Insecticidal Thioureas: Preparation of [*phenoxy*-4-^{3}H]Diafenthiuron, the Corresponding Carbodiimide, and Related Compounds†

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The high insecticidal and acaricidal activity of *N-tert*-butyl-*N'*-(2,6-diisopropyl-4-phenoxyphenyl)-thiourea (diafenthiuron) prompted the development of a procedure for radiosynthesis of this sterically hindered thiourea and two of its photoproducts and metabolites, the corresponding carbodiimide and urea. *N*-[4-(4'-Bromophenoxy)-2,6-diisopropylphenyl]-*N'-tert*-butylurea in ethyl acetate was subjected to debromination with tritium gas over palladium to obtain the [*phenoxy*-4-^{3}H]urea (24 Ci/mmol). Treatment of the labeled urea with phosphorus pentoxide in pyridine yielded the [*phenoxy*-4-^{3}H]-carbodiimide, which was then converted to [*phenoxy*-4-^{3}H]diafenthiuron on addition of hydrogen sulfide. These ^{3}H-labeled compounds of high specific activity are of interest in defining the mechanisms of photochemical and metabolic degradation of diafenthiuron and the potential involvement of carbodiimide-binding proteins in the toxic action.

INTRODUCTION

The most active thiourea insecticides and miticides contain an aryl group with bulky ortho substituents on one nitrogen atom and a bulky alkyl substituent on the other. Particularly effective compounds are *N-tert*-butyl-*N'*-(2,6-diisopropyl-4-phenoxyphenyl)thiourea (1) (diafenthiuron) (Drabek, 1987; Drabek et al., 1990; Steinmann et al., 1989; Streibert et al., 1988) and the corresponding but less active dephenoxy analogue (4) (Enders et al., 1978). Diafenthiuron provides broad spectrum control of insects and mites including those resistant to some or all other classes of insecticides and miticides (Streibert et al., 1988).

Thiourea 1 photodecomposes sequentially to carbodiimide 2 and urea 3 under environmental-type conditions (Drabek et al., 1990), and the same sequence is proposed for oxidative metabolism of 1 in mites (Kadir and Knowles, 1991a,b) (Figure 1). The urea is essentially nontoxic, whereas the carbodiimide is very effective in pest control (Drabek et al., 1990). It is therefore proposed that 1 is a propesticide and 2 is the activated metabolite (Drabek et al., 1990; Kadir and Knowles, 1991a,b). The propesticidal action is not unexpected since many thioureas are bioactivated by sulfur oxidation (Lee et al., 1980; Skellern, 1989). The bulky substituents about the carbodiimide moiety of 2 enhance its hydrolytic stability and insecticidal effectiveness (Drabek et al., 1990). The biological activity of some carbodiimides is associated with their derivatization reactions involving mitochondrial and chloroplast enzymes, binding proteins, and membranes (Williams and Ibrahim, 1981). It is therefore important to define the mechanisms of the photochemical and metabolic transformations of 1–3 and to evaluate the possible relationship of carbodiimide-binding proteins to their toxic action. These investigations require radiolabeling of the compounds at high specific activity.

This paper describes the introduction of tritium via a reductive debromination sequence to obtain the required *phenoxy*-4-^{3}H-labeled compounds. Related chemical studies are carried out on the corresponding dephenoxy analogues 4–6 (Figure 1).

MATERIALS AND METHODS

^{1}H NMR spectra were recorded with a Bruker WM-300 spectrometer at 300 MHz using $CDCl_3$ solutions with tetramethylsilane as the internal reference. MS data were obtained with a Hewlett-Packard 5985 spectrometer using the electron impact mode at 70 eV. IR spectra were determined with KBr disks and a Perkin-Elmer 1600 FT-IR instrument. Distillations were bulb to bulb using a Kügelrohr apparatus unless indicated otherwise. Preparative radial chromatography utilized a Chromatotron with 1-mm silica gel layers. Analytical TLC involved 0.25-mm silica gel F-254 plates. Solid preparations were recrystallized from hexane or hexane/CH_2Cl_2.

Diafenthiuron (1) was provided by Homer M. LeBaron of Ciba-Geigy Corp. (Greensboro, NC) or synthesized along with its dephenoxy analogue and related compounds by procedures described below.

Syntheses. *Cautionary Note.* The reactions described involve several hazardous chemicals as starting materials or intermediates. They include phosgene, thiophosgene, isocyanates, isothiocyanates, and tritium gas. These materials must be used with adequate knowledge of their toxic properties and under careful containment conditions.

