

The ampoule which contained the labeled precursor was rinsed with 1 ml of acetone and the washing was added to the reaction mixture. The mixture was stirred for 8 hr, shaken with water, decanted, and dried over molecular sieves. The calculated activity of the compound was 3.6 mCi (2.5 mCi/mmol). The compound was purified by tlc. Silica gel plates were used. The best solvent system was a 20% solution of dimethyl formamide in diethyl ether as a stationary phase and methyl cyclohexane as the mobile phase, R_f 0.24. The chemical purity was in excess of 90% and the radiochemical purity was in excess of 95%.

^{14}C -Labeled Phoxim. The synthesis of the ^{14}C -labeled phoxim involved three reaction steps. First was the preparation of phenyl acetonitrile, then the sodium salt of phenyl glyoxylonitrile oxime was synthesized, and finally phoxim was prepared.

^{14}C -Labeled NaCN (Amersham/Searle, 56.6 mCi/mmol, 1.0 mCi) was added to 0.5 g of unlabeled NaCN. The synthesis of phenyl acetonitrile was conducted in the manner described earlier, with the following changes. Benzyl chloride, 1.1 g in 1 ml of ethanol, was added to the NaCN in 1 ml of water. After being heated and filtered, the solution was dried with molecular sieves and the ethanol was removed under vacuum. The product was not distilled and in the "cold" run no benzyl chloride or benzyl isocyanide was observed in the ir spectrum of the product.

The labeled phenyl acetonitrile was then reacted with

760 mg of butyl nitrite and 4 ml of a sodium ethoxide solution (sodium, 170 mg, was reacted with 40 ml of ethanol, thus forming the solution used in the synthesis). After the reaction was complete, the volume was concentrated to about 2 ml, and then 4 ml of diethyl ether was added to precipitate the sodium salt of the oxime.

The oxime was then reacted with 750 mg of diethyl phosphorochloridothionate. The overall yield for this reaction sequence was 34.2%. The calculated activity for the compound was 0.34 mCi (0.1 mCi/mmol). The chemical and radiochemical purity were the same as with the ^{32}P synthesis.

Structure Identification. Infrared, nmr, and mass spectra of all of the final products were used to prove their composition. These will be presented later when the metabolite investigation is reported.

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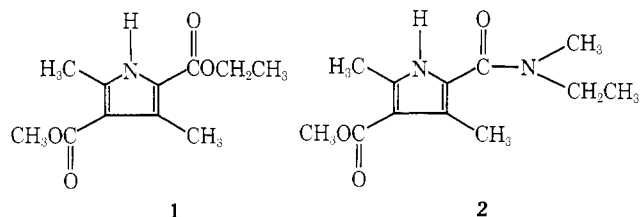
Herbicidal Activity of Ester and Amide Derivatives of Substituted Pyrrole-2,4-dicarboxylic Acids

Allen R. Church, Gerhard A. Hüppi,¹ Malcolm W. Moon,* Arnolds Steinhardt,² and Henry J. Vostrál

Ester and tertiary amide derivatives of 3,5-dimethylpyrrole-2,4-dicarboxylic acid 4-methyl ester were herbicidally active at low rates. The esters were postemergence herbicides, while the amides showed both preemergence and postemergence activity. Compounds in both series were

more active on broadleaved weeds than grasses. The 5-methyl and 4-carbomethoxy substituents and an unsubstituted pyrrole ring nitrogen atom were essential for high activity in these pyrrole herbicides.

Investigations in our laboratories showed that the ethyl ester (1) and ethylmethylamide (2) derivatives of 3,5-di-



methylpyrrole-2,4-dicarboxylic acid 4-methyl ester were active as herbicides. Related pyrroles having certain structural features in common with 1 and 2 also had herbicidal activity. In this report the herbicidal activities of compounds 1 and 2 and related pyrroles are presented.

