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

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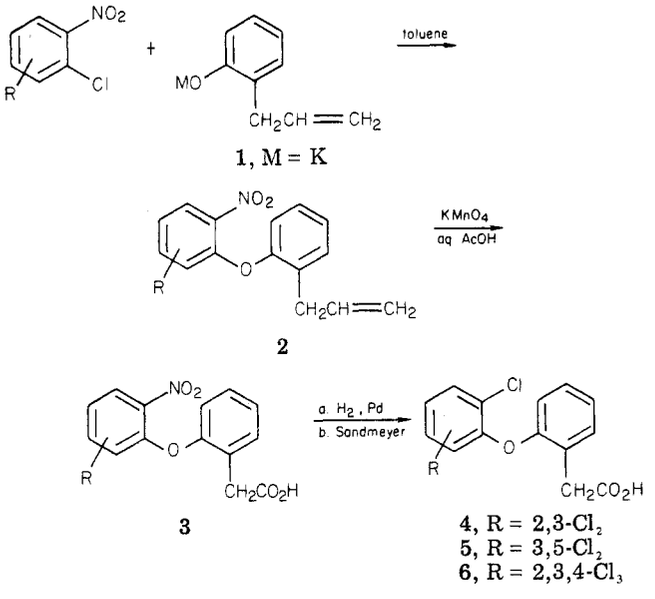
A number of polychlorinated (phenoxyphenyl)acetic acids were prepared as close structural analogues of the antiinflammatory compound fenclofenac, [2-(2,4-dichlorophenoxy)phenyl]acetic acid. Increased potency was shown in several of these compounds, in particular, [2-(2,3,5,6-tetrachlorophenoxy)phenyl]acetic acid (**8**), which was 40 times more potent than fenclofenac in the adjuvant-induced arthritis screen. In further tests it was found to be equipotent with indomethacin but with a much reduced incidence of acute toxicity (LD_{50} and ulcerogenicity). On chronic dosing, however, serious toxicity problems arose (including anemia, neutrophilia, and severe peritonitis), and this led to the abandonment of further work on the compound. Three further analogues were prepared containing NH, S, and SO moieties bridging the phenyl rings. Although the NH compound bore a very close structural resemblance both to the above O-linked compound and the potent antiinflammatory drug diclofenac, [2-[(2,6-dichlorophenyl)imino]phenyl]acetic acid, it showed low activity in primary screens. Similarly, neither the S- or SO-bridged analogues had potencies that approached that of **8**.

Following the discovery of the useful antiinflammatory profile of [2-(2,4-dichlorophenoxy)phenyl]acetic acid (fenclofenac),[1] a search for compounds of greater potency was initiated. It was observed that some trichloro- and tetrachloro-substituted derivatives, particularly those containing chlorine atoms in the 2-, 3-, and 6-positions, possessed increased potency. The results of pharmacological investigations eventually led to the selection of [2-(2,3,5,6-tetrachlorophenoxy)phenyl]acetic acid (**8**) for further study. The introduction of other heteroatoms to replace oxygen in the diphenyl ether linkage of **8** was studied, and of particular interest was the NH-bridged compound **13**, a close structural analogue of the potent antiinflammatory drug [2-(2,6-dichlorophenylimino)-phenyl]acetic acid (diclofenac).

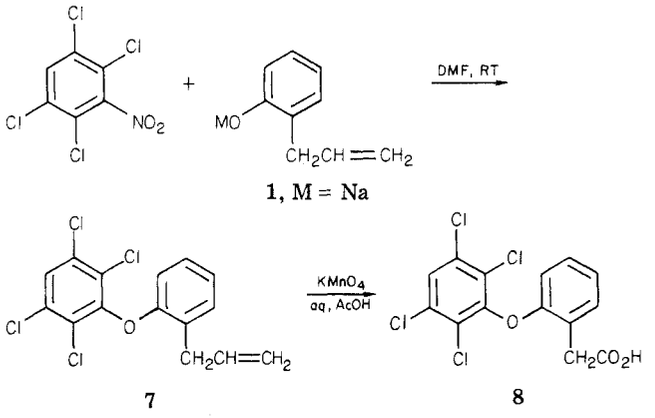
Chemistry. Novel synthetic routes were devised in the preparation of the (phenoxyphenyl)acetic acids, and these are described in Schemes I and II. Three phenylacetic acids were prepared as described in Scheme I by the reaction of the potassium salt of 3-(2-hydroxyphenyl)prop-1-ene (**1**, M = K) with the appropriate nitropoly(halo)-benzene. Potassium permanganate oxidation of the resultant diphenyl ether **2** gave the acid **3**, and hydrogenation of the nitro group, followed by a Sandmeyer reaction,[2] gave the required phenylacetic acids **4**–**6**.

