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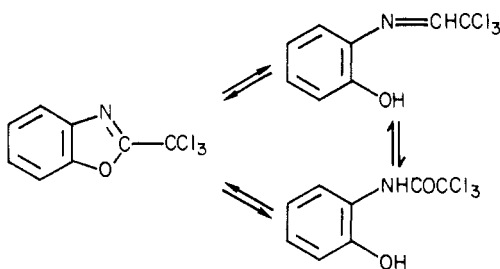   *Lett. Ed.* **1976,** *14* (7), 417.

Synthesis and Plant Growth Regulatory Properties of Substituted 2-(2,2,2-Trichloroethylideneamino)phenols, 2-(Trichloromethyl)benzoxazoles, and Benzothiazoles

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2-(2,2,2-Trichloroethylideneamino)phenols and 2-(trichloromethyl)benzoxazoles and benzothiazoles were synthesized. Their effects were compared on the growth of a number of broad-leaved weeds. Several compounds were shown to be good plant growth retardants. The unsubstituted phenol and benzoxazole showed particularly good plant growth retardant properties and substitutions in the benzene nucleus resulted in loss of activity or an increase in phytotoxicity.

2-(Trichloromethyl)benzoxazole, acquired as an inter-

mediate during a synthesis program, showed plant growth retardant properties when passed through a general herbicide screen. The extent of plant miniaturization accompanied by minimal phytotoxicity prompted a more extensive study of this compound. A literature survey revealed that the parent compound and some derivatives had been shown to possess herbicidal properties (Holan, 1967; Holan and Samuel, 1970). The potential products of reduction and hydrolysis, and therefore possible metabolites, 2-(2,2,2-trichloroethylideneamino)phenol and α,α,α-trichloro-2-hydroxyacetanilide, respectively, were also synthesized and screened as potential plant growth retardants.

2-(2,2,2-Trichloroethylideneamino)phenol was found to possess excellent plant growth retardant properties but α,α,α-trichloro-2-hydroxyacetanilide was essentially inactive. Accordingly, a series of ring-substituted derivatives, 2-(trichloromethyl)benzoxazoles and 2-(2,2,2-trichloroethylideneamino)phenols were synthesized and their effects on plant growth observed.

CHEMICAL METHODS

Analyses were performed by Strauss, Oxford. Infrared spectral data were recorded as nujol mulls on a Perkin-

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Table I. Physical Properties of 2-(Trichloromethyl)benzoxazoles

R	formula	mp, °C	% yield	analyses
4-CH₃	C₉H₆Cl₃NO	68	13	C, H, N
6-CH₃	C₉H₆Cl₃NO	69	30	C, H, N
7-CH₃	C₉H₆Cl₃NO	56	47	C, H, N
4,6-(CH₃)₂	C₁₀H₈Cl₃NO	103.5	28	C, H, N
5,7-(CH₃)₂	C₁₀H₈Cl₃NO	65	64	C, H, N
4,5,6-(CH₃)₃	C₁₁H₁₀Cl₃NO	117	26	C, H, N
4-Cl	C₈H₃Cl₄NO	100	18	C, H, N

Elmer 157 recording spectrophotometer. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements are within 0.4% of the theoretical values.

2-Aminophenols were prepared by the reduction of the appropriate 2-nitro- or 2-phenylazophenols with alkaline dithionite. The method was new for the reduction of the following 2-nitrophenols to known amines (percentage yields in parentheses), 6-methyl (42), 3,5-dimethyl (67), 3,6-dimethyl (49), and 3-chloro (60), and also for 3,4,5-trimethyl-2-phenylazophenol to 2-amino-3,4,5-trimethylphenol (85).

The 2-(trichloromethyl)benzoxazoles were prepared by procedures based upon published methods (Stephens and Bower, 1950); Holan et al., 1967). Equimolar amounts of the appropriate 2-aminophenol and methyl trichloroacetimidate were heated under gentle reflux for 1–4 h in a 10% solution with ethanol. Removal of the solvent followed by repeated crystallizations of the residue gave analytically pure samples.