MATERIALS AND METHODS

Chemical Methods. Diesters of substituted pyrrole-2,4-dicarboxylic acids are readily prepared by nitrosation of a β -keto ester (I) followed by reduction of the resulting oxime II in the presence of a second β -keto ester. The reduction may be effected using zinc dust in acetic acid (Knorr, 1888), sodium amalgam (Knorr and Hess, 1912), or by catalytic hydrogenation (Ochiai *et al.*, 1935). The method of Knorr is convenient in that ester I is converted in acetic acid to the pyrrole without isolation of intermediate II. Using this method compounds 1, 5, 6, 11 (Table II), and 22-39 (Table III) may be prepared.

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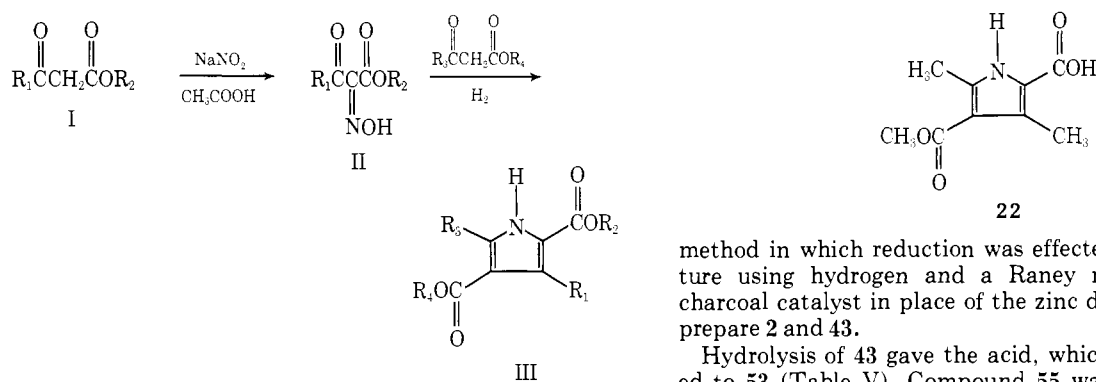
² Deceased.

Table I. Herbicidal Activities of Pyrrole Ester 1^a and Pyrrole Amide 2^b

	1		2		Preemergence	
	3 lb/acre	1 lb/acre	3 lb/acre	1 lb/acre	3 lb/acre	1 lb/acre
Black nightshade (<i>Solanum nigrum</i>)	10	10	10	10	7	2
Chickweed (<i>Stellaria media</i>)	10	8	10	10	10	5
Coffeeweed (<i>Daubentonia texana</i>)	10	0	10	2	10	2
Curlydock (<i>Rumex crispus</i>)	10	5	10	5	10	5
Dandelion (<i>Taraxacum officinale</i>)	7	4	3	0	10	5
Jimsonweed (<i>Datura stramonium</i>)	10	10	10	5	8	0
Morningglory (<i>Ipomoea purpurea</i>)	10	3	7	2	9	8
Pale smartweed (<i>Polygonum lapathifolium</i>)	10	10	10	9	10	9
Purslane (<i>Portulaca oleracea</i>)	10	10	10	10	10	10
Redroot pigweed (<i>Amaranthus retroflexus</i>)	4	0	10	8	10	6
Sesbania (<i>Sesbania exaltata</i>)	6	4	6	0	10	10
Shepherdspurse (<i>Capsella bursa-pastoris</i>)	10	10	10	10	10	10
Velvetleaf (<i>Abutilon theophrasti</i>)	8	5	5	0	6	4
Wild mustard (<i>Brassica kaber</i>)	10	10	10	10	10	10
Yellow rocket (<i>Barbarea vulgaris</i>)	10	10	10	10	10	3
Barnyardgrass (<i>Echinochloa crusgalli</i>)	2	0	2	0	7	4
Bermudagrass (<i>Cynodon dactylon</i>)	8	7	3	0	8	0
Blackgrass (<i>Alopecurus myosuroides</i>)	6	3	5	0	7	2
Crabgrass (<i>Digitaria sanguinalis</i>)	2	2	0	0	10	5
Wild oat (<i>Avena fatua</i>)	2	0	0	0	7	0
Quackgrass (<i>Agropyron repens</i>)	6	4	9	0	9	0
Johnsongrass (<i>Sorghum halepense</i>)	0	0	2	0	6	4
Average reading of broadleaves	9.7	6.5	8.7	6.0	9.3	5.9
Average reading of grasses	3.7	2.3	3.0	0	7.7	2.2

^a The formulation of 1 used in this test was air milled and contained 50% of 1, 1% Nekal BA-75, 2% Polyfon F, and 47% Attaclay.