Preparation and Halogenation of Anilines (7–11) (Figure 2). (*a*) *4-Bromo-2,6-diisopropylaniline (8).* A solution of bromine (16.0 g) in acetic acid (5 mL) was added dropwise over 1 h to a stirred solution of 2,6-diisopropylaniline (7) (17.7 g) in acetic acid (10 mL) and methanol (50 mL) cooled in an ice bath. The solvent was removed in vacuo, and the residue was washed with ether. The insoluble material was treated with ether and aqueous NaOH solution, and the ether-soluble fraction was dried ($MgSO_4$); the solvent was removed to afford 8 as a straw-colored mobile oil (23.6 g): bp 163 °C/0.2 mmHg; MS M$^+$ *m/z* 255, 257; ^{1}H NMR δ 1.24 (CH*Me*$_2$), 2.87 (C*H*Me$_2$), 7.10 (Ar H).

(*b*) *2,6-Diisopropyl-4-iodoaniline (9).* A mixture of 7 (10.1 g), iodine (13.2 g), and anhydrous K_2CO_3 (16.5 g) in ether (100 mL) was stirred at 20 °C for 20 h. The reaction mixture was washed with water, $NaHSO_3$ solution, and water and then dried and the solvent evaporated. The brown mobile liquid residue (14.5 g) was mainly 9 with a small amount of 7 (^{1}H NMR analysis) and, after removal of a small aliquot, was used directly for the next reaction. The aliquot was distilled to give pure 9: bp 195 °C/0.4 mmHg; MS M$^+$ *m/z* 303; ^{1}H NMR δ 1.24 (CH*Me*$_2$), 2.84 (C*H*Me$_2$), 7.27 (Ar H).

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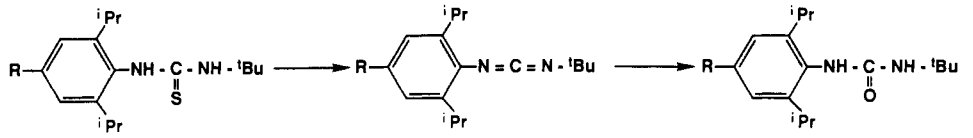

1 R = PhO
4 R = H

2 R = PhO
5 R = H

3 R = PhO
6 R = H

Figure 1. Proposed photochemical and metabolic reactions converting diafenthiuron (1) to the corresponding carbodiimide (2) and urea (3). Analogous chemical conversions are shown with the series 4–6 based on the prototype *N-tert*-butyl-*N'*-(2,6-diisopropylphenyl)-thiourea.

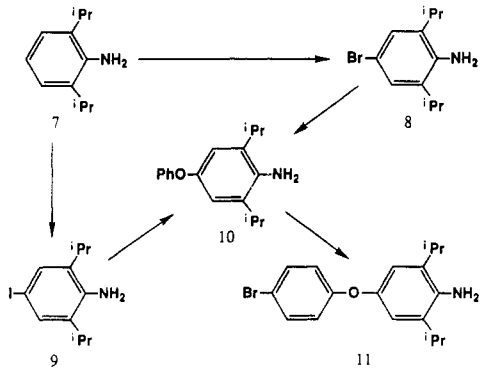

Figure 2. Preparation and halogenation of anilines 7–11.

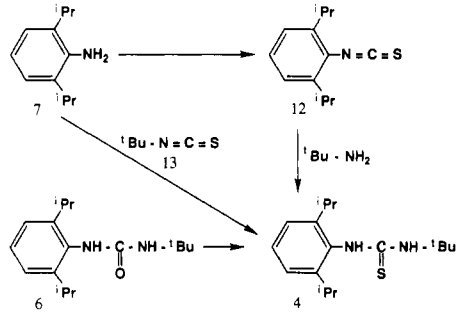

Figure 3. Preparation of thiourea 4.

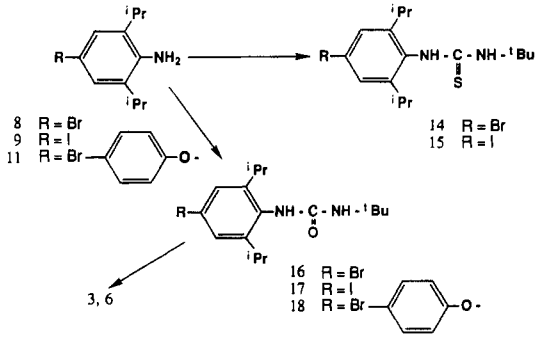

Figure 4. Preparation and reduction studies with halogenated thioureas (14 and 15) and ureas (16–18).

(*c*) *2,6-Diisopropyl-4-phenoxyaniline* (*10*). (*i*) *Starting from Bromoaniline 8.* A mixture of 8 (10.7 g), phenol (4.4 g), anhydrous powdered K_2CO_3 (7.6 g), and Cu_2O (3.6 g) in dry pyridine (35 mL) was stirred and heated at reflux under N_2 for 22 h. The nonphenolic material was then recovered in ether and chromatographed on silica gel. Elution with benzene/hexane (1:1 and 2:1) afforded mixtures of 8 and 10, with 10 predominating in the later eluted fractions. Recrystallization of selected fractions gave pure 10 as well-formed crystals (4.42 g): mp 79–81 °C; MS M^+ *m/z* 269; ^1H NMR δ 1.23 ($CHMe_2$), 2.93 ($CHMe_2$), 6.77 (Ar H-3 and -5), 6.92 (Ar H-2′ and -6′), 6.98 (ArH-4′), 7.26 (ArH-3′ and 5′). Aniline 10 was also obtained from 8 using potassium phenolate (Drabek and Boeger, 1981), but the yield was much inferior.