The 2-(2,2,2-trichloroethylideneamino)phenols were prepared from 2-aminophenols by reaction with anhydrous chloral in acetic acid for 15 min at 60 °C according to the method previously described (Stephens and Bower, 1950). The physical properties and deviations from the standard

(Trichloromethyl)phenols and Benzoxazoles and Properties

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Table II. Physical Properties of 2-(2,2,2-Trichloroethylideneamino)phenols

R	formula	reaction time at 60 °C, min	recrystn solvent	mp, °C	% yield	analyses
H	$C_8H_6Cl_3NO$	15	ethanol	100	73	
3-Me	$C_9H_8Cl_3NO$	15	$CHCl_3$ and PE[b] (60–80)	98–99	31	C, H, N
4-Me	$C_9H_8Cl_3NO$	15	$CHCl_3$ and PE (60–80)	103	70	C, H, N
5-Me	$C_9H_8Cl_3NO$	15	$CHCl_3$	106	63	C, H, N
6-Me	$C_9H_8Cl_3NO$	15	$CHCl_3$ and PE (60–80)	91–92	87	C, H, N
3-Cl	$C_8H_5Cl_4NO$	150	PE (40–60)	48–49	98	C, H, N
4-Cl	$C_8H_5Cl_4NO$	20	$CHCl_3$ and PE (60–80)	91	66	C, N
5-Cl	$C_8H_5Cl_4NO$	15	PE (60–80)	100.5–101.5	65	C, H, N
6-Cl	$C_8H_5Cl_4NO$	15	PE (60–80)	75	51	C, H, N
4-NO_2	$C_8H_5Cl_3N_2O_3$	30	$CHCl_3$ and PE (60–80)	108	66	C, H, N
5-NO_2	$C_8H_5Cl_3N_2O_3$	60[a]	$CHCl_3$	147	80	C, H, N
3,4-Me_2	$C_{10}H_{10}Cl_3NO$	15	$CHCl_3$ and PE (60–80)	130.5–132	82	C, H, N
3,5-Me_2	$C_{10}H_{10}Cl_3NO$	15	$CHCl_3$ and PE (60–80)	81–82	76	C, H, N
3,6-Me_2	$C_{10}H_{10}Cl_3NO$	15	PE (60–80)	71–72	96	C, H, N
4,5-Me_2	$C_{10}H_{10}Cl_3NO$	15	$CHCl_3$ and PE (60–80)	118–119	58	N
4,6-Me_2	$C_{10}H_{10}Cl_3NO$	15	PE (40–60)	53–54	61	N
5,6-Me_2	$C_{10}H_{10}Cl_3NO$	15	PE (60–80)	88–89	82	C, H, N
3,6-Cl_2	$C_8H_4Cl_5NO$	15	PE (40–60)	85	80	C, H, N
3,4,5-Me_3	$C_{11}H_{12}Cl_3NO$	15	$CHCl_3$ and PE (60–80)	125–127	87	C, H, N
3,5,6-Me_3	$C_{11}H_{12}Cl_3NO$	15	PE (60–80)	129.5–130.5	91	C, H, N
3,4,6-Cl_3	$C_8H_3Cl_6NO$	150	PE (40–60)	87–88	92	C, H, N

[a] At 90 °C. [b] PE = petroleum ether.

preparative procedures are recorded in Table I for the benzoxazoles and Table II for the trichloroethylidene-aminophenols.

2-(Trifluoromethyl)benzthiazole was purchased from the Aldrich Chemical Co., and 2-(trichloromethyl)benz-imidazole and 2-(trichloromethyl)benzothiazole were prepared by literature methods (Stephens and Bower, 1950).

Preparation of (a) 2-Amino-3,4,6-trimethylphenol. 3,5,6-Trimethyl-2-nitrophenol was reduced with a hot alkaline solution of sodium dithionite in 35% yield: mp 161 °C. Anal. $C_9H_{13}NO$: C; H. (b) *2-Amino-5,6-dimethylphenol* was prepared in 24% yield in the manner described for 2-amino-3,5,6-trimethylphenol: mp 103–106 °C. Characterized as its Schiff base with chloral (Table II).

