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Synthesis and Herbicidal Activity of α-Heterocyclic Carbinol Carbamates

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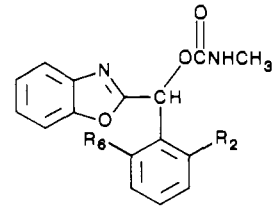
A series of novel α-benzoxazolylbenzyl carbamates exhibit moderate herbicidal activity in preemergence tests. At 0.5 lb/acre, gramineous crops show tolerance. A total of 53 analogues have been synthesized and their herbicidal activities determined in order to examine the structure–activity relationships. The results indicate very specific structural requirements for herbicidal activity. For optimum activity, there is a specific size requirement for the carbamoyl group and α-phenyl ring substituents. Ortho substituents on the phenyl moiety are necessary for high activity, and meta and para substituents invariably diminish herbicidal activity. A novel ring closure was observed involving attack by the carbamoyl nitrogen at the benzoxazole 2-position, with benzoxazole ring opening, to give a 2-(5-imino)oxazolidinone, which was shown to be herbicidally inactive. This result leads to the conclusion that the ring closure–ring opening process does not contribute to the observed herbicidal activity.

A variety of carbamates are known to possess herbicidal activity (Ashton and Crafts, 1981). However, relatively few heterocyclic carbamates have been reported as herbicides. Recently, a series of herbicidal heterocyclic carbamates involving the isoxazole system was disclosed (Theobald et al., 1981). We now report a series of novel benzylcarbamates substituted with a heterocyclic moiety on the α-carbon, represented by structure 1 (Wu et al., 1986).



1

The herbicidal activity of the subject class was discovered during a systematic investigation of the herbicidal activity of the benzylcarbamates related to SIRMATE

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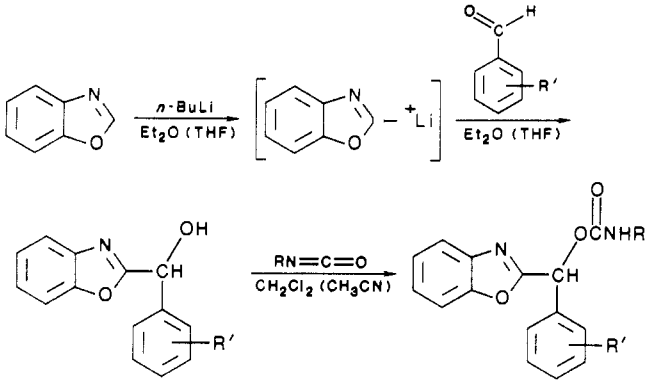
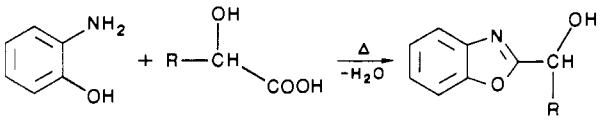
Scheme I



Scheme II



Scheme III

2

(UC22463) (Herrett and Berthold, 1965). This report presents studies of structure–activity relationships that examine the effects on activity exerted by the heterocyclic system, the functional group, the phenyl moiety, and substituents about the structure 1. A novel ring closure resulting in the formation of an oxazolinone was observed, and the structural identification of this compound is described.

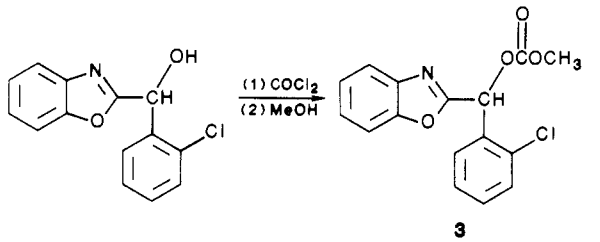
EXPERIMENTAL SECTION

Synthetic Methods. The carbamates were prepared by carbamylation of the carbinols with the appropriate isocyanate in the presence of a catalytic amount of dibutyltin diacetate (Payne and Weiden, 1965). Preparation of the α-heterocyclic benzyl alcohols was achieved by one of two methods: (1) condensation of the carbanion of the heterocycles with the appropriate benzaldehyde (Scheme I) (Beraud and Metzger, 1962; Gilman and Beel, 1949); (2) condensation of aminophenol with appropriate α-hydroxy acids (Gualtiere et al., 1971) (Scheme II).