(*ii*) *Starting from Iodoaniline 9.* Similar treatment of 9 (14.5 g of the crude product described above) afforded a black oil which was immediately distilled. The major fraction (9.8 g), bp 230 °C/0.7 mmHg, was starting 9, and a second fraction (1.9 g), bp 240 °C/0.3 mmHg, was a mixture of 9 and 10 (TLC, ^1H NMR).

(*d*) *4-(4′-Bromophenoxy)-2,6-diisopropylaniline* (*11*). A solution of 10 (34 mg) in $CDCl_3$ (1.0 mL) and trifluoroacetic acid (4 drops) was treated at 20 °C with a solution of bromine in CCl_4 (1 M, 0.13 mL), yielding a dark color. After 22 h at 20 °C, a second portion (0.26 mL) of this bromine solution was added, resulting in evolution of HBr. The mixture was left at 20 °C for 72 h. The product recovered in the usual manner was subjected to radial chromatography with hexane/ethyl acetate (4:1) to obtain 11: ^1H NMR δ 1.23 ($CHMe_2$), 2.93 ($CHMe_2$), 6.74 (Ar H-3 and -5), AA′BB′ centered at 6.79 and 7.36 (Ar H-2′, -3′, -5′, and -6′). Other bromination conditions found to be ineffective were bromine in CCl_4 or glacial acetic acid and dibromoisocyanuric acid in glacial acetic acid or aqueous H_2SO_4 (1:1).

Preparation of Thiourea 4 (Figure 3). (*a*) *2,6-Diisopropylphenyl Isothiocyanate* (*12*). A solution of thiophosgene (7.5 mL) in $CHCl_3$ (120 mL) was added dropwise over 45 min to a stirred solution of triethylamine (24 mL) and 7 (15.2 g) in $CHCl_3$ (150 mL) at 20 °C. The reaction mixture was heated under reflux for 10 h and then cooled to 20 °C, washed with water, and dried. The residue after solvent evaporation was subjected to conventional distillation to afford 12 as a pale yellow viscous oil (13.4 g): bp 160–165 °C/4.5 mmHg; IR 2100 cm^{-1} (C=N=S); MS M^+ *m/z* 219; ^1H NMR δ 1.17 ($CHMe_2$), 3.15 ($CHMe_2$), 7.02 (Ar H-3 and -5), 7.12 (Ar H-4).

(*b*) *N-tert-Butyl-N′-(2,6-diisopropylphenyl)thiourea* (*4*). (*i*) *Starting from Aryl Isothiocyanate 12.* A solution of 12 (13.4 g) and *tert*-butylamine (9.2 g) in ether (130 mL) was stirred at 20 °C overnight. The reaction mixture was then heated to evaporate the ether while hexane was added to replace much of the ether. On cooling, 4 was obtained as well-formed colorless needles (12.9 g): mp 128–129 °C; MS M^+ *m/z* 292; ^1H NMR δ 1.22 and 1.26 ($CHMe_2$), 1.42 (CMe_3), 3.15 ($CHMe_2$), 7.23 (Ar H-3 and -5), 7.37 (Ar H-4).

(*ii*) *Starting from tert-Butyl Isothiocyanate* (*13*). A solution of 13 (0.90 g) and 7 (1.30 g) in ether (5 mL) was stirred at 20 °C for 22 h. Only a small amount of 4 was formed (TLC). The yield was only marginally increased by heating under reflux after the ether was replaced by dimethoxyethane.

(*iii*) *Starting from Arylurea 6.* Urea 6 (236 mg) together with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (174 mg) in dry toluene (8 mL) was heated at 85 °C under N_2 for 8 h. Removal of the solvent and radial chromatography with hexane/ethyl acetate (4:1) gave 4 (TLC, ^1H NMR) in poor yield in an early eluting fraction.