Reaction of the sodium salt of 3-(2-hydroxyphenyl)-prop-1-ene (**1**, M = Na, Scheme II) with 2,3,5,6-tetrachloronitrobenzene in dimethylformamide (DMF) gave the diphenyl ether **7** in good yield as a crystalline solid, which could be filtered from the reaction mixture. Oxidation gave the required acid **8**. This nitro-group displacement from 2,3,5,6-tetrachloronitrobenzene has been reported previously in reactions with substituted catechols to give polychlorinated dibenzo-*p*-dioxins[3] and also with a number of small nucleophiles, including hydrosulfide,[4] methoxide,[5] fluoride,[6] and ammonia.[7] The effect of solvent on the reaction was critical. In toluene, for instance, approximately 95% of the product arose from displacement of the 2-chlorine atom, in tetrahydrofuran the ratio of chloro to nitro displacement was 1:1, and in DMF greater than 90% of the product was due to nitro-group displacement.

Scheme I



Scheme II



The preparation of the hetero-bridged analogues of the phenylacetic acid **8** is described in Schemes III and IV. The sulfur-bridged compound **10** was synthesized in one step by the reaction of the disodium salt of (2-mercaptophenyl)acetic acid **9** with 2,3,5,6-tetrachloronitrobenzene in DMF (Scheme III), and it was later found that the oxygen-bridged analogue **8** could also be made in a similar manner. Oxidation of **10** with acidic hydrogen peroxide

(1) Atkinson, D. C.; Leach, E. C. *Agents Actions* **1976**, *5*, 657.
(2) Mowry, D. T. *Chem. Rev.* **1948**, *42*, 213.
(3) Gray, A. P.; Cepa, S. P.; Solomon, I. J.; Aniline, O. *J. Org. Chem.* **1976**, *41*, 2435.
(4) Coralski, C. T.; Burk, G. A.; Pews, R. G. U.S. Patent 3 923 905 1975.
(5) Berkmans, V. S. F.; Holleman, A. F. *Recl. Trav. Chim. Pays-Bas* **1925**, *44*, 851.
(6) Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 6034.
(7) Peters, A. T.; Rowe, F. M.; Stead, D. M. *J. Chem. Soc.* **1943**, 576.

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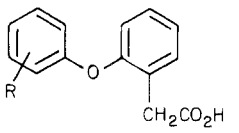
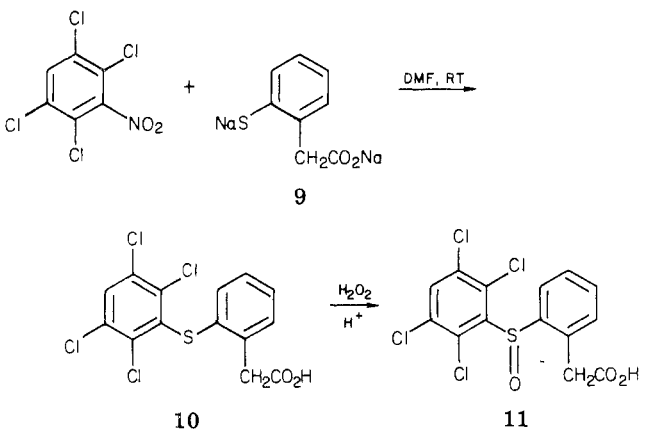
Table I. Pharmacological Data on Compounds 4-6 and 8 and a Standard Antiinflammatory Drug, Fenclofenac