Most of the heterocyclic starting materials **2** were commercially available. The heterocyclic compounds not commercially available were prepared by known procedures (Societe DE Products Chimiques ET DE Sytntheses, 1968) (Scheme III). The tetrahydrobenzoxazole was prepared according to the procedure of Bredereck and Compper (1956). The few benzaldehydes not commercially available were prepared by Rosenmund reduction of available acid chlorides. The carbonate **3** was prepared by the reaction of the heterocyclic carbinol with phosgene, followed by treatment with the appropriate alcohol (Scheme IV). The *N,N*-dimethylcarbamates were prepared by reacting the corresponding alcohol with *N,N*-dimethylcarbamoyl chloride in the presence of 4-(*N,N*-dimethylamino)pyridine as an acid acceptor. (Heep and Emmel, 1976; Peterson and Rogers, 1973) (Scheme V). The dicarbamate sulfide **4** was synthesized by reacting the carbinol with bis[(fluorocarbonyl)methylamino] sulfide (D'Silva, 1976) (Scheme VI).

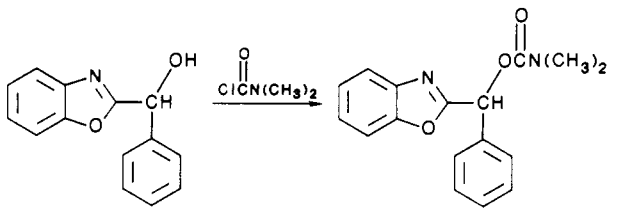
Experimental Procedures. NMR spectra were recorded on a Varian EM-360 spectrometer (Me_4Si as internal reference), and IR spectra were recorded on a Perkin-Elmer Model 197 or Beckman Accu-Lab Model 1 spectrometer. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were done by Galbraith Laboratories, Inc. Melting points and elemental analysis data of most carbamates described herein were reported in a U.S. patent (Wu et al., 1986). Mass spectra were obtained from Research Triangle Institute. For safety precautions, it should be noted that some carbamates reported herein are moderate cholinesterase inhibitors.

Scheme IV

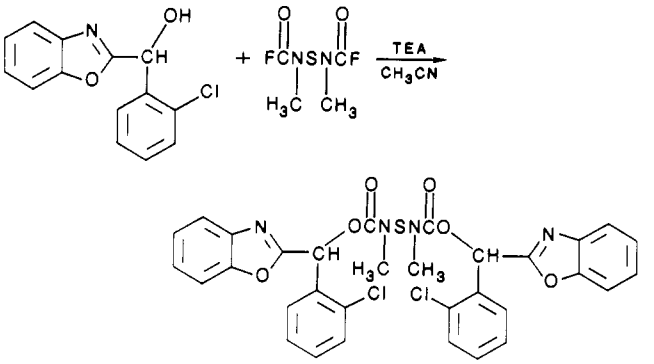


3

Scheme V



Scheme VI



4

2-(2-Chloro-6-fluoro-α-hydroxybenzyl)benzoxazole. To benzoxazole (10 g, 0.084 mol) in anhydrous ether (200 mL) at −76 °C under a nitrogen atmosphere was added 54 mL of 1.55 M *n*-butyllithium (0.084 mol, 1 equiv) in hexane, dropwise, over a period of 15 min. The solution was stirred for 30 min at −76 °C. 2-Chloro-6-fluorobenzaldehyde (14.6 g, 0.092 mol, 1.1 equiv) in ethyl ether (100 mL) was added dropwise over 30 min.

The mixture was stirred 2 h more at −76 °C. The mixture was allowed to warm to room temperature and stirred over a period of 15 h. Aqueous ammonium chloride solution (7.5%, 250 mL) was added. The solution was extracted with ether (3 × 200 mL). The ethereal extract was washed with brine, dried over anhydrous sodium sulfate, and evaporated to give a yellow solid. The solid was recrystallized from hexane–ethyl acetate to give 12.5 g of desired carbinol: 54%; mp 146–147 °C.

α-2-Benzoxazolyl-2-chloro-6-fluorobenzyl Methylcarbamate (5). A mixture of 2-(2-chloro-6-fluoro-α-hydroxybenzyl)benzoxazole (5.7 g, 0.021 mol), methylene chloride (50 mL), dibutyltin diacetate (3 drops via pipet), and methyl isocyanate (1.9 mL, 1.5 equiv) was stirred at

room temperature for 15 h in a sealed bottle. The solvent was evaporated in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was recrystallized from ethyl acetate–petroleum ether to give the desired carbamate: 4.5 g (64% yield); mp 134.5–136.5 °C; ^1H NMR ($CDCl_3$) δ 2,88 (d, 3 H, J = 5.0 Hz), 5.4 (br s, 1 H), 6.70–7.80 (m, 8 H); IR (film) 3320, 1720, 1520, 1450, 1240, 1120 cm^{-1}. Anal. Calcd for $C_{16}H_{12}ClFN_2O_3$: C, 57.40; H, 3.60; N, 8.40. Found: C, 57.49; H, 3.39; N, 8.34.

