methylenedioxyphenyl-substituted analogue of 1 to prevent the antihormonal action of 1 in vivo (Brooks et al., 1979) provides further evidence for an oxidative activation step. If the action of 1 in fact depends on metabolic activation within the CA then the sensitivity of a given species to 1 may reflect the balance between activating and detoxifying metabolic events in target and nontarget tissues.

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Toxicity of *O,O*-Diethyl *O*-Carboalkoxyphenyl Phosphorothionates to the Imported Fire Ant

Thomas H. Fisher,* William E. McHenry, Earl G. Alley, and Howard W. Chambers

A series of diethyl carboalkoxyphenyl phosphorothionates was prepared where R = Me, Et, Pr, Bu, Am, Oct, *i*-Pr, and *i*-Bu for the para series and R = Me and Et for both the ortho and meta series. The toxicities of these phosphorothionates to the imported fire ant were determined for 1.0, 0.1, and 0.01% solutions of the toxicant in soybean oil. All of the toxicant baits were accepted by the ants at the concentrations studied. The I_{50} value of diethyl *p*-carboisopropoxyphenyl phosphate to ant-brain AChE was found to be a power of ten larger than that of paraoxon as expected from electronic considerations. A structure–activity study of the phosphorothionates with *p*-CO_2–R groups showed that the log percent kill was nicely correlated with the hydrophobic constant π. The best fire ant toxicants found here were the ones with para esters of low hydrophobic character.

For years, mirex was the important insecticide used to control the imported fire ants, *Solenopsis richteri* and *Solenopsis invicta*, in the southeastern United States. Problems associated with the use of mirex were surveyed by Alley (1973) and are related to the persistence of this chlorocarbon and to its toxicity to organisms other than the ant. All mirex bait formulations have been cancelled as of 1978 and no viable replacement has been found for general use over large infested areas.

Because of their low persistence, organophosphorus pesticides have often been used as replacements for banned chlorinated hydrocarbon pesticides. The most common

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organophosphorus insecticides are the phosphorothionates, the phosphorothiolothionates, and the phosphonates (Eto, 1974). An effective fire ant toxicant has the additional burden of needing to show delayed kill (less than 15% mortality after the first day) over at least a 10-fold dose range (Stringer et al., 1964). Most organophosphorus insecticides kill too fast and do not meet this delay requirement.

The enzyme phosphorylating ability of organophosphorus insecticides is directly dependent upon the presence of a good leaving group on the phosphorus atom. In dialkyl aryl phosphorothionates like parathion, the *p*-nitrophenoxide ion is such a leaving group. In general, the more electron-withdrawing the substituent on the phenoxide, the better the leaving group. In order to help meet the delay requirements, a slightly poorer leaving group than *p*-nitrophenoxide was needed. A phenoxide with a carboxyl ester, $-CO_2R$, substitutent on it fits this reduced electron-withdrawing criteria and has the additional benefit of having an alkyl group that can be varied in an effort to optimize the desired effect. Several common organophosphorus insecticides like malathion, mevinphos, and coumaphos (lactone) contain a carboxyl ester substituent. This study reports the synthesis of a series of diethyl carboalkoxyphenyl phosphorothionates and their evaluation as potential fire ant toxicants.

EXPERIMENTAL SECTION

Materials. Acetone was dried over calcium chloride and then distilled over phosphorus pentoxide. Diethyl phosphorochloridothionate (Aldrich), ethyl *p*-hydroxybenzoate (Aldrich), and refined soybean oil were commercially available and used without purification. All other phenols were synthesized.

Spectra. All NMR spectra were run on a Varian A-60 spectrometer. The samples were run in $CDCl_3$ with added Me_4Si. The IR spectra were run on a Nicolet 7199 spectrophotometer. Liquid samples were run neat between salt prisms, and solid samples were deposited as a film on the prism from $CHCl_3$ solvent.

Alkyl Hydroxybenzoate Syntheses. The procedure of de Leon et al. (1966) was used to convert *o*-, *m*-, and *p*-hydroxybenzoic acids into their esters by using sulfuric acid as the catalyst and an excess of the alcohol. Typically 0.10 mol of hydroxybenzoic acid was refluxed overnight with 0.35 mol of alcohol and 2.5 g of H_2SO_4 in 45 mL of ethylene dichloride in a water separator. The sulfuric acid was then removed by washing with water and sodium bicarbonate. After drying the mixture with sodium sulfate, the solvent was removed on a rotary evaporator under vacuum. The hydroxybenzoate esters were then purified by recrystallization from ethanol/water or by vacuum distillation. The melting points or boiling points of each of the 11 esters prepared agreed with previously reported values, and the IR and NMR spectra of each ester were consistent with the expected structure.