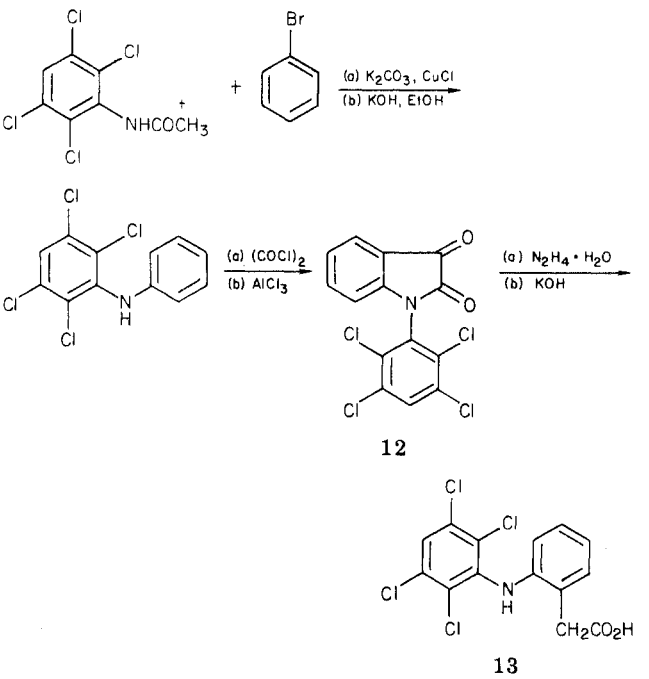
		adjuvant-induced polyarthritis				
compd	R	dose, mg/kg po	% inhibn	P^a vs. controls	potency rel[b,c] to fenclofenac	min ulcerogenic[c] dose (MUD), mg/kg po (24 h)
fenclofenac	2,4-Cl_2	100	35	<0.001	1	400-800
4	2,3,6-Cl_3	10[d]	51	<0.001	14	200-400
5	2,3,5-Cl_3	10[d]	21	<0.001	1.5	ND
6	2,3,4,6-Cl_4	10[d]	43	<0.001	8	ND
8	2,3,5,6-Cl_4	10[e]	44	<0.001	40	100-200
8		2	38	<0.001		

[a] The statistical significance of the difference between experimental groups was calculated by using the two-tailed Student's *t* test. [b] Potency ratios were determined by using a standard parallel line assay method. [c] Average of at least three determinations. [d] Significant toxicity at 100 mg/kg. [e] Showed some toxicity at this dose level; ND, not determined.

Scheme III



Scheme IV



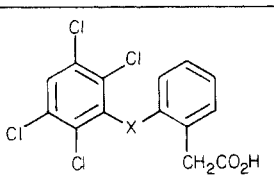
gave the required sulfoxide 11.

[[(2,3,5,6-Tetrachlorophenyl)imino]phenyl]acetic acid (13) was prepared by a route similar to that used in the synthesis of the 2,6-dichloro analogue, diclofenac;[8] this involved the preparation and reductive ring opening of the isatin 12 as described in Scheme IV.

Pharmacology. Assessment of anitinflammatory activity was carried out by using the adjuvant-induced arthritis test in rats as the primary screen.[1] In the event of interesting activity being shown, the compounds were then subjected to a secondary evaluation, which included the measurement of potency relative to a standard compound (in this case, fenclofenac) and a determination of the minimum ulcerogenic dose.[1]

Previous results[9] have shown that compounds that retain the 2,4-dichloro substitution pattern of fenclofenac but that also include a third chlorine atom in the chlorine-containing ring, e.g., [2-(2,4,5-trichlorophenoxy)phenyl]-acetic acid and [2-(2,4,6-trichlorophenoxy)phenyl]acetic acid, have reduced potency compared to fenclofenac. Also, both the 2-(2,3-dichlorophenoxy) and 2-(2,6-dichlorophenoxy) compounds have similarly reduced potencies. The activity shown by the 2,3,6-trichloro compound 4 (Table I) was therefore surprising. The importance of the 2,3,6-trichloro substitution patern was highlighted by the relatively low potency of the 2,3,5-trichloro analogue 5. It also appeared important that the 4-position remained unsubstituted, since the 2,3,4,6-tetrachloro compound 6 showed approximately half the potency of the trichlorinated analogue 4 and was substantially less potent than the 2,3,5,6-tetrachloro derivative 8, which was found

Table II. Effect of Compounds 8, 10, 11, and 13 on Adjuvant-Induced Polyarthritis in Rats



		adjuvant-induced polyarthritis			
no.	X	dose, mg/kg po	% inhibn	P^a vs. control	potency rel[b] to 8
8	O	0.08	38	<0.001	1
10	S	0.08	22	<0.01	0.21[c]
11	SO	0.08	19	NS	ND
13	NH	0.08	18	NS	ND

[a-c] See corresponding footnotes in Table I; ND, not determined; NS not significant.