Preparation and Reduction Studies with Halogenated Thioureas (14 and 15) and Ureas (16–18) (Figure 4). (*a*) *N-(4-Bromo-2,6-diisopropylphenyl)-N′-tert-butylthiourea* (*14*). A solution of thiophosgene (1.5 mL) in $CHCl_3$ (30 mL) was added over 1 h to a stirred solution of 8 (3.04 g) and triethylamine (4.8 mL) in $CHCl_3$ (50 mL). The reaction mixture was heated under reflux for 90 min and then washed with water and dried, and the solvent was removed. The dark oily residue was distilled at 0.7 mmHg to afford 4-bromo-2,6-diisopropylphenyl isothiocyanate as a yellow solid (2.00 g): IR 2114 cm^{-1}; MS M^+ *m/z* 297, 299; ^1H NMR δ 1.25 ($CHMe_2$), 3.21 ($CHMe_2$), 7.23 (Ar H). This isothiocyanate (1.95 g) was stirred with *tert*-butylamine (0.67 g) in ether (20 mL) at 20 °C for 44 h, and following workup as above the light tan solid residue (1.64 g) was crystallized from hexane/benzene to afford 14 as colorless crystals (1.10 g): mp 168–169 °C; MS M^+ *m/z* 370, 372; ^1H NMR δ 1.19 ($CHMe_2$), 1.41 (CMe_3), 3.15 ($CHMe_2$), 7.34 (Ar H).

(*b*) *N-tert-Butyl-N′-(2,6-diisopropyl-4-iodophenyl)thiourea*

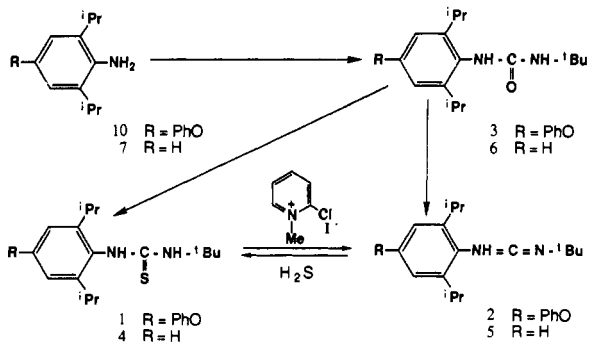

Figure 5. Preparation of thiourea 1, carbodiimides 2 and 5, and ureas 3 and 6.

(*15*). A mixture of 9 (3.83 g), thiophosgene (1.70 g), and triethylamine (3.5 mL) in $CHCl_3$ (30 mL) was stirred at 20 °C for 5 h. Workup in the usual manner afforded a dark mobile liquid which was essentially the desired 2,6-diisopropyl-4-iodophenyl isothiocyanate: ^{1}H NMR δ 1.24 (CH*Me*$_2$), 3.18 (C*H*Me$_2$), 7.43 (Ar H). This crude isothiocyanate in tetrahydrofuran (THF) (10 mL) was treated with *tert*-butylamine (2.5 mL) by dropwise addition and then heated under reflux for 5 h. Evaporation of the volatile components gave a red solid froth (1.8 g) which was crystallized as pale red tinted crystals of 15: mp 170–172 °C; MS M$^+$ *m/z* 418; ^{1}H NMR δ 1.19 and 1.20 (CH*Me*$_2$), 1.41 (CMe$_3$), 3.12 (C*H*Me$_2$), 7.53 (Ar H).

(*c*) *N-(4-Bromo-2,6-diisopropylphenyl)-N′-tert-butylurea* (*16*). A solution of 8 (2.60 g) in toluene (7 mL) was added dropwise over 45 min to a stirred solution of phosgene in toluene (1.93 M, 6 mL) cooled in an ice bath, and the reaction mixture was then stirred at 20 °C for 15 h. Distillation gave 4-bromo-2,6-diisopropylphenyl isocyanate as a colorless mobile liquid (1.45 g): bp 100 °C/0.1 mmHg; MS M$^+$ *m/z* 281, 283; ^{1}H NMR δ 1.23 (CH*Me*$_2$), 3.18 (C*H*Me$_2$), 7.22 (Ar H). The isocyanate (1.35 g) in ether (25 mL) was cooled in an ice bath and treated with *tert*-butylamine (0.5 g) and the reaction mixture stirred at 20 °C for 1 h. Filtration gave 16 as a colorless solid (1.56 g): mp 227–230 °C; MS M$^+$ *m/z* 354, 356; ^{1}H NMR δ 1.19 (CH*Me*$_2$), 1.26 (C*Me*$_3$), 3.27 (C*H*Me$_2$), 7.30 (Ar H).

(*d*) *N-tert-Butyl-N′-(2,6-diisopropyl-4-iodophenyl)urea* (*17*). A solution of 9 (3.03 g) and triethylamine (2.75 mL) in $CHCl_3$ (30 mL) was added dropwise over 20 min to a solution of phosgene in toluene (1.93 M, 5.0 mL) at 20 °C. The reaction mixture was then heated under reflux for 24 h and the crude 2,6-diisopropyl-4-iodophenyl isocyanate recovered in the usual way as a dark mobile liquid: ^{1}H NMR δ 1.19 (CH*Me*$_2$), 3.11 (C*H*Me$_2$), 7.39 (Ar H). This isocyanate was dissolved in ether (20 mL) and *tert*-butylamine (2.0 mL) added to it dropwise over a few minutes. A thick precipitate formed within 15 min which, after filtration, gave a colorless solid. Crystallization afforded 17 (2.5 g) as an off-white powder: mp 198–200 °C; MS M$^+$ *m/z* 402; ^{1}H NMR 1.18 (CH*Me*$_2$), 1.25 (CMe$_3$), 3.25 (C*H*Me$_2$), 7.48 (Ar H).