2-(α-Hydroxybenzyl)benzoxazole. A stirred mixture of *o*-aminophenol (20.4 g, 0.187 mol), *dl*-mandelic acid (25 g, 0.16 mol), and xylene (500 mL) was heated to reflux for 4 days. Water formed from the reaction was removed by a Dean–Stark trap. The mixture was cooled to room temperature and washed with 1 N HCl aqueous solution (500 mL), 5% Na_2CO_3 aqueous solution (500 mL), and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was recrystallized from CH_2Cl_2–hexane to give the desired carbinol: 12.0 g (33% yield); mp 105–108 °C; ^1H NMR ($CDCl_3$) δ 4.48 (br s, 1 H), 6.08 (br s, 1 H), 7.20–7.90 (m, 9 H); IR (film) 3330 cm^{-1} (OH). Anal. Calcd for $C_{14}H_{11}NO_2$; C, 74.65; H, 4.92, N, 6.23. Found: C, 74.70; H, 4.84; N, 6.29.

α-2-Benzoxazolyl-2-chlorobenzyl Methyl Carbonate (3). To 2-(2-chloro-α-hydroxybenzyl)benzoxazole (5.0 g, 0.019 mol) in toluene (35 mL) was added at room temperature 24 mL of 2.0 M phosgene in toluene (0.046 mol, 2.4 equiv). The resulting mixture was stirred under a nitrogen atmosphere for 15 h. The mixture was concentrated in vacuo, followed by addition of dry MeOH (large excess) dropwise at 0 °C. The solution was stirred and allowed to warm to room temperature over 15 h. The reaction mixture was concentrated. The residue was purified by flash chromatography (silica gel) using 25% EtOAc in hexane to give 780 mg (13% yield) of the desired carbonate as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.86 (s, 3 H), 7.00–7.90 (m, 9 H); IR (film) 1760, 1430, 1260 cm^{-1}. Anal. Calcd for $C_{16}H_{12}ClNO_4$: C, 60.48; H, 3.81. Found: C, 60.04; H, 3.84.

***N,N'*-Thiobis[α-[(*N*-methylcarbamoyl)oxy]-α-2-benzoxazolyl-2-chlorotoluene] (4).** To 2-(2-chloro-α-hydroxybenzyl)benzoxazole (4.7 g, 0.018 mol) in CH_3CN (50 mL) was added bis[(fluorocarbonyl)methylamino] sulfide, followed by addition of triethylamine (2.5 mL, 0.018 mol, 1.0 equiv) in CH_3CN (50 mL) at room temperature. The resulting mixture was stirred under a nitrogen atmosphere for 15 h. The mixture was evaporated and the residue partitioned between CH_2Cl_2 and H_2O. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica gel) using 40% EtOAc in hexane to give 940 mg (16% yield) of the desired dicarbamate sulfide: mp 93–95 °C; ^1H NMR ($CDCl_3$) δ 3.36 (s, 6 H), 7.10–7.94 (m, 18 H); IR (film) 1720, 1450, 1280, 1100 cm^{-1}. Anal. Calcd for $C_{32}H_{24}Cl_2N_4O_6S$: S, 4.83. Found: S, 4.94.

5-(*o*-Chlorophenyl)-4-[(*o*-hydroxyphenyl)imino]-3-methyl-2-oxazolidinone (57). A mixture of 920 mg of α-(2-benzoxazolyl)-2-chloro-6-fluorobenzyl methylcarbamate, 11 mL of 0.02 M phosphate buffer solution (pH 8.9), and 40 mL of CH_3CN was allowed to stand with frequent swirling at room temperature for 5 days. The mixture was partitioned between methylene chloride and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was analyzed by ^1H NMR, which indicated about 50% conversion to the oxazolidinone. The residue was purified by flash chromatography (silica gel) using 2% MeOH in CH_2Cl_2 to give 90 mg (9.8% yield) of the desired oxazolidinone **57** as an amorphous solid: ^1H NMR ($CDCl_3$) δ 3.20 (s, 3 H), 6.34 (s, 1 H), 6.40–7.40 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 27.593, 78.110, 114.895, 119.906, 120.014, 125.865, 127.084, 128.844, 130.226, 130.659, 131.282, 132.853, 133.937, 147.995, 155.769, 156.907; IR (film) 3400, 1790, 1680, 1440, 1220, 1130 cm^{-1}; UV λ_{max} 228 nm, 272, 278, 301; high-resolution mass spectrum, calcd for $C_{16}H_{13}ClN_2O_3$ 316.0614, found 316.0611. Diagonostic fragments follow: calcd for $C_8H_8N_2O$ 148.0636, found 148.0646; calcd for $C_{15}H_{13}ClN_2O$ 272.0715, found 272.0711; calcd for $C_{16}H_{12}ClN_2O_2$ 299.0587, found 299.0583.