(8) Netherlands Patent 68 17965, 1967.
(9) Atkinson, D. C.; Godfrey, K. E.; Meek, B.; Saville, J. F.; Stillings, M. R. *J. Med. Chem.*, preceding paper in this issue.

Table III. Comparison of Compound 8 with Indomethacin

compd	rel potency in adjuvant-induced polyarthritis	LD_{50}, mg/kg po	MUD (24 h), mg/kg po
indomethacin	1	19.8[a]	1.25-5[a]
8	1.2[b]	303[a]	100-200[a]

[a] See footnote c, Table I. [b] Average of two determinations.

to be at least 40 times more potent than fenclofenac. This remarkable increase in activity prompted the synthesis and testing of the hetero-bridged analogues **10**, **11**, and **13**. The results, however, were disappointing (Table II), particularly so for the NH-bridged compound **13**, which had structural similarities both to **8** and to the potent antiinflammatory drug diclofenac. The most promising compound, the sulfur-bridged derivative **10**, which showed significant activity at 0.08 mg/kg in primary screening, had only 0.21 times the activity of **8** in a relative potency determination.

The two most potent compounds in the oxygen-bridged series, **4** and **8**, were subsequently tested for their ulcerogenic potential. Although both were substantially more ulcerogenic than fenclofenac (Table I), their overall profiles were favorable, particularly compound **8**, which had a therapeutic ratio 10 times that of fenclofenac; [2-(2,3,5,6-tetrachlorophenoxy)phenyl]acetic acid (**8**) was therefore chosen for further evaluation.

In comparison with indomethacin, **8** was of comparable potency in the adjuvant arthritis test but was substantially less toxic (LD_{50}) and ulcerogenic (Table III). However, toxicity appeared on chronic administration. After rats were dosed for 14 days at 50 mg/kg, compound **8** killed seven out of eight animals, apparently from severe peritonitis. Surprisingly, at the intermediate (7 mg/kg) and low (1 mg/kg) dose levels, there were no deaths and no overt signs of toxicity. Unfortunately, a longer term trial (1 month) in rats and baboons revealed a number of toxicity problems. In both rats and baboons, significant toxicity appeared at a relatively low dose (10 mg/kg), which was manifested by anemia and neutrophilia; severe peritonitis was also noted in a number of animals. As a result, further work on this compound was terminated. The possibility that the 2,3,6-trichloroanalogue **4** might possess a more encouraging profile was considered but was not pursued due to its relatively poor therapeutic ratio and the probability that similar long-term toxicological problems would be encountered.

Experimental Section

Pharmacology. Acute Toxicity. Median lethal dose (LD_{50}) was calculated by the method of Finney,[10] using 10 rats per dose.

Adjuvant-Induced Polyarthritis and Minimum Ulcerogenic Dose (MUD). Both tests were conducted according to the method of Atkinson and Leach.[1] Groups of seven rats were used in the adjuvant-arthritis experiments, and groups of ten rats were used for MUD determinations.

Chemistry. Melting points were determined in a Buchi apparatus in glass capillary tubes and are uncorrected. IR, NMR, and MS spectra were recorded on Perkin-Elmer 700, Varian Associates T-60, and LKB-2091 instruments, respectively, and were consistent with the assigned structures. Elemental analyses for all new compounds were within ±0.4% of the theoretical values.

The following method is common to the preparation of three compounds, [2-(2,3,6-trichlorophenoxy)phenyl]acetic acid (**4**), [2-(2,3,5-trichlorophenoxy)phenyl]acetic acid (**5**), and [2-(2,3,4,6-tetrachlorophenoxy)phenyl]acetic acid (**6**), and is exemplified by the preparation of the 2,3,6-trichloro compound **4**.

[2-(2,3,6-Trichlorophenoxy)phenyl]acetic Acid (4). A mixture of the potassium salt of 3-(2-hydroxyphenyl)prop-1-ene (**1**, M = K; 69.2 g, 0.4 mol), 2,3,4-trichloronitrobenzene (90.0 g, 0.4 mol), and toluene (100 mL) was heated with stirring at 110 °C under nitrogen for 4 h. After cooling, the mixture was poured into water, which was then extracted with ethyl acetate. The extracts were washed with 2 N sodium hydroxide solution and water, dried, and evaporated to dryness to give a brown oil. Purification with column chromatography [Kieselgel/diethyl ether/petroleum ether (bp 40–60 °C)] gave pure 3-[2-(2,3-dichloro-6-nitrophenoxy)phenyl]prop-1-ene (**2**, R = 2,3-Cl_2): yield 61.0 g (47%); IR ($CHBr_3$) ν_{max} 1630 (w), 1540 (s), 1350 (s) cm^{-1}.