Reduction Studies with Brominated Ureas and Thioureas (Figure 4). (*i*) Bromoarylurea 16 was reductively debrominated to give 6 by two procedures. In the first, 16 (107 mg) was stirred for 3 h in ethanol (12 mL) with triethylamine (100 μL) and 10% Pd on charcoal (67 mg) under H_2. Workup in the usual manner gave 6 (TLC, ^{1}H NMR) in near quantitative yield as a white solid. In the second procedure, 16 (48 mg) was stirred with triphenyltin hydride (50 mg) and bis(azoisobutyronitrile) (AIBN) (11 mg) in THF (4 mL) while exposed to UV light (>300 nm). After 20 h, the reaction mixture was filtered and evaporated to give 6 (TLC, ^{1}H NMR).

(*ii*) The bromophenoxyarylurea (18, synthesis described later) (10 mg) in ethyl acetate (1.5 mL) with triethylamine (12 μL) and 10% Pd on charcoal (9 mg) was stirred at 20 °C for 2 h under H_2 to give 3 in quantitative yield (HPLC, ^{1}H NMR).

Preparation of Thiourea 1, Carbodiimides 2 and 5, and Ureas 3 and 6 (Figure 5). (*a*) *Diafenthiuron* (*1*). Two procedures were used to prepare 1. In the first method, urea 3 (10 mg) together with Lawesson's reagent (25 mg) and dry toluene (2 mL) were heated at reflux under N_2 for 4 h. Solvent removal and chromatography on a Chromatotron silica gel plate (hexane/CH_2Cl_2 2:1) afforded thiourea 1 in poor yield (TLC, ^{1}H NMR).

In the second procedure, carbodiimide 2 (2 mg) was treated with a saturated solution of H_2S in methanol (300 μL) at 20 °C for 3 h. The residue following evaporation was identified as predominantly 1 with a trace of 2 (TLC, ^{1}H NMR).

(*b*) *N-tert-Butyl-N′-(2,6-diisopropyl-4-phenoxyphenyl)carbodiimide* (*2*). Carbodiimide 2 was formed from urea 3 by two procedures and also from thiourea 1. In the preferred method, urea 3 (23 mg) was added to a mixture of P_2O_5 (229 mg), clean dry sand (550 mg), and dry pyridine (1.0 mL) and stirred and heated at reflux for 3 h in an apparatus with a silica gel drying tube. The pyridine was then removed in vacuo and the residue extracted with ether. This solution was washed with saturated aqueous $NaHCO_3$ and water and dried, and the ether was evaporated to afford a gummy residue (12 mg) which was essentially pure 2: IR 2139 cm^{-1} (N=C=N); MS M$^+$ *m/z* 350; ^{1}H NMR ($CDCl_3$) δ 1.21 (CH*Me*$_2$), 1.39 (C*Me*$_3$), 3.40 (C*H*Me$_2$), 6.78 (Ar H-3 and -5), 6.98 (Ar H-2′ and -6′), 7.07 (Ar H-4′), 7.32 (Ar H-3′ and -5′); ^{1}H NMR (C_6D_6) 1.14 (CH*Me*$_2$), 1.18 (C*Me*$_3$), 3.61 (CH*Me*$_2$), 6.85 (Ar H-4′), 6.99–7.08 (Ar H).

In the other method involving urea 3 and triphenylphosphine dibromide, bromine (8 mg) in dry benzene (300 μL) was added dropwise over a few minutes to triphenylphosphine (13 mg) in dry benzene (300 μL) cooled in an ice bath. After warming to 20 °C, the reaction mixture was stirred for 15 min and then cooled in an ice bath and a solution of triethylamine (10 mg) and benzene (300 μL) added dropwise over a few min followed by 3 (18.4 mg). The reaction mixture was heated at reflux for 1 h and then cooled and added to a small column of silica gel. Elution with hexane/THF (19:1) gave 2 (7 mg), and then hexane/THF (3:1) gave 3 (7 mg).

To convert thiourea 1 to carbodiimide 2, a solution of 1 (1.93 g) and triethylamine (1.19 g) in acetonitrile (25 mL) together with *N*-methyl-2-chloropyridinium iodide (1.53 g) was heated at reflux under a N_2 atmosphere for 2.5 h. The solvent was evaporated, and the ether-soluble material from the residue was distilled to obtain 2 as a pale yellow liquid (0.77 g), bp 150 °C/1 mmHg, which crystallized on standing.