^b The formulation of 2 used was hammer milled and contained 75% of 2, 1% Nekal BA-77, 2% Polyfon F, and 22% Barden Clay.



Bromo compound 7 (Table II), prepared from 1 by the general method of Corwin *et al.* (1942), was reduced to 3. Compound 1 reacted with sulfur chloride in ether to give 4. Hydrolysis of 1 under acidic conditions (Fischer and Walach, 1925) gave acid 8 which was converted, *via* the acid chloride, into the thioester 10 and amide derivatives 11–13. Decarboxylation of 8 afforded 14 and this was used to prepare compounds 15–19 by known methods (Fischer and Schubert, 1926; Fischer *et al.*, 1928, 1929).

Hydrolysis of 1 under alkaline conditions gave acid 22. This was converted to the acid chloride, which was reacted with the appropriate amine to give amides 39–52 (Table IV). The dialkylamides were more conveniently obtained by the method of Knorr, using an *N,N*-dialkyl acetoacetamide in place of ester I. A modification of this

method in which reduction was effected at room temperature using hydrogen and a Raney nickel or palladium charcoal catalyst in place of the zinc dust was also used to prepare 2 and 43.

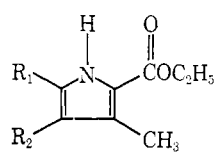
Hydrolysis of 43 gave the acid, which was decarboxylated to 53 (Table V). Compound 55 was prepared by reaction of 53 with propionyl chloride in the presence of aluminum chloride. Compounds 54, 56, and 57 were prepared by the general method of Knorr (1888) described above.

Structures and purities were confirmed by nmr, tlc, gc, and ir analyses; satisfactory elemental analyses ($\pm 0.3\%$) were obtained for all compounds.

Two methods for the preparation of pyrrole amides are described below for the synthesis of 48 and 2; these methods are generally applicable for the synthesis of compounds 39–52.

Preparation of Amide 48 from 22. A mixture of 3,5-dimethylpyrrole-2,4-dicarboxylic acid 4-methyl ester, compound 22 (16.8 g), and acetyl chloride (400 ml) was refluxed for 30 min. The dark brown reaction solution was cooled to -40° and the precipitate was filtered off and

Table II. Chemical Data and Herbicidal Activities of Substituted Ethyl 3-Methylpyrrole-2-carboxylates

Compound no.				Mp, °C	Post-emergence herbicidal activity, 12 lb/acre
	R ₁	R ₂	R ₃		
3 ^a	H	-C(=O)OCH ₃	CH ₃	69-71	0
2 ^b	CH ₃	-C(=O)OCH ₃	CH ₃	130-132	8.2
4	CH ₂ Cl	-C(=O)OCH ₃	CH ₃	157-159	0
5	CH ₂ CH ₃	-C(=O)OCH ₃	CH ₃	131	2.4
6	CH ₂ CH ₂ CH ₃	-C(=O)OCH ₃	CH ₃	101-102	0
7 ^a	Br	-C(=O)OCH ₃	CH ₃	189-191	0
8 ^c	CH ₃	-C(=O)OH	CH ₃	272-274	0
9 ^{d,e}	CH ₃	-C(=O)OCH ₂ CH ₃	CH ₃	127-130	0
10	CH ₃	-C(=O)SCH ₃	CH ₃	136-137	0
11	CH ₃	-C(=O)NHCH ₃	CH ₃	218-219	6.3 ^f
12	CH ₃	-C(=O)NHCH ₂ CH ₃	CH ₃	197-199	1.1
13	CH ₃	-C(=O)N(CH ₃) ₂	CH ₃	143-145	0
14 ^g	CH ₃	H	CH ₃	123-124	0
15 ^h	CH ₃	-CH=O	CH ₃	142-143	0
16 ^g	CH ₃	-C(=NOH)H	CH ₃	194-196	0
17 ^{i,j}	CH ₃	-C(=O)CH ₃	CH ₃	143-144	5.8 ^k
18 ^l	CH ₃	-C(=O)CH ₂ CH ₃	CH ₃	138-139	6.0 ^m
19 ^l	CH ₃	-C(=O)CH ₂ CH ₂ CH ₃	CH ₃	114-117	0