The propene **2** (R = 2,3-Cl_2; 61.0 g, 0.188 mol) was dissolved in a mixture of glacial acetic acid (900 mL) and water (300 mL) to which potassium permanganate (148.7 g, 0.94 mol) was added portionwise over 3.5 h at 0–5 °C. After stirring for 1.5 h at room temperature, the mixture was poured into water, and solid sodium metabisulfite was added until all the precipitated manganese dioxide had been removed. The solution was extracted with ethyl acetate, and the organic layer was washed with water, dried, and evaporated to give crude [2-(2,3-dichloro-6-nitrophenoxy)-phenyl]acetic acid (**3**, R = 2,3-Cl_2) as a yellow solid. Crystallization from ethanol–water gave a pure sample: yield 28.0 g (43%); mp 162–163 °C. Anal. ($C_{14}H_9Cl_2NO_5$) C, H, N.

The nitro acid **3** (R = 2,3-Cl_2; 23.0 g, 0.067 mol) was dissolved in a mixture of ethanol (1500 mL) and palladium on charcoal (10%, 1.0 g) and hydrogenated under a pressure of 3 atm at room temperature. After 3 h, the catalyst was removed by filtration, and the mixture was evaporated to give [2-(6-amino-2,3-dichlorophenoxy)phenyl]acetic acid: yield 18.0 g (86%); mp 198–202 °C; IR ($CHBr_3$) ν_{max} 3475 (w), 3385 (w), 1700 (s) cm^{-1}.

The amino acid (18.0 g, 0.058 mol) was dissolved in glacial acetic acid (40 mL) and added to a mixture of sodium nitrite (8.88 g, 0.13 mol) in concentrated H_2SO_4 (57.7 mL) dropwise with stirring over 30 min at 12.5 °C. After stirring for 1 h at 10 °C, the mixture was poured into a solution of cuprous chloride (9.7 g) in concentrated HCl (75 mL) over 1–2 min. The resultant viscous solution was heated at 100 °C until evolution of nitrogen had ceased (ca. 0.5 h), and it was then poured into water. The mixture was extracted with ethyl acetate, and the organic layer was washed with water, dried, and evaporated to give **4**. Purification via column chromatography (Kieselgel/chloroform) and crystallization from ethyl acetate/petroleum ether (bp 60–80 °C) gave a pure sample: yield 7.4 g (39%); mp 141.5–143.5 °C. Anal. ($C_{14}H_9Cl_3O_3$) C, H. Overall yield from 3-(2-hydroxyphenyl)prop-1-ene is 6.7%.

Similarly prepared were **5** [overall yield 8.5%; mp 140–142 °C. Anal. ($C_{14}H_9Cl_3O_3$) C, H] and **6** [overall yield 5.6%; mp 173–175 °C. $C_{14}H_8Cl_4O_3$) C, H]

[2-(2,3,5,6-Tetrachlorophenoxy)phenyl]acetic Acid (8). The sodium salt of 3-(2-hydroxyphenyl)prop-1-ene (**1**, M = Na; 312.0 g, 2.0 mol) was dissolved in dry DMF (1 L), the solution was stirred and cooled to 0 °C, 2,3,5,6-tetrachloronitrobenzene (522 g, 2.0 mol) was added, and the mixture was stirred at 0–10 °C for 1 h. The solution was stirred overnight at room temperature, and the resulting precipitate was removed by filtration, washed with water, and dried (376 g). The mother liquors were cooled, and a further batch of the required product (51 g) was precipitated and removed by filtration. The two crops were combined, dissolved in ethyl acetate, dried, and evaporated to give **7**: yield 427 g (62%); mp 69.5–71 °C. Anal. ($C_{15}H_{10}Cl_4O$) C, H, Cl.