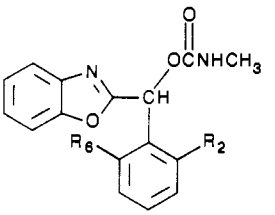
α-2-Benzoxazolyl-2-chloro-6-fluorobenzoxy Ethyl Thiocarbonate (55). To a suspension of sodium hydride (0.73 g, 0.030 mol, 1.2 equiv) in dry THF (200 mL) at 0 °C under a nitrogen atmosphere was added 2-(2-chloro-6-fluoro-α-hydroxybenzyl)benzoxazole (7.0 g, 0.025 mol, 1.0 equiv) in dry THF (150 mL). The resulting mixture was stirred at 0 °C for 30 min. A solution of ethyl chlorothioformate (3.1 mL, 0.030 mol, 1.2 equiv) in dry THF was added dropwise. The mixture was stirred at room temperature overnight. The mixture was quenched with NH_4Cl solution dropwise at 0 °C under a nitrogen atmosphere. THF was removed under reduced pressure. The mixture was partitioned between H_2O and CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica gel) with 20% EtOAc in hexane to afford 5.6 g (61% yield) of the desired thiocarbonate as an oil: ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 2.88 (q, J = 7 Hz, 2 H), 6.80–7.80 (m, 8 H); IR (film) 1710, 1601, 1580, 1450, 1240, 1120 cm^{-1}. Anal. Calcd for $C_{17}H_{13}ClFNO_3S$: C, 55.82; H, 3.58; N, 3.83; S, 8.77. Found: C, 55.80; H, 3.57; N, 3.82; S, 8.75.

α-2-Benzoxazolylbenzyl *N,N*-Dimethylcarbamate (44). To a solution of 2-(α-hydroxybenzyl)benzoxazole (5.0 g, 0.022 mol) in CH_2Cl_2 (150 mL) were added triethylamine (2.25 g, 0.022 mol, 1.0 equiv), (*N,N*-dimethylamino)-pyridine (2.7 g, 0.022 mol, 1.0 equiv), and *N,N*-dimethylcarbamyl chloride (2.0 mL, 0.022 mol, 1.0 equiv). The resulting mixture was heated to reflux under a nitrogen atmosphere for 5 days. The mixture was cooled to room temperature and aqueous $NaHCO_3$ solution added. The resultant mixture was stirred overnight, and the two phases were then separated. The organic layer was washed twice with $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by flash chromatography (silica gel) with 50% EtOAc in CH_2Cl_2 to give the desired carbamate, which was recrystallized from CH_2Cl_2–hexane to give white crystals: (2.1 g (32% yield); mp 107.0–108.0 °C; ^1H NMR ($CDCl_3$) δ 2.98 (s, 3 H), 3.06 (s, 3 H), 6.98 (s, 1 H), 7.12–7.32 (m, 9 H); IR (film) 2940, 1715, 1502, 1390, 1170, 1055, 890, 840 cm^{-1}. Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44. Found: C, 69.07; H, 5.50.

Biological Methods. Compounds were evaluated as preemergence and postemergence herbicides. The test plants (terrestrial) were mustard (*Brassica kaber*), teaweed (*Sida spinosa*), sicklepod (*Cassia obtusifolia*), velvetleaf (*Abutilon theophrasti*), crabgrass (*Digitaric spp.*), giant foxtail (*Setaria faberi*), wild oats (*Avena fatua*), barnyardgrass (*Echinochloa crus-galli*), morningglory (*Ipomoea spp.*), snapbeans (*Phaseolus vulgaris*), nutsedge (*Cyprus esculentus*), cucumber (*Cucumis sativus*), marigold (*Tagetes patula*), and nightshade (*Solanum nigrum*).

In the preemergence tests, the soil was sprayed with a solution of the test compound immediately after seeds were

Table I. Herbicidal Activity



A. Prominent Compounds,[a] Preemergence at 0.5 lb/acre

R_2	R_6	compd	SB	corn	cotton	MG	MT	TW	VL	GF	PW
Cl	H	**10**	4	0	0	0	87	0	68	0	26
Cl	F	**5**	83	0	100	12	100	100	100	6	100
Me	H	**6**	14	20	100	100	100	20	100	20	100
F	F	**8**	26	0	21	10	100	98	100	14	

B. **5** and **6** in Post- and Preemergence Tests at 8 lb/acre

	pre-emergence		post-emergence			pre-emergence		post-emergence	
	5	**6**	**5**	**6**		**5**	**6**	**5**	**6**
crabgrass	100	100	6	0	wild oats	100	100	0	0
cucumber	100	100	100	86	giant foxtail	100	100	0	6
barnyard grass	100	100	0	0	mustard	100	100	22	50
velvetleaf	100	100	65	93					

[a] Key: SB = soybean; MG = morningglory; MT = mustard; TW = teaweed; VL = velvetleaf; GF = giant foxtail; PW = pigweed.

planted. The compounds were applied in acetone–H_2O solution at the rate of 8 lb/acre of soil surface. Approximately 3 weeks after spraying, the herbicidal activity of the compound was determined by visual observation of the treated areas in comparison with untreated controls. These observations are reported on a scale of 0–10, where 0 indicates no effect and 10 is 100% control of plant growth.