BIOLOGICAL METHODS

Pre- and postemergence assays were made by using the following test plants: groundsel (*Senecio vulgaris*); shepherds purse (*Capsella bursa pastoris*); chickweed (*Stellaria media*); pale persicaria (*Polygonum lapathifolium*); ryegrass (*Lolium perenne*). The chemicals were applied as aqueous acetone solutions or suspensions at a rate equivalent to 4.48 kg/ha in the manner previously described (Clifford et al., 1976). For postemergence tests the stage of spraying is indicated by the number of true leaves, recorded in parentheses: for the tests of Table III, chickweed (four pairs), shepherds purse (three), groundsel (three), and ryegrass (two); for Tables IV and V, chickweed (three to four pairs), groundsel (three to four), pale persicaria (one to three), and ryegrass (three, and one tiller).

For postemergence tests, assessments were made 10 days after spraying and for preemergence 30–35 days after spraying. Plant height was determined by removing the above-ground part and measuring from the base to the growing point on the main shoot (chickweed, shepherds purse, and groundsel) or to the tip of the longest leaf (pale persicaria and reygrass). Fresh weight was determined by weighing the above-ground parts. Each test had three replicates with untreated controls and used ten plants per replicate.

The results are expressed as a mean and for the purposes

Table III. Control of Several Weed Species by 2-(Trichloromethyl)- and 2-(Trifluoromethyl)benzoxazoles, Benzothiazoles, and Benzimidazoles as Postemergent Applications

			control[a] against			
R	X	Y	chickweed	groundsel	shepherd's purse	ryegrass
H	NH	Cl	0	0	0	0
H	S	Cl	30	40	30	20
H	O	Cl	46	40	33	33
H	O	Cl[b]	72	22	0	21
H	S	F	6	0	0	0

[a] Reduction in plant growth expressed as the percentage difference between the weight of untreated plants and that of treated plants. [b] Preemergence application: the control of 72% and 21% on chickweed and ryegrass included 7% and 21% reduction, respectively, due to dead plants.

of comparison recorded as a percentage in relation to the untreated control (Tables IV and V). In Table III the percentage control is derived as previously reported (Clifford et al., 1976).

RESULTS AND DISCUSSION

Plant growth regulatory (PGR) effects are defined here as those effects produced by the chemical that leaves the plant species indistinguishable from the untreated control except in size. The term herbicide is used only when the treatment with chemical results in plant death. Compounds causing plant damage but not death are graded on an arbitrary scale reflecting the amount of scorch. For 2-(trichloromethyl)benzoxazoles and 2-(2,2,2-trichloro-ethylideneamino)phenols, all of these effects were observed, the extent varying with concentration and/or plant species. Whenever observed, PGR effect was manifested in vegetative and reproductive growth, resulting in small plants with reduced internodal length, leaf area, and de-

Table IV. Plant Growth Regulatory Effects of Some 2-(Trichloromethyl)benzoxazoles as Postemergent Applications

	plant growth regulatory effects against														
	chickweed			pale persicaria				groundsel				ryegrass		
R	scorch[a]	kill[b]	fresh[c] wt	scorch[a]	kill[b]	fresh[c] wt	plant ht, cm	scorch[a]	kill[b]	fresh[c] wt	plant ht, cm	scorch[a]	kill[b]	fresh[c] wt
H	3	0	16	2	0	47	10	2	0	20	4	0	0	89
4-Me	3	20	26	0	0	100	15	0	0	100	9	0	0	97
5-Me	0	0	90	0	0	100	16	0	0	100	8	0	0	100
6-Me	1	0	93	1	11	100	14	0	0	100	8	0	0	97
7-Me	3	27	39	0	0	69	13	0	0	100	7	0	0	100
4-Cl	5	100	0	4	45	28	11	0	0	90	8	0	0	100
5-Cl	2	0	43	4	33	44	13	0	0	47	7	0	0	100
7-Cl	5	60	2	3	22	31	9	3	0	11	4	0	0	90
5-NO$_2$	5	60	3	5	89	3	11	0	0	100	9	0	0	100
4,6-Me$_2$	2	13	64	0	0	100	12	0	0	100	8	0	0	96
5,7-Me$_2$	5	40	40	0	0	69	13	0	0	100	9	0	0	100
4,5,6-Me$_3$	1	7	77	0	0	81	15	0	0	100	8	0	0	100
control	0	0	100	0	0	100	14	0	0	100	8	0	0	100

[a] Expressed according to an arbitary scale where 0 = no effect and 5 = severe scorch. [b] Expressed as a percent. [c] Expressed as a percent of the control.