Phosphorothionate and Phosphate Syntheses. The *O,O*-diethyl *O*-carboalkoxyphenyl phosphorothionates were synthesized by a modification of a previously described procedure (Fletcher et al., 1950; Hall, 1950; Hoeberg and Cassady, 1951). The substituted phenol (0.96 mmol) and sodium carbonate (1.19 mmol) were refluxed for 1 h in 2.7 mL of acetone. After addition of 1.0 mL of acetone, diethyl phosphorochloridothionate (0.96 mmol, 0.15 mL) was added from a 0.5-mL syringe. The reaction was then refluxed overnight. The solvent was removed by passing a stream of nitrogen gas over the sample while heating at 50–55 °C. The product was dissolved in 65 mL of diethyl ether and then extracted with 15-mL portions of 5% sodium carbonate, 2% sodium hydroxide three times, and water three times. The base extractions removed any unreacted phenol that was still present. After drying over sodium sulfate, the ether was removed by blowing N_2 over the sample in a 10-mL concentrator tube at 35–40 °C. After the ether was all gone, the tube was heated at 65–70 °C for 30 min still under a stream of N_2. Finally, the sample was heated at 70–80 °C (0.7 mm) for 30 min to remove any chloridothionate starting material that was still present. The NMR and IR spectra were then run to identify and to determine the purity of the phosphorothionate products. Each of the phosphorothionates was obtained with less than 10% impurities, and these were used without further purification.

The diethyl phosphate of isopropyl 4-hydroxybenzoate was prepared by addition of diethyl phosphite (15 mmol) in carbon tetrachloride to the phenol (10 mmol) in dry acetone in an ice bath, followed by addition of triethylamine (15 mmol). The reaction mixture was stirred and allowed to warm to room temperature. After about 2 h, sufficient ethyl acetate was added to reduce the specific gravity to less than 1.0 and the mixture was washed sequentially with 1.0 N hydrochloric acid (two times), saturated sodium bicarbonate (three times), and distilled water (two times). The organic phase was dried over anhydrous sodium sulfate and the solvent was removed on a rotary evaporator. The oily residue was dissolved in hot hexane with addition of the minimal amount of chloroform to achieve solution. Upon cooling, a clear oily product which chromatographed as a single spot on TLC was recovered and used without further purification.

Toxicity Tests. The toxicity of each phosphorothionate was measured by C. S. Lofgren and his co-workers at the Insects Affecting Man and Animals Research Laboratory in Gainesville, FL. Details of the method used to determine the toxicity of the phosphorothionates in soybean oil to the imported fire ant were described by Banks et al. (1977). Each toxicant was tested at 1.0, 0.1, and 0.01% concentrations in soybean oil. The results of these studies are shown in Table I.

The toxicity of each phosphorothionate was also determined by another procedure designed to more closely resemble field conditions. These tests were done by K. L. Allen and co-workers of the Mississippi State Chemical Laboratory in Starkville, MS. These two tests will be referred to as the Lofgren test and the Allen test, respectively. The results of the Allen test are also shown in Table I. The major differences of the two methods are as follows: (1) the Lofgren test uses a soybean oil solution of the toxicant placed on a cotton swab, whereas the Allen test uses the same soybean oil solution on a corn cob grit; (2) the Lofgren test uses a small enclosed cup and the Allen test uses a larger cup with the top left open to help prevent fumigation; (3) the Lofgren tests were done on *Solenopsis invicta* and the Allen tests were done on *Solenopsis richteri*. Otherwise, the two test procedures are the same. Each test was done in triplicate with a control and a mirex standard for each run.

Bait Acceptance Studies. In these tests the ants were fed a bait containing the toxicant and the dye Rhodamine B in soybean oil. After 24 h the ants were crushed on a filter paper to determine how many of the ants contained the dye. The results of this test on a representative phosphorothionate are shown in Table II.