In the postemergence tests, the soil and developing plants were sprayed at rates of 8 lb/acre about 2 weeks after the seeds were sown. Approximately 2 weeks after spraying, the herbicidal activity of the compound was determined by visual observation of the treated areas in comparison with the untreated controls. The rating scale was the same as that for the preemergence tests.

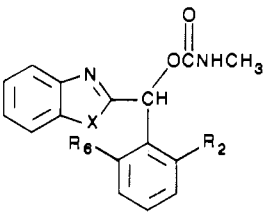
The herbicidal activities presented in the Tables II–VIII are average percentage controls of all tested species at 8 lb/acre in the preemergence tests.

RESULTS AND DISCUSSION

In general, these compounds exhibit moderate postemergent herbicidal activity on broadleaf species and relatively good preemergence herbicidal activity on a broad spectrum of broadleaf and grass species at 8 lb/acre (Table IB). Nevertheless, at 0.5 lb/acre, only preemergent activity on broadleaves was observed. Gramineous crops such as corn were tolerant at rates giving satisfactory broadleaf control (Table IA). The symptoms observed of the effected species are mainly chlorosis and necrosis along with some leaf albinism. In general, these carbamates are slow-acting herbicides. When applied below 1.0 lb/acre rate, more than 10 days is required for symptoms to be observed.

The size of substituents at the ortho positions of the α-phenyl ring is critical to activity. The most active analogue in the series is the 2-chloro-6-fluorophenyl carbamate **5**. The introduction of groups with combined sizes larger than a chlorine and a fluorine atom at the ortho positions, including 2,6-dichloro or 2,6-dimethyl in the benzoxazole series and 2-methoxy or 2-nitro groups in the benzothiazole series, resulted in a sharp decrease in activity (compare compounds in Table II). As the substituents at these positions became smaller than the total chlorine plus fluorine size, herbicidal activity decreased slightly

Table II. Effect of α-Phenyl Ring Substituents on Preemergent Herbicidal Activity at 8 lb/acre



compd	X	R_2	R_6	% control[a]
5	O	Cl	F	92
6	O	CH_3	H	90
7	O	CF_3	H	83
8	O	F	F	75
9	O	Br	H	75
10	O	Cl	H	73
11	O	F	H	70
12	O	Et	H	70
13	O	H	H	49
14	O	CH_3	CH_3	43
15	O	Cl	Cl	24
16	S	Cl	H	22
17	S	NO_2	H	6
18	S	OCH_3	H	3

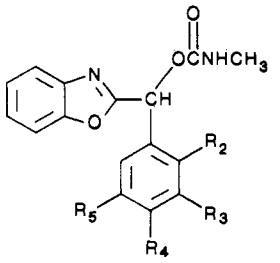
[a] Average control of all tested species: mustard, teaweed, velvetleaf, crabgrass, giant foxtail, wild oats, barnyard grass, morningglory, snapbeans, nutsedge, cucumber, marigold, and nightshade.

(analogues **11** and **8**, with 2-fluoro and 2,6-difluoro substituents, respectively). Other than size, the nature of the ortho substituents (halogen, alkyl) does not cause a major difference in the level of activity and the selectivity pattern.

Substitutents at the para position of the α-phenyl ring proved to be detrimental (compounds **25** and **26**) to herbicidal activity. The analogues with a methyl, chloro, or fluoro substituent at this position were devoid of activity. Even with the presence of an ortho substituent of suitable size, compound **27** with a para substituent was nearly inactive. The effect was independent of the electronic character of the substituent.

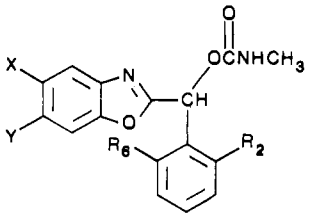
Substituents at the meta position of the α-phenyl ring

Table III. Effect of α-Phenyl Ring Meta and Para Substituents on Preemergent Herbicidal Activity at 8 lb/acre



compd	R_2	R_3	R_4	R_5	% control
19	H	CH_3	H	H	59
20	H	OCH_3	H	H	35
21	H	CF_3	H	H	10
22	H	F	H	H	10
23	H	H	H	H	49
24	CH_3	H	H	CH_3	45
25	H	H	F	H	0
26	H	H	Cl	H	0
27	CH_3	H	CH_3	H	15