^a Prepared from 1 using the method of Corwin *et al.* (1942). ^b Küster (1922). ^c Fischer and Walach (1925). ^d Knorr (1888). ^e Previously reported inactive as a herbicide by Thompson *et al.* (1946). ^f In the tests at 6, 3, and 1 lb/acre this compound showed average weed control readings of 3.7, 2.9, and 1.6, respectively. ^g Fischer *et al.* (1923). ^h Fischer *et al.* (1928). ⁱ Fischer *et al.* (1929). ^j Reported as a herbicide by Thompson *et al.* (1946). ^k In the tests at 6, 3, and 1 lb/acre 17 showed average weed control readings of 3.3, 2.1, and 0. ^l Fischer and Schubert (1926). ^m In the tests at 6, 3, and 1 lb/acre 18 showed average weed control readings of 3.3, 2.4, and 0.

washed with hexane. This gave 12.7 g (67%) of acid chloride, mp 126-129°, which was used without further purification.

The acid chloride (4.0 g) was added to a stirred solution of *N*-methyl allylamine (8.0 g) in methylene chloride (50 ml) at 25°. After 1 hr the reaction solution was evaporated; the residual oil crystallized on addition of water to give 3.8 g (85%) of methyl 5-(allylmethylcarbamoyl)-2,4-dimethylpyrrole-3-carboxylate (compound 48), mp 116-119°. Two recrystallizations from benzene-hexane gave the analytical sample, mp 116.5-118.5°.

Anal. Calcd for C₁₃H₁₈N₂O₃: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.61; H, 7.34; N, 11.14.

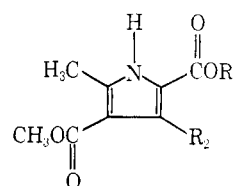
Preparation of Amide 2 by Catalytic Hydrogenation Method. A solution of sodium nitrite (13.0 g, 0.19 mol) in water (20 ml) was added dropwise to a stirred solution of *N*-ethyl *N*-methyl acetoacetamide (31.0 g, 0.22 mol) in acetic acid (125 ml) at 10°. The solution was allowed to warm to 25° after addition was completed. After 30 min at 25°, methyl acetoacetate (34.8 g, 0.30 mol) and 10% palladium charcoal (1.0 g) were added and the solution was hydrogenated (50 lb initial hydrogen pressure) until the uptake of hydrogen ceased (30 hr, 0.3 mol hydrogen absorbed). The catalyst was filtered off and the reaction solution diluted with water to give 39.8 g (76%) of methyl 5-(ethylmethylcarbamoyl)-2,4-dimethylpyrrole-3-carboxylate (compound 2), mp 116-119°. The analytical sample was recrystallized from methylene chloride-hexane, mp 115-119°.

Anal. Calcd for C₁₂H₁₈N₂O₃: C, 60.48; H, 7.61; N, 11.71. Found: C, 60.29; H, 7.58; N, 11.87.

Biological Methods. Herbicide results were obtained in the greenhouse using a soil mixture composed of equal parts by volume of top soil, peat moss, and sand. Initial testing involved a single treatment on seven weed species sown in rows across a 5 × 7 in. tray. All other testing involved two replications with four species planted in the corners of 5 × 5 in. trays.