Acetylcholinesterase Assay. Heads of fire ants were removed and homogenized in 0.8 M sucrose in a Ten Broeck tissue grinder. The homogenate was centrifuged at about 3000*g* for 5 min and the supernate was used for

Table I. Fire Ant Percent Mortality Data for Several Concentrations of $(EtO)_2P(=S)OC_6H_4Y$ in Soybean Oil

	1%				0.1%				0.01%	
	Lofgren		Allen		Lofgren		Allen		Lofgren	
Y	day 1	day 14	day 1	day 14	day 1	day 14	day 1	day 14	day 1	day 14
4-CO_2-Me	57	95	0	62	0	80	0	54	0	3
4-CO_2-Et	75	83			0	38			0	15
4-CO_2-Pr	100	100	37	94	30	78	0	37	0	18
4-CO_2-*i*-Pr	98	100	1	52	18	75	0	84	0	13
4-CO_2-Bu	100	100	64	100	18	58	0	23	2	10
4-CO_2-*i*-Bu	100	100	33	82	2	42	0	20	0	14
4-CO_2-Am	100	100	18	91	17	45	3	25	0	8
4-CO_2-Oct	100	100	46	86	2	25	0	71	0	8
3-CO_2-Me	68	85	76	95	0	5	0	16	2	5
3-CO_2-Et	93	100	31	80	0	8	2	29	0	5
2-CO_2-Me	100	100			0	30	8	90	0	5
2-CO_2-Et	100	100	25	49	2	12	3	50	0	17

Table II. Results of Fire Ant Bait Acceptance Tests on $(EtO)_2P(=S)OC_6H_4CO_2$-*i*-Pr

concn of 3, %	total ants used	no. of dyed ants	% acceptance
4.0	16	14	88
3.0	15	13	87
2.0	15	15	100
1.0	15	13	87
0.75	16	16	100
0.75	16	11	69
0.5	15	15	100
0.5	13	12	92
0.5	15	11	73
0.35	14	8	57
0.2	14	13	93
0.05	14	14	100
0.05	16	16	100

enzyme determinations. The method of Ellman et al. (1961) was used for measurement of acetylcholinesterase activity. Final homogenate concentration was 0.5 head/mL in pH 7.4 Tris buffer and the reaction time was 15 min.

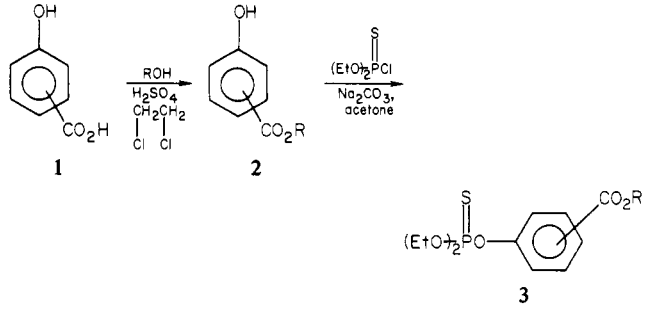
Inhibition was determined by incubation of homogenate for 15 min with serial dilutions of the phosphate prior to addition of the substrate (acetylthiocholine). Remaining activity was compared to activity of an untreated sample to calculate percent inhibition. Linear regression analysis (percent I vs. log concentration) of the data was used to determine the I_{50} values. The I_{50} values of diethyl *p*-carboisopropoxyphenyl phosphate and paraoxon were found to be 1.86×10^{-7} M and 1.3×10^{-8} M, respectively.

RESULTS AND DISCUSSION

The 12 phosphorothionates used in this study were prepared by traditional synthetic methods. The alkyl hydroxybenzoate esters (2) were synthesized by the esterification of *o*-, *m*-, and *p*-hydroxybenzoic acids (1) with an excess of alcohol by using concentrated sulfuric acid as the catalyst in ethylene chloride solvent. The alkyl hydroxybenzoates were then converted to *O,O*-diethyl *O*-aryl phosphorothionates (3) by reaction with diethyl phosphorochloridothionate in acetone. The reactions used are shown in Scheme I.

One of the three criteria for an effective fire ant toxicant proposed by Stringer et al. (1964) was that it not be repellant to the ants. Since there is a strong odor associated with many phosphorothionates, it was feared that the fire ants would not accept the soybean oil baits if the toxicant odor was too strong. Acceptance was not found to be a problem with the toxicants made in this study. The results of a detailed acceptance study on 3-*p*-CO_2-*i*-Pr are shown in Table II. Over the concentration range of 4.0 to 0.05%, there was an average acceptance of 88% and no test was less than 50%. The four tests at 1% or more phosphorothionate in soybean oil (not bait) all showed a better than 85% acceptance. Three other compounds (3-*p*-CO_2Me, 3-*p*-CO_2-*n*-Pr, and 3-CO_2-*n*-Bu) were also tested for acceptance at 0.5%, and acceptances of 67-93% were found.