Table IV. Effect of Benzoxazolyl Substituents on Preemergent Herbicidal Activity at 8 lb/acre



compd	X	Y	R_2	R_6	% control
28	Cl	H	F	H	4
29	Cl	H	CH_3	H	16
30	Cl	H	Cl	F	15
31	Cl	H	Cl	H	9
32	CH_3	H	CH_3	H	1
33	CH_3	H	Cl	H	7
34	CH_3	H	Cl	F	2
35	H	CH_3	Cl	F	18
36	H	CH_3	CH_3	H	7

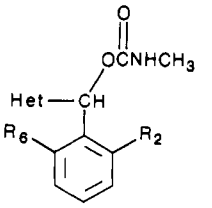
are also detrimental to activity but to a lesser degree than para substituents (Table III). With the presence of ortho substituents of suitable size, introduction of a meta substituent results in a substantial loss of activity (compound **24**).

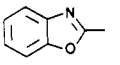
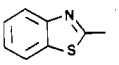
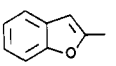
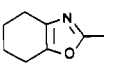
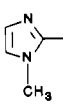
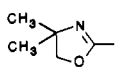
The substituents (CH_3, Cl) at the 5- or 6-position of the benzoxazolyl moiety are detrimental to herbicidal activity. Introducing the 5-Cl on the active **11** results in a complete loss of activity. Comparison of **5** with **34** illustrates the negative effect of the 5-methyl substituent (Table IV).

Replacement of the nitrogen of the benzoxazolyl ring with a CH group virtually nullifies activity (compound **37**, Table V). Similarly, replacing the oxygen with a sulfur diminishes activity (compound **10** vs. **16**). Different ring systems such as *N*-methylimidazolyl and 5,5-dimethyloxazolyl gave inactive compounds. Although the tetrahydrobenzoxazolyl carbamate **38** exhibited moderate activity, it was weak compared with its benzoxazolyl counterpart **5**. Thus, benzoxazole appears to be the optimum ring system for herbicidal activity.

The length of the carbamoyl group has a significant impact on activity with the *N*-methylcarbamate optimal and an *N*-ethyl group resulting in a substantial activity loss (Table VI). Molecular variations where the phenyl ring replaced by a cyclohexyl, *N*-methylpyrroyl, α-naphthyl, or a pyridinyl substituent were inactive (Table VII).

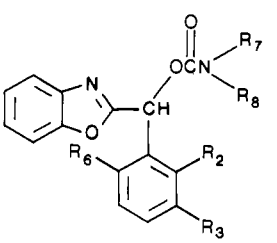
Table V. Effect of the Heterocyclic Ring on Preemergent Herbicidal Activity at 8 lb/acre



compd	heterocycle	R_2	R_6	% control
5		Cl	F	92[a]
16		Cl	H	22
37		Cl	F	6
38		Cl	F	47 (at 4 lb/acre)
39		Cl	F	0
40		Cl	H	0

[a] At 4 lb/acre, **5** was rated having 90% total average control.

Table VI. Effect of Carbamyl N-Substituents on Preemergent Herbicidal Activity at 8 lb/acre

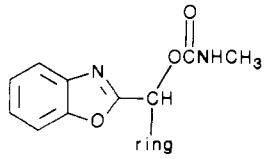


compd	R_7	R_8	R_2	R_3	R_6	% control
5	CH_3	H	Cl	H	F	92
41	CH_3	CH_3	Cl	H	F	53
42	Et	H	Cl	H	F	45
43	Et	H	H	H	H	44
44	CH_3	CH_3	H	H	H	29
45	Et	H	H	CH_3	H	5
46	*i*-Pr	H	Cl	H	F	0
47	Bu	H	Cl	H	F	0
48	C_6H_5O	H	Cl	H	F	0

The nitrogen function attached to the ester carbonyl appears to be critical for activity (Table VIII). Replacement of the carbamyl group with an acetyl, a carbonyl, or a thiocarbamyl group renders the molecule inactive. Coupling two active carbamate **10** by means of a sulfenyl linkage between carbamyl nitrogens results in an inactive compound (compound **4**).

It was found that several analogues, particularly those having a bulky α-phenyl ortho substituent underwent an unusual cyclization, followed by oxazolyl ring opening to form cyclic carbamates. Thus, about 50% of the carbamate **10** in basic solution (pH 8.9) underwent the cyclization–ring opening to give the 2-oxazolidinone **57** (Scheme VII). The parent carbamate and the oxazolidinone have very close R_f values on TLC but are separable by flash column chromatography. The structure of the oxazoli-

Table VII. Effect of the α-Ring System on Herbicidal Activity at 8 lb/acre



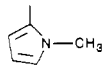
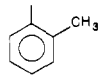
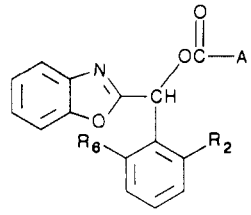
compd	ring	% control
49		0
50		0
51		0
52		0
53		0
6		90

