwise at 0–5 °C to a rapidly stirred suspension of 2-amino-4-*n*-butylchlorobenzene (60 g, 0.3 mol) in a mixture of concentrated HCl (72.2 mL) and water (284 mL). A small amount of tarry material was removed before sodium acetate (16.2 g, 0.2 mol) was added to the solution, which was then introduced dropwise, under the surface, to a stirred mixture of acetaldoxime (28.5 g, 0.48 mol), cupric sulfate (15.8 g, 0.1 mol), anhydrous sodium sulfate (2.5 g, 0.018 mol), anhydrous sodium acetate (121 g, 1.5 mol), and water (253 mL) at 10–15 °C. After the addition, the mixture was stirred for a further 1 h, and then concentrated HCl was added to pH 7, followed by a further portion of concentrated HCl (292 mL). The resulting solution was heated under reflux for 3 h, after which it was steam distilled, and the volatile product was extracted into ether. The organic layer was dried and evaporated to give an oil, which was distilled under reduced pressure to give 5-*n*-butyl-2-chloroacetophenone: yield 29.7 g (43%); bp 113 °C (0.16 mm); NMR (CCl_4) δ 0.7–1.9 (7 H, m, $CH_2CH_2CH_3$), 2.4–2.8 (5 H, m, CH_2Ar, $COCH_3$) [2.55 (s, $COCH_3$)], 7.0–7.4 (3 H, m, ArH). Addition of tris(dipivaloylmethanato)-europium induces contact shifts of the acetyl methyl group and the aromatic protons. The latter form an analyzable pattern, which confirms the 1,2,4-substitution pattern.

Acknowledgment. The authors thank Pat Southwell and Keith Jones for their expert technical assistance.

Registry No. **1**, 25563-02-4; **2**, 81682-40-8; **3**, 25563-04-6; **4**, 34645-85-7; **5**, 34645-84-6; **6**, 34645-86-8; **7**, 34645-87-9; **8**, 34645-88-0; **9**, 86308-28-3; **10**, 86308-29-4; **11**, 86308-30-7; **12**, 34643-00-0; **13**, 34645-89-1; **14**, 34645-90-4; **15**, 34643-08-8; **16**, 34645-91-5; **17**, 34645-92-6; **18**, 86308-31-8; **19**, 86308-32-9; **20**, 86308-33-0; **21**, 86308-34-1; **22**, 86308-35-2; **23**, 86308-36-3; **24**, 86308-37-4; **25**, 86308-38-5; **26**, 86308-39-6; **27**, 86308-40-9; **28**, 86308-41-0; **29**, 70958-20-2; **30**, 86308-42-1; **31**, 86308-43-2; **32**, 57388-57-5; **33**, 34665-03-7; **34**, 34665-04-8; **35**, 86308-44-3; **36**, 34645-93-7; **37**, 34645-94-8; **38**, 34645-95-9; **39**, 86308-45-4; **40**, 36467-35-3; **41**, 34645-96-0; **42**, 86308-46-5; **43**, 86308-47-6; **44**, 86308-48-7; **45**, 86308-49-8; **46**, 86308-50-1; **47**, 86308-51-2; **48**, 86308-52-3; **49**, 86308-53-4; **50**, 86308-54-5; **51**, 34665-05-9; **52**, 34642-96-1; **53**, 34645-97-1; **54**, 34642-98-3; **55**, 34643-03-3; **56**, 34645-79-9; **57**, 34643-09-9; **58**, 34645-80-2; **59**, 34643-10-2; **60**, 34643-11-3; **61**, 34665-07-1; **62**, 34643-12-4; **63**, 34643-13-5; **64**, 34645-82-4; **65**, 34643-14-6; **66**, 34643-15-7; **67**, 34643-16-8; **68**, 34643-17-9; **69**, 34643-18-0; **70**, 34639-50-4; **71**, 86308-55-6; **72**, 86308-56-7; **73**, 86308-57-8; **74**, 34642-97-2; **75**, 81682-42-0; **76**, 34646-01-0; **77**, 