Each chemical was pulverized with an equal weight of Clintland clay and then suspended in water containing

Table III. Chemical Data and Herbicidal Activities for Ester Derivatives of Substituted 5-Methylpyrrole-2,4-dicarboxylic Acid 4-Methyl Ester^a

Compound no.				Mp, °C	Postemergence herbicidal activity		
	R ₁	R ₂	6 lb/acre		3 lb/acre	1 lb/acre	
22 ^b	H	CH ₃	CH ₃	227-229			
23 ^b	-CH ₃	CH ₃	CH ₃	175-176			
1 ^b	-CH ₂ CH ₃	CH ₃	CH ₃	130-132	8.5	7.1	2.3
24	-CH ₂ CF ₃	CH ₃	CH ₃	123-124	8.9	7.4	4.2
25	-CH ₂ CH ₂ CH ₃	CH ₃	CH ₃	99-100	8.0	3.9	2.0
26	-CH(CH ₃) ₂	CH ₃	CH ₃	149-150	7.3	7.0	5.4
27	-CH ₂ CH ₂ CH ₂ CH ₃	CH ₃	CH ₃	87-88	2.4	2.0	0
28	-CCH ₃ HCH ₂ CH ₃	CH ₃	CH ₃	145-146	7.9	6.3	3.0
29	-CH ₂ CH(CH ₃) ₂	CH ₃	CH ₃	129-130	9.0	6.9	2.6
30 ^c	-C(CH ₃) ₃	CH ₃	CH ₃	144-145	6.9	6.2	3.9
31	-CH(CH ₂ CH ₃) ₂	CH ₃	CH ₃	99-101	6.9	5.6	0
32	-CH ₂ C(CH ₃) ₃	CH ₃	CH ₃	138-139	7.0	4.6	1.9
33 ^c	-C(CH ₃) ₂ CH ₂ CH ₃	CH ₃	CH ₃	98-100	4.4	3.3	1.3
34	-CCH ₃ H(CH ₂) ₃ CH ₃	CH ₃	CH ₃		4.6	4.0	0
35	-CH ₂ CH ₃	H	CH ₃	158-159	2.3	0	0
36	-CH ₂ CH ₃	CF ₃	CH ₃	105	7.6	6.9	2.3
37	-CH ₂ CH ₃	CH ₂ CH ₃	CH ₃	110-111	4.8	3.5	1.8
38	-CH ₂ CH ₃	CH ₂ CH ₂ CH ₃	CH ₃	104-105	6.2	4.7	2.0

^a Compounds 24-38 have been described by Hüppi and Church (1971). ^b Küster (1922). ^c Fritz (1963).

Table IV. Chemical Data and Herbicidal Activities of Amide Derivatives of 3,5-Dimethylpyrrole-2,4-dicarboxylic Acid 4-Methyl Ester

Compound no.	Chemical structure		Mp, °C	Herbicidal activity						
	R ₁	R ₂		Preemergence			Postemergence			
	6 lb/acre	3 lb/acre		1 lb/acre	6 lb/acre	3 lb/acre	1 lb/acre			
39 ^a	H	H	205-207							
40 ^a	H	CH ₃	228-232							
41 ^a	H		195-196							
42 ^a	H	CH ₂ CH ₃	178-179							
43	CH ₃	CH ₃	149-150	7.3	5.4	2.1	7.8	5.0	1.8	
2	CH ₃	CH ₂ CH ₃	115-119	9.7	8.7	5.4	10.0	9.4	3.4	
44	CH ₃	CH ₂ CH ₂ CH ₃	124-126	9.4	5.8	4.1	9.4	6.6	2.7	
45	CH ₃	CH(CH ₃) ₂	158-161	9.5	5.8	3.3	7.5	4.6	0.9	
46	CH ₃	CH ₂ CH ₂ CH ₂ CH ₃	89-91	8.1	4.1	0.6	4.6	3.5	2.0	
47	CH ₃		165-168	5.6	4.8	2.6	3.1	2.4	0	
48	CH ₃	CH ₂ CH=CH ₂	116-118	8.4	6.9	3.4	9.0	7.1	4.6	
49 ^a	CH ₃		173-175							
50	CH ₂ CH ₃	CH ₂ CH ₃	135-136	1.5	0	0	2.6	1.4	0.5	
51	CH ₂ CH ₂ CH ₃	CH ₂ CH ₂ CH ₃	94-96							
52		-CH ₂ CH ₂ CH ₂ CH ₂ -								

^a These compounds were inactive at 12 lb/acre.