Table VIII. Effect of the Carbamyl Functional Group on Preemergent Herbicidal Activity at 8 lb/acre



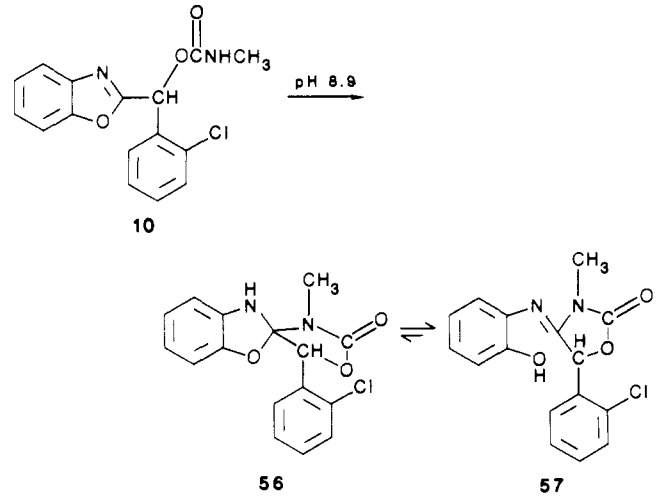
compd	A	R_2	R_6	% control
10	$NHCH_3$	Cl	H	73
3	OCH_3	Cl	H	9
54	CH_2CH_3	Cl	F	3
55	SCH_2CH_3	Cl	F	0

dinone **57** was defined on the basis of IR, ^1H NMR, ^{13}C NMR, UV, and high-resolution mass spectral data. The IR peaks at 1790 and 1680 cm^{-1} suggest the oxazolidinone and imidocarbamate functions, respectively. The characteristic *N*-methyl absorption in the ^1H NMR is at δ 3.32 as a singlet, suggesting no proton attached to the carbamoyl nitrogen. The additional evidence was provided by the electron impact high-resolution mass spectrum. The molecular formula was found to be $C_{16}H_{13}ClN_3O_3$ (*m/e* 316), the same as parent carbamate **10**. The prominent diagonostic fragments were at *m/e* 148 (base) ($C_8H_8N_2O$), 272 ($C_{15}H_{13}ClN_2O$), and 299 ($C_{16}H_{12}ClN_2O_2$). They are postulated to be the fragments in Scheme VIII.

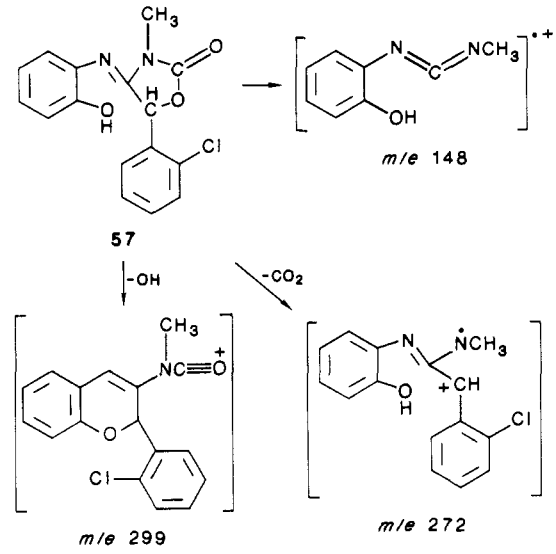
The λ_{max} at 301 nm in the UV spectrum indicates the isolated cyclic carbamate is **57** instead of the tetrahedral **56**. This isolated material was accompanied by approximately 5% of a second compound, which appeared to be the tetrahedral intermediate **56**. These findings are analogous to those reported by Jackson et al. (1972) and Goetz and Rathburn (1972) in the hydrolysis of benzoxazoles.

The oxazolidinone **57** was bioassayed and shown to be inactive at 1.2 lb/acre while its parent carbamate **10** was very active at the same rate, indicating that the herbicidal activity of **10** does not result from its cyclization.

Scheme VII



Scheme VIII



In summary, the results of this study indicate that very specific structural features are required for herbicidal activity. The optimum structure appears to be best represented by the 2-chloro-6-fluorobenzyl carbamate **5**.

ACKNOWLEDGMENT

We are grateful to E. Shulson for carrying out biological evaluations and to D. T. Manning, M. H. J. Weiden, and P. R. Timmons for helpful discussions.