Scheme I



para, R = Me, Et, *n*-Pr, *n*-Bu, *n*-Am, *n*-C_8H_{17}, *i*-Pr, *i*-Bu
meta, R = Me, Et
ortho, R = Me, Et

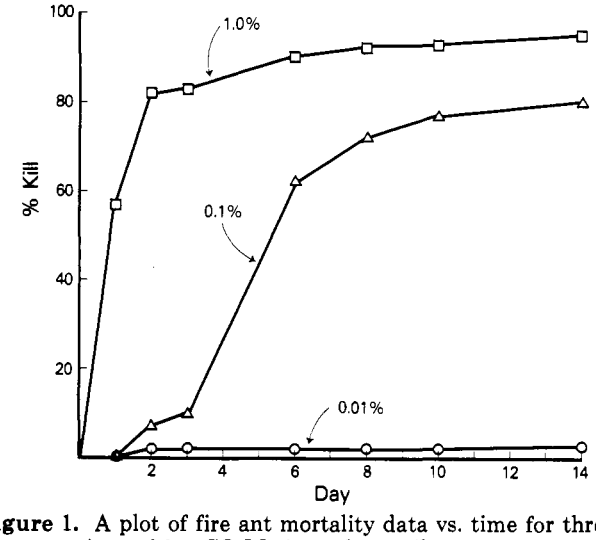


Figure 1. A plot of fire ant mortality data vs. time for three concentrations of 3-*p*-CO_2Me in soybean oil.

The efficacies of the phosphorothionate toxicants were determined by the Lofgren and Allen tests. In these tests, percent mortality was observed at the end of 1, 2, 3, 6, 8, 10, and 14 days. Figure 1 shows a typical complete set of mortality data. The effect of a 100-fold dilution is clearly illustrated in this plot. Interpolation of this data between 1.0 and 0.1% shows that delayed kill occurs in concentrations slightly greater than 0.1%, but the 10–100-fold dosage range criterion of Stringer et al. (1964) is obviously not met. Because of the large amount of mortality data generated in this study, only the data for the two most

critical days—the first and 14th days—are shown in Table I. The 14th day is important because the toxicity of the compound comes from this day's data; the first day is important because the delay criteria come from this data. All of the phosphorothionates were studied at three concentrations: 1.0, 0.1, and 0.01% of toxicant in soybean oil.

The 14-day mortality data in Table I are remarkably similar for the two test procedures, considering the differences in them. All of these phosphorothionates are very toxic to the imported fire ant at 1.0% with 9 of the 12 killing 100% in the Lofgren test. The 14-day mortality data for the 0.1% soybean oil solutions falls off, and a wide variation (5–90%) is found from compound to compound. Thus, structural differences are most evident in the 14-day mortality data at 0.1%. There is only a minor amount of toxicity in the 0.01% solution, with none killing more than 20% of the ants in 14 days.

In order to get effective control of imported fire ant mounds, the queen ant must be killed. She is carefully protected and purposefully located far down the food chain. For this reason, the insecticide must not kill immediately but must kill after a delay period. Delayed toxicity was defined by Lofgren et al. (1967) as less than 15% mortality after 24 h and more than 89% mortality at the end of the test period. Most organophosphorus insecticides kill too fast and do not show the required delay period. The 1-day mortality data for phosphorothionates **3** are also shown in Table I. There are significant differences in the Lofgren and Allen 1-day kill data at 1.0%. The Lofgren test showed consistent higher mortality at the end of the first day than did the Allen test. This is consistent with the way the two tests were run. The Lofgren test uses a smaller container that is closed and fumigation is possible, in addition to the closer association with the toxicant forced on the ant by the smaller environment. The Allen test more closely approximates the conditions present in the field. Both tests showed very little 1-day mortality at 0.1 and 0.01%.