(*c*) *N-tert-Butyl-N′-(2,6-diisopropylphenyl)carbodiimide* (*5*). A solution of 4 (590 mg), *N*-methyl-2-chloropyridinium iodide (600 mg), and triethylamine (480 mg) in dry acetonitrile (10 mL) was heated for 2.5 h at reflux under N_2. Workup and distillation gave 5 as a colorless mobile liquid (250 mg): bp 130 °C/0.1 mmHg; MS M$^+$ *m/z* 258; ^{1}H NMR δ 1.24 (CH*Me*$_2$), 1.37 (C*Me*$_3$), 3.40 (C*H*Me$_2$), 7.09 (Ar H). Alternatively, triphenylphosphine dibromide prepared as above converted urea 6 to 2 isolated by chromatography on a silica gel column (hexane/CH_2Cl_2 2:1).

(*d*) *N-tert-Butyl-N′-(2,6-diisopropyl-4-phenoxyphenyl)urea* (*3*). A solution of 10 (988 mg) and triethylamine (1.2 mL) in dry toluene (10 mL) was added dropwise to a stirred and cooled (ice bath) solution of phosgene in toluene (2.0 mL, 1.93 M) under N_2. The mixture was heated under reflux for 24 h and then cooled, diluted with ether, and filtered. Solvent evaporation from an aliquot gave the isocyanate as an oil: ^{1}H NMR δ 1.21 (CH*Me*$_2$), 3.20 (C*H*Me$_2$), 6.78 (H-3, H-5), 6.99 (H-2′, H-6′), 7.09 (H-4′), 7.33 (H-3′, H-5′). The remainder of the filtered solution was treated with *tert*-butylamine (1.5 mL) at 20 °C for 24 h and then evaporated and the residue crystallized from ether/hexane to give 3 as fluffy crystals (780 mg): mp 183–184 °C; MS M$^+$ *m/z* 368; ^{1}H NMR ($CDCl_3$) δ 1.15 (CH*Me*$_2$), 1.27 (CMe$_3$), 3.28 (C*H*Me$_2$), 6.82 (Ar H-3 and -5), 7.13 (Ar H-4′), 7.15 (Ar H-2′ and -6′), 7.36 (Ar H-3′ and -5′); ^{1}H NMR (C_6D_6) δ 1.16 (CH*Me*$_2$), 1.19 (CMe$_3$), 3.54 (CH*Me*$_2$), 6.86 (Ar H-4′), 7.03–7.10 (Ar H).

(*e*) *N-tert-Butyl-N′-(2,6-diisopropylphenyl)urea* (*6*). Aniline 7 (17.7 g) was treated with phosgene in toluene (60 mL, 1.93 M) and then with *tert*-butylamine as above to afford the urea 6 as hard colorless crystals: mp 184–185 °C; MS M$^+$ *m/z* 276; ^{1}H NMR δ ~1.11 (CH*Me*$_2$), 1.16 (C*Me*$_3$), 3.24 (C*H*Me$_2$), 7.06–7.24 (Ar H).

Radiosynthesis of [*phenoxy*-4-^{3}H]Diafenthiuron ([^{3}H]-1) and Precursors Thereof (Figure 6). (*a*) *N-[4-(4′-Bromophenoxy)-2,6-diisopropylphenyl]-N′-tert-butylurea* (*18*). A solution of phenoxyarylurea 3 (1.10 g) in methanol/acetic acid (5:1) (25 mL) was stirred at 0 °C while bromine (0.65 g) was added dropwise over 25 min. The reaction mixture was stirred at 20 °C, and after 4 h, more bromine (0.65 g) was added. After 20 h, the reaction was worked up in ether using an aqueous

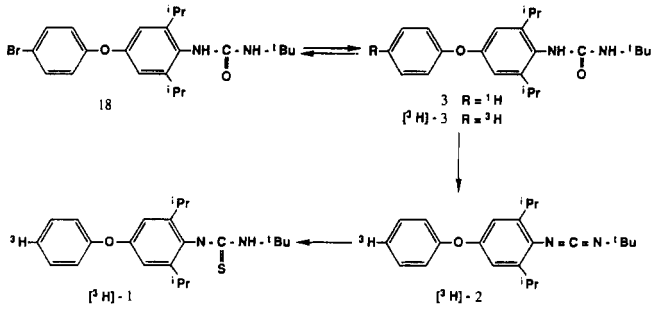

Figure 6. Radiosynthesis of [*phenoxy*-4-^{3}H]diafenthiuron ([^{3}H]-1) and precursors thereof.

$NaHCO_3$ wash to obtain a yellow solid froth (1.33 g). Chromatography on a silica gel column and elution with CH_2Cl_2/hexane (1:1) gave 2,4,5-tribromophenol (TLC, ^{1}H NMR) as a minor byproduct. Subsequent elution with CH_2Cl_2/methanol (99:1) gave **18** as colorless crystals (467 mg): mp 148–150 °C; MS M^+ *m/z* 446, 448; ^{1}H NMR δ 1.15 ($CHMe_3$), 1.28 (CMe_3), 3.28 ($CHMe_2$), 6.80 (Ar H-3 and -5), AA'BB' centered at 6.90 and 7.46 (ArH-2', -3', -5', -6'). This was the same product obtained on treatment of crude **11** with phosgene in toluene and then with *tert*-butylamine in the usual manner (Figure 4).