Registry No. **3**, 109243-63-2; **4**, 109243-64-3; **5**, 104029-63-2; **6**, 104029-90-5; **7**, 104029-74-5; **8**, 104029-64-3; **9**, 104029-65-4; **10**, 104029-72-3; **11**, 104029-64-3; **12**, 104030-02-6; **13**, 104029-89-2; **14**, 104029-67-6; **15**, 104030-11-7; **16**, 104030-01-5; **17**, 104030-04-8; **18**, 104030-05-9; **19**, 104029-69-8; **20**, 104029-70-1; **21**, 104029-77-8; **22**, 104029-68-7; **23**, 104029-89-2; **24**, 104167-14-8; **25**, 109243-65-4; **26**, 109243-66-5; **27**, 104029-71-2; **28**, 104029-98-3; **29**, 104029-97-2; **30**, 104029-96-1; **31**, 104029-95-0; **32**, 104029-94-9; **33**, 104029-93-8; **34**, 104029-72-3; **35**, 104030-00-4; **36**, 104029-99-4; **37**, 109243-67-6; **38**, 104030-14-0; **39**, 104030-16-2; **40**, 109243-68-7; **41**, 104029-82-5; **42**, 104029-78-9; **43**, 104029-80-3; **44**, 104029-81-4; **45**, 104029-83-6; **46**, 109243-69-8; **47**, 104029-66-5; **48**, 109243-70-1; **49**, 109243-71-2; **50**, 109243-72-3; **51**, 109243-73-4; **52**, 109243-74-5; **53**, 109243-75-6; **54**, 109282-05-5; **55**, 109243-76-7; **56**, 109243-77-8; **57**, 109243-78-9; 2-(2-chloro-6-fluoro-α-hydroxybenzyl)benzoxazole, 109243-79-0; benzoxazole, 273-53-0; 2-chloro-6-fluorobenzaldehyde, 387-45-1; 2-(α-hydroxybenzyl)benzoxazole, 109243-80-3; o-aminophenol, 95-55-6; *dl*-mandelic acid, 611-72-3; phosgene, 75-44-5; bis-[(fluorocarbonyl)methylamino] sulfide, 109243-81-4.

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Endothal and Cantharidin Analogues: Relation of Structure to Herbicidal Activity and Mammalian Toxicity

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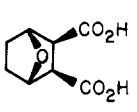
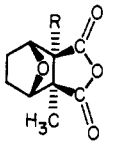
Analogues of the herbicide endothal (*exo,exo*-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid) with various ring substituents and including several geometrical isomers were synthesized via Diels–Alder reactions. They were assayed as inhibitors of root elongation in barnyard grass and wild mustard and for acute toxicity to mice on intraperitoneal administration. Studies with 43 analogues demonstrate the importance for herbicidal activity of the spatial arrangement of the bridged oxygen and the exo,exo positions of the two carboxylic acid groups. The exo,exo positions facilitate intramolecular hydrogen bonding and formation of stable metal ion complexes. The herbicidal activity of endothal is reduced on adding ring substituents due to steric hindrance around the bridged oxygen. Mammalian toxicity generally follows the same pattern except that 2,3-dimethyl substitution to form cantharidin increases activity. Somewhat similar structure–activity relationships for herbicidal activity and toxicity to mice suggest the possibility of a related oxabicycloheptane target site in plants and mammals.

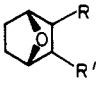
Endothal is an important herbicide, desiccant, and defoliant that is also toxic to mammals (Tischler et al., 1951; Simsiman et al., 1976; Keckemet, 1980). It is similar in



endothal (1)



cantharidin (2, R = CH_3)
palasonin (R = H)



2,3-disubstituted
7-oxabicyclo[2.2.1]heptane

structure to the natural products cantharidin (2,3-dimethylendothal anhydride), an extremely toxic vesicant and counterirritant produced by blister beetles (Sollman, 1949; Cavill and Clark, 1971), and palasonin (2-methylendothal anhydride), an anthelmintic isolated from the seeds of the tree *Butea frondosa* (Raj and Kurup, 1967; Bochis and Fisher, 1968). The common structural features of these highly bioactive compounds are the 7-oxabicyclo[2.2.1]-heptane system with *exo,exo*-2,3-dicarboxylic acid or -2,3-dicarboxylic anhydride substituents. Several related dicarboxylic acids, some with the oxabicycloheptane system, also have herbicidal activity (Koch, 1970).

The relative toxicities of **1**, **2**, and related compounds to plants and mammals may be dependent on the oxabicycloheptane system and specific ring substituents. This study therefore examines the structure–activity relationships of various endothal analogues for inhibition of root growth in barnyard grass and wild mustard and for acute toxicity to mice.

MATERIALS AND METHODS

Syntheses. *General Procedures and Intermediates.* The endothal and cantharidin analogues were usually prepared by Diels–Alder reactions of appropriate dienes and dienophiles followed by reduction and hydrolysis (Figure 1). No attempt was made to resolve optical isomers formed from certain reactions. In general, the furans in dry ether (10–20 volumes) were stirred at room temperature for 24 h with equimolar maleic anhydride or other dienophile alone or in the presence of a catalytic amount of boron trifluoride etherate (for 3-furancarboxylic acid

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