Since both the Lofgren and Allen data for a 0.1% soybean oil solution of **3**-*p*-CO_2-*i*-Pr were favorable, additional toxicity tests were run on this compound to determine its promise for a field test. The Allen tests were conducted on ten different concentrations ranging from 4.0 to 0.01%, a 400-fold dilution range. Delayed kill was found in at least one test at 0.1, 0.2, and 0.8%, where the 1-day/14-day mortality data were 4/84, 12/97, and 0/84 for these three concentrations, respectively. Two of these 14-day mortality data are slightly less than the 90% recommended by Lofgren, but were considered close enough to warrant a field test.

Fukuto and Metcalf (1956) found that the molar concentration of diethyl phenyl phosphates needed for 50% inhibition (I_{50}) of fly-brain AChE was a direct function of the electron-withdrawing capacities of the substituents on the benzene nucleus. The I_{50} values of diethyl *p*-carboisopropoxyphenyl phosphate and paraoxon were determined in this study for acetylcholinesterase from homogenized fire ant brains. The values of 0.013 μM for paraoxon (*p*-NO_2) and 0.186 μM for the *p*-CO_2-*i*-Pr phosphate are consistent with the reduced electron-withdrawing nature of the ester group compared to the nitro group. The *p*-CO_2-*i*-Pr phosphate, while not as effective as paraoxon, is still a very powerful cholinesterase inhibitor.

Structure–Activity Correlations. All of the structure–activity correlations done in this study use the Lofgren percent mortality data of Table I for the 0.1% phosphorothionate baits. The 0.1% data was used because it was the only concentration studied where wide variations in mortality data were found; all of the phosphorothionates gave near complete kill at 1.0% and very little kill at 0.01%. The 14-day mortality data from the Lofgren test is considered more reliable than that obtained in the Allen test because the latter test had great difficulty keeping the control ants alive and healthy for the entire 2 weeks needed for the toxicity tests. The 1-day mortality data are considered equally reliable in the two tests.

Table III. Fourteen-Day Mortality Data for a 0.1% Soybean Oil Solution of $(EtO)_2PSOC_6H_4CO_2R$ and Some Substituent Parameters of R

R	log % kill[a]	σ	π	E_s
CH_3	1.903	−0.17	0.56	0.00
n-Pr	1.892	−0.13	1.55	−0.36
i-Pr	1.875	−0.15	1.53	−0.47
n-Bu	1.763	−0.16	1.79[c]	−0.39
n-Am	1.653	−0.15	2.40[c]	−0.40
i-Bu	1.623	−0.15[b]	1.99[c]	−0.93
Et[d]	1.580	−0.15	1.02	−0.07
n-C_8H_{17}	1.398	−0.15[b]	3.78[c]	−0.33

[a] Lofgren data. [b] Estimated. [c] Calculated values assuming additivity of the following groups: CH_3-, 0.56; $-CH_2-$, 0.46; CH, 0.41; C, 0.30, using the additivity method of Leo et al. (1975). [d] This data point was omitted in the seven point correlation.

Eight phosphorothionates (**3**) were studied with the $-CO_2R$ group in the para position. These eight esters were varied enough in structure to allow differences in steric and hydrophobic effects to surface if they were important. The electronic nature of all eight para ester substituents is essentially constant, as can be seen by the similar values of σ_p, the Hammett substituent constant, in Table III. The hydrophobic nature of these eight substituents varies greatly from the methyl to the octyl group. Hydrophobic character is most often measured by π, the partition constant for the octanol–water solvent system (Hansch et al., 1973). The steric size of these eight alkyl groups can be approximated by E_s, the steric substituent constant of Taft.

The classic structure–activity study in this area was the work of Fukuto and Metcalf (1956) on the toxicity of diethyl phenyl phosphates to the housefly. Both log LD_{50} and in vitro log fly-brain AChE I_{50} were found to be linear functions of Hammett's σ values. Additional studies by Hansch and Deutsch (1966) and Hansch (1970) showed that the para substituents were nicely correlated by σ alone:

$$pI_{50} = 3.45\sigma + 4.46 \qquad r = 0.954,\ s = 0.51,\ n = 6 \qquad (1)$$

When meta substituents were included, a steric factor must also be included, but no important dependence on π was found in these studies. The lack of a dependence on π for antiacetylcholinesterase insecticides is believed to be a result of their extracellular action, where the enzyme inactivation occurs in the synaptic junction of the nerve cells (Hansch and Fujita, 1964).