Table V. Plant Growth Regulatory and Herbicidal Properties of Substituted 2-(2,2,2-Trichloroethylideneamino)phenols and α,α,α-Trichloro-2-hydroxyacetanilide

	plant growth regulatory effects against												
	chickweed			pale persicaria				groundsel				ryegrass
R	scorch[a]	kill[b]	fresh[c] wt	scorch[a]	kill[b]	fresh[c] wt	plant[d] ht, cm	scorch[a]	kill[b]	fresh[c] wt	plant ht, cm	fresh[c] wt
H	0	0	26	2	0	36	9	0	0	27	7	94
3-Me	0	0	100	0	0	80	13	0	0	86	17	100
4-Me	0	0	100	0	0	80	14	0	0	100	15	100
5-Me	0	0	100	0	0	100	16	0	0	100	19	97
6-Me	0	0	95	0	0	74	15	0	0	100	26	95
3-Cl	0	0	58	0	0	100	19[e]	0	0	96	13	100
4-Cl	1	0	98	0	0	100	14[e]	0	0	35	7	94
5-Cl	0	0	60	1	0	32	9	1	0	12	4	96
6-Cl	2	0	10	2	0	27	9	2	0	10	5	89
4-NO$_2$	0	0	100	0	0	100	17	0	0	81	16	95
5-NO$_2$	0	0	100	0	0	70	13	0	0	86	15	87
3,4-Me$_2$	5	100	0	0	0	100	18[g]	0	0	100	17	100
3,5-Me$_2$	0	0	56	0	0	94	15	0	0	100	19	100
3,6-Me$_2$	2	7	20	0	0	83	13	0	0	100	16	94
4,5-Me$_2$	0	0	90	0	0	100	18[f]	0	0	100	22	100
4,6-Me$_2$	0	0	67	0	0	100	17	0	0	98	19	100
5,6-Me$_2$	3	20	19	0	0	79	15	0	0	100	19	100
3,6-Cl$_2$	1	0	48	0	0	79	16	0	0	68	14	91
3,4,5-Me$_3$	5	80	1	0	0	58	11[f]	0	0	100	18	97
3,5,6-Me$_3$	5	87	2	0	0	86	14	0	0	100	18	78
3,4,6-Cl$_3$	1	0	45	3	0	32	10	1	0	52	11	100
TCHA[h]	0	0	97	0	0	91	18[e]	0	0	84	16	97
control	0	0	100	0	0	100	17	0	0	100	19	100

[a] Expressed according to an arbitary scale where 0 = no effect and 5 = severe scorch. [b] Expressed as a percent. [c] Expressed as a percent of the control. [d] Five leaves. [e] Six leaves. [f] Four leaves. [g] Seven leaves. [h] TCHA = α,α,α-trichloro-2-hydroxyacetanilide.

layed reproductive onset.

The effect of varying the heteroatom and side-chain halogen of 2-(trichloromethyl)benzoxazoles are recorded in Table III. The presence of the trichloromethyl group or trifluoromethyl on an oxazole or thiazole ring was necessary for growth regulatory action. The thiazole, however, showed more pronounced phytotoxic effects than the oxazole when applied at higher dosages.

2-(Trichloromethyl)benzoxazole and 2-(2,2,2-trichloroethylideneamino)phenol were the most effective and least damaging to plants as plant growth regulators against the broad-leaved species chickweed, pale persicaria, and groundsel but showed only modest effects against ryegrass (Tables IV and V, respectively). Of the substituents used, only the chloro group in both of these series showed significant PGR effects in the order 6-Cl > 5-Cl > 4-Cl > 3-Cl for II and 7-Cl > 5-Cl for 2-(trichloromethyl)benzoxazoles in which the 4-chloro derivative was herbicidal. For 2-(2,2,2-trichloroethylideneamino)phenols the 3,6-dichloro

compound showed properties midway between the highly active 6-chloro compound and the less active 3-chloro derivative while the inclusion of a 4-chloro substituent (R = 3,4,6-Cl$_3$) improved the activity slightly. Clearly, a measure of additivity of substituent potentiating effects is in evidence.