(*b*) [*phenoxy*-4-^{3}H]-*N*-*tert*-Butyl-*N*'-(2,6-diisopropyl-4-phenoxyphenyl)urea ([^{3}H]-**3**). Bromophenoxyarylurea **18** (50 mg) dissolved in ethyl acetate (3 mL) and triethylamine (67 μL) was stirred with 10% Pd on charcoal (50 mg) under $^3H_2$ (740 mm) for 3 h. Excess $^3H_2$ was removed and the solvent evaporated. Methanol was stirred with the residue and then evaporated and this cycle repeated. The residue gave a single HPLC peak (300 × 8 mm column of 10-μm Porasil, hexane/THF (17:3) at 2 mL/min, UV diode array detector) at the R_t of the urea (**3**), and this corresponded with a single peak of radioactivity (solid scintillant detector). Comparison of the mass (UV peak area) and radioactive content of the recovered radioactive fraction established a specific activity for [^{3}H]-**3** of 24 Ci/mmol. The radioactivity recovered from this reaction was 2.85 Ci (88%), corresponding to 43.9 mg (107%). [^{3}H]-**3** cochromatographed with the unlabeled standard on TLC (silica gel, $CHCl_2$/methanol 99:1). The ^{1}H NMR spectrum (C_6D_6) of [^{3}H]-**3** relative to that of unlabeled **3** showed a much reduced signal at δ 6.86 attributable to H-4 of the phenoxy group (<20%). The ^{3}H NMR spectrum (C_6D_6, ^{1}H decoupled) showed only a sharp singlet at δ 6.90.

(*c*) [*phenoxy*-4-^{3}H]-*N*-*tert*-Butyl-*N*'-(2,6-diisopropyl-4-phenoxyphenyl)carbodiimide ([^{3}H]-**2**). [^{3}H]-**3** (1.52 Ci) was dissolved in pyridine (1.5 mL) in a flask protected by a Drierite guard tube, and then dry sand (80 mg) and P_2O_5 (50 mg) were added. The mixture was stirred and heated under reflux for 4.5 h. The pyridine was then removed in vacuo and the residue extracted with CH_2Cl_2 (3 × 1.5 mL). This solution was washed with saturated aqueous $NaHCO_3$ and water and then dried ($MgSO_4$) and evaporated. The residue in benzene (1 mL) was applied to a short column of silica gel. Most of the radioactivity (785 mCi, 52%) was eluted with hexane/THF (50:1) and cochromatographed on TLC (hexane/CH_2Cl_2 2:1) with [^{3}H]-**2** (care is required in TLC analysis to avoid hydrolysis of the carbodiimide during spotting and chromatography). Additional radioactivity (98 mCi), which was eluted with THF/methanol (50:1), cochromatographed on TLC with [^{3}H]-**3**. [^{3}H]-**2** appeared to be homogeneous from HPLC and NMR spectroscopy and was found to have a specific activity of 24.5 Ci/mmol determined as above. The ^{1}H NMR spectrum established ^{3}H labeling exclusively at the 4-position of the phenoxy ring (δ 6.85, <20% of ^{1}H), and consistent with this the ^{3}H NMR spectrum (^{1}H decoupled) showed one singlet at δ 6.89.

(*d*) [*phenoxy*-4-^{3}H]-*N*-*tert*-Butyl-*N*'-(2,6-diisopropyl-4-phenoxyphenyl)thiourea ([^{3}H]-**1**). In a prototype reaction at reduced specific activity [^{3}H]-**2** (212 μCi) in anhydrous methanol (500 μL) was treated with H_2S by bubbling slowly through the solution at 20 °C for 100 min, resulting in 83% conversion based on TLC (CH_2Cl_2/hexane 2:1) and radioautography. The residue from solvent evaporation was dissolved in hexane/CH_2Cl_2 (2:1) and applied to a column of silica gel (8 × 100 mm) which was eluted with this solvent and then with CH_2Cl_2/hexane (2:1). The latter eluate contained radiochemically pure [^{3}H]-**1** (11.2 mCi/mmol, 35% radiochemical yield) which cochromatographed on TLC with standard compound and gave the appropriate ^{1}H NMR spectrum.