Table V. Chemical Data and Herbicidal Activities of Various Pyrrole Amides

Compound no.	Chemical structure		Herbicidal activity, 12 lb/acre	
	R ₁	Mp, °C	Pre-emergence	Post-emergence
53	H	128-130	0	0
43	C(=O)OCH ₃	149-150	6.6	7.6
54	-C(=O)CH ₃	158-160	0	3.0
55	-C(=O)CH ₂ CH ₃	144-146	4.7 ^a	6.5 ^b
56	-C(=O)NHCH ₃	186-189	5.6 ^c	0.2
57	-C(=O)N(CH ₃) ₂	214-217	0	0

^a In the tests at 6, 3, and 1 lb the average readings were 4.3, 1.0, and 0, respectively. ^b At 6, 3, and 1 lb average readings were 5.8, 3.1, and 0, respectively. ^c At 6, 3, and 1 lb average readings were 1.5, 0, and 0, respectively.

0.15% Tween 20 for spraying; all application rates were calculated on the basis of the pyrrole ingredient. The chemicals were first applied pre- and postemergence at 12 lb/acre to the following species: field bindweed (*Convolvulus arvensis*), buckhorn plantain (*Plantago lanceolata*), large crabgrass (*Digitaria sanguinalis*), curly dock (*Rumex crispus*), johnsongrass (*Sorghum halepense*), wild oat (*Avena fatua*), and yellow foxtail (*Setaria glauca*). Post-emergence treatments were sprayed 2 weeks after seeding and all treatments were rated visually 3 weeks after application using a 0 (no effect) to 10 (plants dead) scale relative to an untreated check; the data are averaged for the seven weed species.

Active chemicals were then applied at rates of 6, 3, and 1 lb/acre to the following weeds: jimsonweed (*Datura*

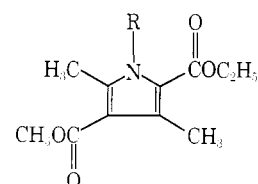
stramonium), redroot pigweed (*Amaranthus retroflexus*), purslane (*Portulaca oleracea*), pale smartweed (*Polygonum lapathifolium*), barnyardgrass (*Echinochloa crus-galli*), bermudagrass (*Cynodon dactylon*), blackgrass (*Alopecurus myosuroides*), and johnsongrass (*Sorghum halepense*). Postemergence applications were made 2 weeks after seeding; ratings were recorded and averaged as in the initial testing.

Compounds 1 and 2 were further evaluated at 3 and 1 lb/acre on the additional species shown in Table I.

RESULTS AND DISCUSSION

Compounds 1 and 2 at equivalent rates exhibited similar postemergence activities, being considerably more phytotoxic to broadleaved weeds than grasses (Table I). While ester 1 showed little preemergence activity, amide 2 was highly active as a preemergence broadleaf herbicide.

Analogs of 1 in which substituents at ring positions 4 and 5 varied were less active than the parent compound. Any change in the 5-methyl substituent essentially eliminated activity (compounds 3-7). The 4-carbomethoxy substituent also was required for optimum activity. Among other acid derivatives (compounds 8-13, Table II), only the methylamide 11 was active, and of the related ketones (15-19) only 17 and 18 were active. The activity of compounds 11 and 18 suggested that, *inter alia*, the size of the carbonyl substituent at position 4 was important for activity.



20, R = CH₃

21, R = C₂H₅

Herbicidal activity was also lost when the ring nitrogen in 1 was alkylated (20 and 21).