86308-58-9; **78**, 34643-05-5; **79**, 86308-59-0; **80**, 34645-98-2; **81**, 34643-02-2; **82**, 34643-19-1; **83**, 86308-60-3; **84**, 34643-06-6; **85**, 34643-04-4; **86**, 34645-83-5; **87**, 34645-99-3; **88**, 34646-00-9; **89**, 86308-61-4; **90**, 34646-02-1; **91**, 34642-99-4; **92**, 34665-06-0; **93**, 34643-07-7; **94**, 34643-01-1; **95**, 77172-79-3; **96**, 86308-62-5; **97**, 86308-63-6; **98**, 86308-64-7; **99**, 86308-65-8; **100**, 86308-66-9; **101**, 86308-67-0; **102**, 86308-68-1; **103**, 86308-69-2; **104**, 86308-70-5; **105**, 86308-71-6; **106**, 86308-72-7; **107**, 86308-73-8; **108**, 86308-74-9; **109**, 86308-75-0; **110**, 86308-76-1; **111**, 86308-77-2; **112**, 86308-78-3; **113**, 86308-79-4; **114**, 86308-80-7; **115**, 86308-81-8; **116**, 86308-82-9; **117**, 86308-83-0; **118**, 86308-84-1; **119**, 86308-85-2; **120**, 36480-65-6; **121**, 86308-86-3; **122**, 86308-87-4; **123**, 86308-88-5; **124**, 86308-89-6; **125**, 86308-90-9; **126**, 86308-91-0; **127**, 86308-92-1; 2,5-dichloroacetophenone, 2476-37-1; sodium 2,4-dichloro-5-methylphenoxide, 86308-93-2; 2,4-dichloro-5-methylphenol, 1124-07-8; 2-(2,4-dichloro-5-methylphenoxy)-5-chloroacetophenone, 34643-20-4; [2-(2,4-dichloro-5-methylphenoxy)-5-chlorophenyl]thioacetomorpholide, 34643-21-5; 2-[3-(trifluoromethyl)phenoxy]benzoic acid, 6641-59-4; 2-[2-[3-(trifluoromethyl)phenoxy]phenyl]acetamide, 86308-94-3; 2-(2-chloro-4-nitrophenoxy)benzaldehyde, 86308-95-4; [2-(2-chloro-4-nitrophenoxy)phenyl]methanol, 86308-96-5; 2-(2-chloro-4-nitrophenoxy)benzyl chloride, 86308-97-6; [2-(2-chloro-4-nitrophenoxy)-phenyl]acetonitrile, 86308-98-7; methyl (2-hydroxyphenyl)acetate, 22446-37-3; 2,4-dinitrofluorobenzene, 70-34-8; methyl [2-(2,4-dinitrophenoxy)phenyl]acetate, 86308-99-8; methyl [2-(2,4-diaminophenoxy)phenyl]acetate, 86309-00-4; ethyl 2-carbethoxy-2-[2-(2,4-dichlorophenoxy)phenyl]acetate, 34643-24-8; ethyl 2-carbethoxy-2-[2-(2,4-dichlorophenoxy)phenyl]propionate, 86309-01-5; 2-carboxy-2-[2-(2,4-dichlorophenoxy)phenyl]propionic acid, 86309-02-6; 2-(2,4-dichlorophenoxy)phenacyl bromide, 86309-03-7; methyl [2-(2,4-dichlorophenoxy)phenyl]glyoxylate, 86309-04-8; 2-(2,4-dichlorophenoxy)acetophenone, 86309-05-9; 2-(2,4-dichlorophenoxy)benzaldehyde, 86309-06-0; [2-(2,4-dichlorophenoxy)phenyl]acetyl chloride, 70458-41-2; chlorobenzene, 108-90-7; 4-*n*-butanoylchlorobenzene, 4981-63-9; 4-*n*-butanoyl-2-nitrochlorobenzene, 66353-38-6; 2-amino-4-*n*-butanoylchlorobenzene, 2001-00-5; 2-amino-4-*n*-butylchlorobenzene, 2000-95-5; 5-*n*-butyl-2-chloroacetophenone, 86309-07-1; 3,4-dichloronitrobenzene, 99-54-7; 3-(trifluoromethyl)phenol, 98-17-9; 2-chlorobenzoic acid, 118-91-2; 2-[3-(trifluoromethyl)phenoxy]benzoyl chloride, 86309-08-2; potassium salicylaldehyde, 33838-32-3; potassium 5-nitrosalicylaldehyde, 86309-09-3; 2,4-dichlorophenol, 120-83-2; 2-bromobenzaldehyde, 6630-33-7; sodium 2,4-dichlorophenoxide, 3757-76-4; *n*-butanoyl chloride, 141-75-3; acetaldoxime, 107-29-9.