RESULTS

Five substituted anilines (**7**–**11**) shown in Figure 2 served as intermediates for further chemical transformations. Bromoaniline **8** was readily obtained from aniline **7** according to the same procedure as for the 2,6-dimethyl analogue (Noelting et al., 1901). Further conversion of **8** to phenoxyaniline **10** was achieved by a modification of the published method (Drabek and Boeger, 1981). A parallel pathway from **7** via iodoaniline **9**, unexpectedly, proved to be a less efficient route to **10**. Conversion of **10** to bromophenoxyaniline **11** was achieved by treatment with bromine in the presence of trifluoroacetic acid, although the yield was only moderate. Other bromination conditions were ineffective.

Standard procedures were used to convert the substituted anilines (**7**–**11**) to urea (**3**, **6**, **16**–**18**) and thiourea (**1**, **4**, **14**, **15**) derivatives (Figures 3–5). Aryl isocyanate and isothiocyanate intermediates (e.g., **12**) were formed from the reaction of the anilines with phosgene and thiophosgene, respectively, and the products thereof were directly treated with *tert*-butylamine. The alternative route to arylthiourea **4** from the reaction of aniline **7** with *tert*-butyl isothiocyanate (**13**) (Figure 3) proceeded more slowly and less completely.

In preparation for the tritium-labeling experiments, methods were examined in the dephenoxy series for the reductive replacement of the bromine atom of bromoarylthiourea **14** and bromoarylurea **16** (Figure 4). Unfortunately, this replacement was not successful with **14** either on treatment with triphenyltin hydride (Kuivila, 1970) or on catalytic hydrogenation with palladium on charcoal. However, bromoarylurea **16** underwent smooth reductive debromination to **6** under both of these conditions.

Additional experiments in the dephenoxy series showed that urea **6** can be converted to thiourea **4** by treatment with Lawesson's reagent (Cava and Levinson, 1985), albeit in only moderate yield (Figure 3), and to carbodiimide **5** by treatment with triphenylphosphine dibromide and triethylamine (Bestmann et al., 1968) but not with triphenylphosphine in CCl_4 (Appel et al., 1971) (Figure 5). These results indicated that a radiolabeled urea would have a central position for the radiosynthesis of the desired radiolabeled thiourea and carbodiimide products.

The findings from studies in the dephenoxy series were verified and expanded in the phenoxyaryl series. Thus, parallel conversions of phenoxyarylurea **3** to thiourea **1** and carbodiimide **2** were similarly achieved (Figure 5). Additional interconversions were established in the phenoxyaryl series. Thus, **3** was converted to **2** by treatment with P_2O_5 in pyridine at reflux [procedure of Stevens et al. (1967)], and **2** in turn was conveniently converted to **1** by stirring with a solution of H_2S in methanol at 20 °C. Further, **1** was converted in high yield to **2** by treatment with *N*-methyl-2-chloropyridinium iodide [procedure of Shibanuma et al. (1977)]. The radiosynthesis methods were selected from this plethora of procedures. The preferred method involved the conversion sequence **3** → **2** → **1**.

Radiosynthesis of [*phenoxy*-4-^{3}H]-**3** was based on tritium replacement of the bromine atom in bromophenoxyarylurea **18** (Figure 6). Due to the low overall yield of **18** from **10** via **11** (Figure 4), it proved more satisfactory to proceed via bromination of phenoxyarylurea **3**, which

produced a moderate yield of bromophenoxyarylurea 18. Preliminary experiments showed that 18 was readily and completely converted to 3 by treatment with hydrogen in the presence of triethylamine and 10% Pd on charcoal. Repetition of this reaction using tritium in place of hydrogen gave [^{3}H]-3 (Figure 6) of high specific activity (24 Ci/mmol) in 88% radiochemical yield with ^{3}H attached exclusively at the 4'-position.

The preferred procedure to convert [^{3}H]-3 to [^{3}H]-2 was treatment with the P_2O_5/pyridine reagent, which resulted in 52% yield of [^{3}H]-2 (24.5 Ci/mmol) with appropriate ^{1}H and ^{3}H spectra after chromatographic purification. [^{3}H]Diafenthiuron ([^{3}H]-1) was then readily obtained in high yield by treatment of [^{3}H]-2 with H_2S in methanol (Figure 6) followed by purification on a silica gel column; this procedure was carried out at 4.9 mCi/mmol but is equally applicable at 24 Ci/mmol. The high specific activity of these radiolabeled compounds makes them appropriate for metabolism studies and examination of the potential involvement of carbodiimide-binding proteins in their mode of action.

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Registry No. 1, 80060-09-9; [^{3}H]-1, 140411-16-1; 2, 104961-68-4; [^{3}H]-2, 140411-17-2; 3, 136337-67-2; [^{3}H]-3, 140411-18-3; 4, 66608-87-5; 5, 104961-67-3; 6, 140411-19-4; 7, 24544-04-5; 8, 80058-84-0; 9, 140411-20-7; 10, 80058-85-1; 11, 140411-21-8; 12, 25343-70-8; 13, 590-42-1; 14, 140411-22-9; 15, 140411-23-0; 16, 140411-24-1; 17, 140411-25-2; 18, 140411-26-3.