Many analogs of 1 in which substituents at ring positions 2 and 3 varied were highly active as herbicides (Table III). Acid 22 showed no activity. Methyl ester 23 was surprisingly inactive, while the ethyl (1) and higher esters (24-34) were all highly active. The *n*-propyl (25) and *n*-butyl (27) esters were both less active than their branched-chain isomers (26 and 28-30, respectively). The methyl substituent at position 3 (R_2) was not essential for activity; compounds in which R_2 was hydrogen, trifluoromethyl, ethyl, and propyl (35-38) were all herbicidal.

Amide 2 also was one of a series of related pyrrole herbicides (Table IV). Primary (39) and secondary (40-42) amides were inactive while tertiary aliphatic amides 2, 43-48, and 50 were herbicidal. For high activity one of the alkyl groups (R_1 , R_2 , Table IV) must be methyl (2, 43-48). The diethylamide 50 showed low activity and dipropylamide 51 was inactive. Also inactive were tertiary aromatic amide 49 and cyclic amide 52.

As was found for the pyrrole ester herbicides (Table II), the 4-carbomethoxy substituent was necessary for optimum activity in the amide series (Table V). The propionyl (55) and methylcarbonyl (56) derivatives also were herbicidal but were less active than 43.

Under field conditions, postemergence applications of 1 and incorporated treatments of 2 have controlled tall morningglory (*Ipomoea purpurea*), lambsquarters (*Chenopodium album*), and redroot pigweed (*Amaranthus retroflexus*). Compound 2 has also shown promising results in the greenhouse on cocklebur (*Xanthium pensylvanicum*) and jimsonweed (*Datura stramonium*). Corn (*Zea mays*) exhibited tolerance to both compounds, while peanut (*Arachis hypogaea*) is also tolerant to 1.

The exact mode of action of compounds 1 and 2 has not been studied, but they appear to be slow-acting translocated herbicides. Injury symptoms become apparent about 1 week after treatment. Chlorotic cotyledonary leaf margins are the first visible symptoms, followed by overall chlorosis and then necrosis of the whole leaf. Usually vegetative buds produce only one or two more true leaves following treatment. Neither compound inhibits germination, and plants treated preemergence with 2 rarely produce true leaves.

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New Potent Pyrethroid, Bromethrin

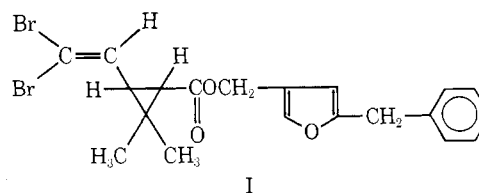
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A new pyrethroid was synthesized with insecticidal characteristics similar to those of resmethrin. The new compound, called bromethrin, resembles resmethrin in structure, with replace-

ment of the isobutenyl methyls by bromine atoms. Toxicity studies indicate the *dl-trans*-bromethrin to be similar in toxicity to *d-trans*-resmethrin.

Several studies reported in the literature have indicated that the major pathway of catabolism of pyrethroids in houseflies is through the oxidative degradation of the isobutenyl *trans*-methyl group of the chrysanthemic acid moiety to an inactive carboxyl function (Yamamoto and Casida, 1966, 1969). These findings suggested to us that replacement of the isobutenyl methyl groups by functions resistant to degradation might yield an insecticide of enhanced stability and potency. Farkas *et al.* (1958) have reported the replacement of the isobutenyl methyl groups by chlorine atoms; the resulting toxicity in the allethrin series was found to be similar to that of allethrin. The replacement of the methyl groups by bromine atoms was

proposed because of the successes of such replacements in the synthesis of other bioactive analogs (Davern, 1960). We now report the synthesis and preliminary toxicity data for the dibromo analog (5-benzyl-3-furyl)methyl 2-(2,2-dibromovinyl)-3,3-dimethylcyclopropanecarboxylate (I).



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The acid II was synthesized using commercial ethyl chrysanthemate as the starting material. The ester was ozonized according to the procedure of Ueda and Matsui (1970). The aldehyde produced was then reacted with