The diphenyl ether **7** (160 g, 0.46 mol) was dissolved in a mixture of acetic acid (2400 mL) and water (800 mL), and the solution was stirred and cooled to 0–5 °C. Potassium permanganate (366 g, 2.3 mol) was added portionwise over ca. 6 h while making sure that the temperature did not exceed 5 °C. The solution was stirred at this temperature for 1.5 h and then at room temperature for 1.5 h and then poured into water (10 L). Sufficient sodium metabisulfite was added to remove the manganese dioxide, and the precipitated product was removed by filtration, taken up in ethyl acetate (4 L), dried, and evaporated. Two crystallizations from ethyl acetate gave **8**: yield 117.5 g (70%); mp 216–217 °C. Anal. ($C_{14}H_8Cl_4O_3$) C, H, Cl.

(10) Finney, D. J. "Statistical Methods in Biological Assays", 2nd ed.; Charles Griffin: London, 1964.

The alternative synthesis of **8** from (2-hydroxyphenyl)acetic acid is also described. A solution of sodium hydroxide (1.6 g, 0.04 mol) in methanol (20 mL) was added to (2-hydroxyphenyl)acetic acid (3.0 g, 0.0197 mol), and the solution was evaporated to dryness. Dry toluene was added, and the suspension reevaporated to give the disodium salt as a white solid. Dry DMF (30 mL) was added, and the solution was cooled and stirred at 0–5 °C before the addition of 2,3,5,6-tetrachloronitrobenzene (5.2 g, 0.0199 mol). After stirring at 0 °C for 0.5 h, the solution was allowed to warm to room temperature, and stirring was continued overnight. The solid that had formed was removed by filtration and dissolved in water, the solution was acidified, and the resulting white precipitate was removed by filtration and dried (3.5 g). Recrystallization from ethyl acetate gave **8**: yield 2.5 g (35%); mp 213–216 °C.

[2-[(2,3,5,6-Tetrachlorophenyl)thio]phenyl]acetic Acid (10). (2-Mercaptophenyl)acetic acid (8.3 g, 0.049 mol) was added to a solution of sodium (2.27 g, 0.099 mol) in methanol (50 mL), and the resulting solution was evaporated to give the disodium salt **9** as a white solid. DMF (50 mL) was added, and the solution was cooled to 0 °C before the addition of 2,3,5,6-tetrachloronitrobenzene (30 g, 0.11 mol). After 15 min at 0 °C, cooling was stopped, and the solution was allowed to stand at room temperature overnight. A yellow solid had precipitated; the suspension was poured into 2 N sodium hydroxide solution (200 mL) and extracted with ether. The aqueous layer was acidified with dilute HCl and extracted with ether, and the combined layers were washed with water, dried, and evaporated to give a yellow solid (11.3 g). The solid was triturated with cold methanol and then subjected to column chromatography (Kieselgel/chloroform). The product was eluted as a white crystalline solid. Crystallization from ethyl acetate/petroleum ether (bp 80–100 °C) gave **10**: yield 4.7 g (25%); mp 181.5–183.5 °C. Anal. ($C_{14}H_8Cl_4O_2S$) C, H.

[2-[(2,3,5,6-Tetrachlorophenyl)sulfinyl]phenyl]acetic Acid (11). [2-[(2,3,5,6-Tetrachlorophenyl)thio]phenyl]acetic acid (**10**; 0.8 g, 0.0021 mol) was dissolved in glacial acetic acid (10 mL), and hydrogen peroxide solution (30%, 2 mL) was added. The mixture was warmed to 45 °C and stirred at this temperature for 72 h. The mixture was evaporated to dryness to give a white crystalline solid, which was washed with water and crystallized from ethanol to give **11**: yield 0.33 g (40%); mp 210–213 °C. Anal. ($C_{14}H_8Cl_4O_3S$) C, H.

[2-[(2,3,5,6-Tetrachlorophenyl)imino]phenyl]acetic Acid (13). 2,3,5,6-Tetrachloraniline (73 g, 0.32 mol) was heated at reflux in a mixture of acetic acid (370 mL) and acetic anhydride (73 g, 0.72 mol) for 2 h. After evaporation, water was added, and the solid residue was filtered, dried, and triturated for 0.5 h with excess chloroform. After filtration the white solid that remained was pure 2,3,5,6-tetrachloroacetanilide: yield 40.5 g (46%); IR ($CHBr_3$) $\nu/_{max}$ 3200 (s), 1660 (s) cm^{-1}. Anal. ($C_8H_5Cl_4NO$) C, H, N. A melting point was not recorded for this compound.