It appeared prior to the synthesis and testing of substituted derivatives that the balance between a PGR effect and herbicidal action might be influenced by steric factors. Small steric modifications were made by substituting the parent compounds with methyl groups (a small group with minimal electronic interactions) in a number of ways. No general pattern of activity with steric factors was observed for methyl-substituted 2-(trichloromethyl)benzoxazole, although a clear distinction between the 5 and 6 (inactive) and 4 and 7 (herbicide) substitution patterns was evident. Monomethylation of 2-(2,2,2-trichloroethylideneamino)-phenol resulted in inactive compounds. Multiple methyl substitutions in both series generally resulted in herbicidal

compounds.

No clear-cut dependence of the type of activity on electronic (ν), lipophilicity (π), or steric factors (MR) was observed.

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Mutagenicity of Products Obtained from a Maltol–Ammonia Browning Model System

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The methylene chloride extract obtained from a reaction mixture of a maltol and ammonia browning model system was separated into five fractions by thin-layer chromatography (TLC). Each fraction was examined for mutagenicity by the Ames' *Salmonella* test using strains TA 98 and TA 100, both with and without S-9 mix. The fraction which exhibited the strongest mutagenicity toward strain TA 98 with S-9 mix was further fractionated into three fractions by TLC. The new fractions were also tested for mutagenicity, with positive responses. 2-Ethyl-3-hydroxy-6-methylpyridine and acetamide isolated from one of new fractions, however, exhibited no mutagenicity. Twenty-two compounds were positively identified in the methylene chloride extract by GC/MS. 2-Ethyl-3-hydroxy-6-methylpyridine was identified by NMR and IR in addition to GC/MS.

In the beginning of this century, Maillard (1912) proposed the browning reaction to account for the brown pigments and polymers produced from the reaction of the amino group of an amino acid and the carbonyl group of a sugar. Hodge (1953) summarized the nonenzymatic browning reactions and indicated that simple model systems could be used to learn about complex food systems. Model systems consisting of an amino acid and a sugar have been most widely used to study the formation of food flavors (Koehler et al., 1969; Shigematsu et al., 1975). More simplified browning systems such as a sugar–ammonia (protein or amino acid decomposition product) have also been used to investigate the formation mechanism of flavor volatiles (van Praag et al., 1968; Shibamoto and Bernhard, 1976).

Certain browning reaction mixtures have exhibited some mutagenic activities toward *Salmonella typhimurium* strains (Mihara and Shibamoto, 1980; Spingarn and Garvie, 1979; Shibamoto, 1980; Toda et al., 1981). In order to investigate the formation and biological nature of browning products, we chose a simple system: maltol [sugar degradation products (Hodge, 1967)] and ammonia. There is much evidence that maltol forms from certain sugars as a product of a nonenzymatic browning reaction (Hodge and Nelson, 1961). Patton (1950) reported that maltol was obtained from lactose and maltose upon heating aqueous solutions of these sugars with glycine. Maltose gave maltol with piperidine salts in nearly dry reactions (Hodge et al., 1963).

In an actual food system, maltol can be formed from a carbohydrate or sugar constituent; it is possible that maltol

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Table I. Results of TLC of the Methylene Chloride Extract

fraction no.	R_f values	amount of sample recovered, %[a]
1	0.78–0.87	2.9
2	0.56–0.78	2.3
3	0.48–0.56	3.5
4	0.10–0.48	16.1
5	0.00–0.10	11.7

[a] [(Amount of sample recovered)/(amount of sample applied)] × 100.

Table II. Results of TLC of Fraction 4

fraction no.	R_f values	amount of sample recovered, %[a]
4a	0.35–0.45	17.2
4b	0.23–0.35	41.4
4c	0.11–0.23	14.7

[a] [(Amount of sample recovered)/(amount of sample applied)] × 100.

contacts ammonia formed from protein or amino acid during heat treatment (cooking). Maltol itself showed some mutagenic activities toward *S. typhimurium* strain TA 100 with metabolic activation (Bjeldanes and Chew, 1979). It is, therefore, interesting to observe the behavior of maltol in a browning reaction system.

EXPERIMENTAL SECTION

Sample Preparation. Maltol (0.1 mol) was dissolved into 60 mL of deionized water in a Kjeldahl flask. Ammonium hydroxide solution (0.5 mol as NH_3) was then added. The neck of the flask was flame-sealed and the flask placed in an oven at 100 °C for 5 h. The reaction solution was extracted with 300 mL of methylene chloride by using a liquid–liquid continuous extractor for 16 h. The