A structure–activity study of the eight *p*-carboalkoxy phosphorothionates **3** was done, using the data of Table III. The following equations were found:

$$\log\ \%\ \text{kill} = -0.14\pi + 1.96 \qquad (2)$$

$$r = 0.736, \quad s = 0.13, \quad n = 8, \quad F = 7.1$$

$$\log\ \%\ \text{kill} = -0.17\pi + 2.07 \qquad (3)$$

$$r = 0.928, \quad s = 0.08, \quad n = 7, \quad F = 30.9$$

The *F* value reported is a measure of the overall significance of the equation obtained from a traditional backward

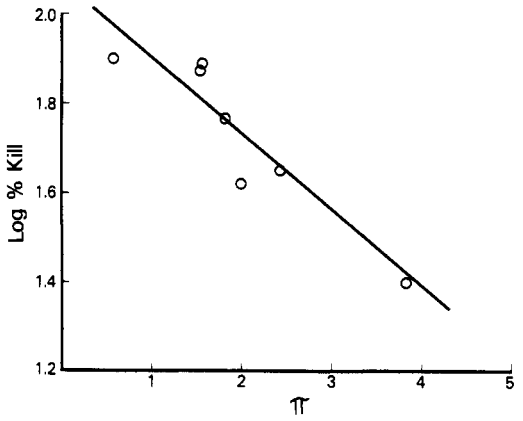


Figure 2. Correlation between log percent kill and the hydrophobic constant π for 0.1% 3-*p*-CO_2R in soybean oil.

elimination procedure (Draper and Smith, 1966). The correlation with π was poor for all eight substituents as shown in eq 2, where the correlation coefficient, r, was only 0.736. However, if the ethyl ester was omitted, an excellent correlation was found with π as shown in eq 3. The ethyl ester may be hydrolyzed easier than the other esters with the corresponding loss of toxicity. The coefficient of π is negative in these correlations, meaning that the most hydrophobic R's are the poorest toxicants. This is one of the first correlations of the toxicity of a phosphate–phosphorothionate type insecticide where the hydrophobic effect was found to be the dominant effect. It should be emphasized that the reason the electronic effects were not more prominent in this study is that they were purposely kept constant. Figure 2 graphically illustrates that this correlation of log percent kill with π is fairly respectable for an in vivo study.

The methyl and ethyl esters were studied in the ortho, meta, and para positions of phosphorothionate **3**. In each case, the para ester was found to be most toxic, the ortho ester second, and the meta ester the least toxic. An insufficient number of substituents were studied to know if this is a general trend. The Allen test data confirmed this trend with the exception of the *o*-CO_2Me group, which was found to be more toxic than the para isomer.

Diethyl carboalkoxyphenyl phosphorothionates show good potential as insecticides for the imported fire ant and the most promising substituents are the para esters with low hydrophobic character.

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Peanut Uptake and Metabolism of [^{14}C]Oxadiazon from Soil

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Peanuts were planted in 25-cm diameter pots, and [^{14}C]oxadiazon was mixed into the surface 0.64 cm of the soil. Cotyledons contained about 0.27 ppmw oxadiazon equivalent at 30 days after planting, while hypocotyls had a 0.10 ppmw concentration. After 61 days, pegs and immature nuts which were in direct contact with [^{14}C]oxadiazon-treated soil contained the highest concentration of herbicide. Hulls contained about 1 ppmw oxadiazon equivalent after 131 days (similar to a field commercial harvest); however, nuts accumulated only about 0.12 ppmw. The total peanut plant had an average of 0.59 ppmw oxadiazon equivalent at maturity. Hulls were found to have at least three ^{14}C-labeled compounds other than [^{14}C]oxadiazon. All other plant parts contained some [^{14}C]oxadiazon, but degradation products were below the level of detection, using TLC and autoradiography.

Oxadiazon [2-*tert*-butyl-4-[2,4-dichloro-5-(isopropoxy)-phenyl]-Δ^2-1,3,4-oxadiazolin-5-one] provided preemergence control of annual grasses and certain broadleaf weeds in peanuts, soybeans, rice, ornamentals, orchards, and turfgrasses (Burgaud et al., 1969). Oxadiazon was among a group of oxadiazole compounds discovered to have herbicidal properties in 1963 in the research laboratories of the Societe Usines Chimigues Rhone-Poulenc (Boesch and Metivier, 1965). Absorption, translocation, and metabo-

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