A mixture of 2,3,5,6-tetrachloroacetanilide (61.4 g, 0.225 mol), bromobenzene (450 mL), anhydrous potassium carbonate (16.4 g, 0.12 mol), and cuprous chloride (1.65 g) was heated at reflux with stirring. Water that was generated was removed with a Dean–Stark apparatus. Heating and stirring was continued for 5 days. The mixture was steam distilled until all excess bromobenzene had been removed, water was added, and the residue was filtered and dissolved in ethyl acetate. The organic layer was dried and evaporated to give a black oil, which was immediately dissolved in ethanolic potassium hydroxide (27.3 g in 270 mL) and heated at reflux for 18 h. After evaporation, water was added, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with water, dried, and evaporated to give a black solid (71 g). This was purified via column chromatography (Kieselgel/chloroform), and pure *N*-(2,3,5,6-tetrachlorophenyl)aniline was recovered as a light brown solid: yield 40 g (58%). A small sample, crystallized for analytical purposes (petroleum ether, bp 40–60 °C), had mp 99–101 °C; IR ($CHBr_3$) ν_{max} 3380 (m) cm^{-1}.

The diphenylamine (18.0 g, 0.059 mol) was dissolved in dry benzene (77.5 mL), and the solution was cooled to 0–5 °C. Oxalyl chloride (32.7 g, 22.5 mL, 0.28 mol) was added dropwise over 20 min; the solution was stirred at room temperature for 1 h and then at 50 °C for 18 h. The mixture was evaporated, and the residual oxalyl chloride was removed by adding dry benzene and reevaporating. The red oil that remained was dissolved in tetrachloroethane (116 mL), and powdered aluminium chloride (77 g, 0.057 mol) was added. The solution was stirred at room temperature for 60 h, after which it was poured into a mixture of ice (ca. 300 mL) and dilute HCl (50 mL). The resulting mixture was extracted with chloroform, and the organic layer was washed with water, dried, and evaporated to give a red/orange solid. The product was purified by trituration with petroleum ether (bp 40–60 °C) and gave **12**: yield 17.7 g (83%); mp 217–219 °C; IR ($CHBr_3$) ν_{max} 1740 (s), 1760 (s) cm^{-1}.

The isatin **12** (5.5 g, 0.015 mol) was suspended in diethylene glycol (27 mL) at room temperature, and hydrazine hydrate (2.0 mL, 0.04 mol) was added. The mixture was stirred at ambient temperature for 4 h. Potassium hydroxide (2.0 g, 0.035 mol) was added, and the mixture was heated with stirring at 140 °C for 1 h. After pouring into iced water, the mixture was acidified with concentrated HCl and extracted with ether. The combined organic layers were then extracted with saturated sodium carbonate solution, which was acidified with 2 N HCl to give a brown precipitate. The solid was filtered, and the filtrate was washed with water and dried (4.4 g). Purification via column chromatography (Kieselgel/chloroform), followed by crystallization from ethyl acetate, gave **13**: yield 1.2 g (22%); mp 187–190 °C. Anal. ($C_{14}H_9Cl_4NO_2$) C, H, N.

Acknowledgment. The authors thank Linda Bentley for her valuable technical assistance.

Registry No. **1**·K, 79015-70-6; **1**·Na, 3383-08-2; **2**, 86335-22-0; **3**, 86350-18-7; **4**, 86335-23-1; **5**, 81682-41-9; **6**, 86335-24-2; **7**, 86335-25-3; **8**, 86335-26-4; **9**, 79099-23-3; **10**, 86335-31-1; **11**, 86335-32-2; **12**, 86335-30-0; **13**, 86335-33-3; diclofenac, 15307-86-5; fenclofenac, 34645-84-6; 2,3,4-trichloronitrobenzene, 17700-09-3; [2-(6-amino-2,3-dichlorophenoxy)phenyl]acetic acid, 86335-27-5; 2,3,5,6-tetrachloronitrobenzene, 117-18-0; (2-hydroxyphenyl)acetic acid, 614-75-5; (2-mercaptophenyl)acetic acid, 39161-85-8; 2,3,5,6-tetrachloroaniline, 3481-20-7; 2,3,5,6-tetrachloroacetanilide, 86335-28-6; bromobenzene, 108-86-1; *N*-(2,3,5,6-tetrachlorophenyl)aniline, 86335-29-7; oxalyl chloride, 79-37-8.