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A number of related 1,3,4-thiadiazole derivatives have been synthesized and their herbicidal activities have been evaluated by pre-emergence, postemergence, and irrigated water treatment methods. Some 1-substituted-3-(5-substituted-1,3,4-thiadiazol-2-yl)ureas showed excellent herbicidal activity. This activity depends upon the molecular size of the substituent in the 5-position of 1,3,4-thiadiazole ring. In particular, activity is maximized when the substituent is the tertiary-butyl group, while replacement of the O atom in the urea moiety with a S atom resulted in decreased herbicidal activity. Further correlations of chemical structure to herbicidal activity are discussed.

In the course of the work with 1,3,4-thiadiazole derivatives, the authors noted that some compounds possess remarkably strong herbicidal activity. Since no clear picture could be obtained from the available data on the herbicidal properties of 1,3,4-thiadiazole derivatives, it was decided to investigate the relationship between molecular structures and herbicidal properties.

The following five general types of derivatives have been prepared starting from 2-amino-5-substituted-1,3,4-thiadiazoles (the R, R', or R" in these formulas have been varied systematically):

Type I R
$$-$$
 S $-$ NH₂ R = alkyl or aryl radical

K1 K1

Type III
$$R \xrightarrow{N}_{S} NHCNHR'$$
 R, R' = alkyl or
aryl radical

. .

Type IV
$$R = \frac{N - N}{Cal}$$
 $NHCR'$ $R, R' = alkyl radical$

Type V
$$R \xrightarrow{N-N}_{S}$$
 NHSO₂CH₃ $R = alkyl radical$

After preparation, these compounds were subjected to herbicidal tests using pre-emergence, post-emergence, and irrigated-water treatment methods. As a result of the studies some compounds belonging to Type II showed the most prominent herbicidal activity among the above five types of derivatives. Some correlations of herbicidal activity have been made by changing the substituents in the 5-position of 1,3,4-thiadiazole nucleus and in the urea moiety. The optimum herbicidal activity was found to be in the structure of 1-methyl or 1,1-dimethyl-3-(5-*tert*-butyl-1,3,4-thiadiazol-2-yl)-urea.

COMPOUND SYNTHESIS

2-Amino-5-substituted-1,3,4-thiadiazoles (Type I). A series of 2-amino-5-alkyl-1,3,4-thiadiazoles were prepared by the conventional method of using thiosemicarbazide and aliphatic carboxylic acids in the presence of concentrated sulfuric acid (Chuff and Nissenbaum, 1959; Potts and Huseby, 1966). 2-Amino-5-aryl-1,3,4-thiadiazoles were prepared by cyclization of 1-aryloylthiosemicarbazides in concentrated sulfuric acid (Maffii *et al.*, 1958).

1-Substituted-3-(5-substituted-1,3,4-thiadiazol-2-yl)ureas (Type II). Methylisocyanate was obtained from a commercial source. Allylisocyanate was supplied through the courtesy of Chemetron Chemicals, New York. The various arylisocyanates were prepared according to the method of Shriner *et al.* (1950). The following general procedure was used throughout, for the preparation of 1-methyl- and 1-allyl-3-(5-substituted-1,3,4-thiadiazol-2-yl)ureas:

In the typical experimental run, 34 grams (0.6 mole) of methylisocyanate was added to a suspension of 78.6 grams (0.5 mole) of 2-amino-5-*tert*-butyl-1,3,4-thiadiazole in 200 ml. of dioxane. The mixture was stirred at room temperature for 1 hour, heated on a steam bath for 1 hour, and concentrated in a vacuum. The white crystalline product was recrystallized from aqueous alcohol. The other ureas were prepared in the same manner, but the procedure used for the syntheses of the 1-aryl-3-(5-*tert*-butyl-1,3,4-thiadiazol-2-yl) ureas was performed by using three times more dioxane solvent. The melting points (uncorrected), and analytical data of 1-substituted-3-(5-substituted-1,3,4-thiadiazol-2-yl)ureas are listed in Table I.

1,1-Dimethyl-3-(5*-tert***-butyl-1,3,4-thiadiazol-2-yl)urea** (Type II). Fifteen grams (0.14 mole) of dimethylcarbamoyl chloride and 11.2 grams (0.11 mole) of triethylamine were added successively to a suspension of 15.7 grams (0.1 mole) of 2-amino-5-*tert*-butyl-1,3,4-thiadiazole in 40 ml. of acetone. The mixture was refluxed for 2 hours, and concentrated under vacuum. The residue was dissolved in dichloromethane, and concentrated after washing with dilute hydro-chloric acid and water successively. The residue crystallized after standing several days in a freezer. Recrystallization from 10% aqueous alcohol gave the crystalline product, which melts at 80–82° C. and weighed 20 grams (88% yield).

1-Substituted-3-(5-*tert*-butyl-1,3,4-thiadiazol-2-yl)2-thioureas (Table III). A mixture of 3.14 grams (0.02 mole) of

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Table I. Physical Properties and Herbicidal Activity of 1-Substituted-3-(5-substituted-1,3,4-thiadiazol-2-yl)ureas

Herbicidal Activity at a Dosage of 5 kg./ha.

-p	:	soiA	0	0	0	0	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
rrigate sr Metl	der spikerush	nslen	0	0	0	-	0	0	ŝ	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Iwate	ssergerass	Ilgu	0	0	1	ŝ	0	0	S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
P	ardgrass	Orcl	0	7	7	S	0	0	ŝ	0	0	0	0	-	7	0	0	0	1	0	1	7	0	0
Metho	.6L	volD	0	3	ŝ	5	0	0	S	0	0	0	0	0	0	0	0	0	1	0	-	-	0	0
rgence	ysi	рвЯ	0	4	5	S	1	1	Ś	0	Ι	1	1	0	5	0	0	0	5	0	5	S	0	0
st-eme	18	əų _Λ	0	-	1	5	0	0	2	0	0	1	0	0	1	0	0	0	-	0	-	7	0	0
Pe		sviЯ	0	1	1	S	0	0	ŝ	0	0	1	0	0	-	0	0	0	-	0	-	7	0	0
po	ssergbras	Orcl	0	0	0	0	0	0	ŝ	0	0	0	0	0	0	0	0	0	0	0	0	Ś	0	0
Meth	.er	V0ID	0	0	0	0	0	0	S	0	0	0	-	0	0	0	0	0	0	0	0	S	0	0
gence	u si	рвЯ	0	0	0	0	0	0	S	0	0	0	-	0	0	0	0	0	0	0	0	Ś	0	0
e-emei	18	эųМ	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pre	1	siЯ	0	0	0	0	0	0	7	0	0	0	0	0	0	0	0	0	0	0	0	-	0	0
	ĺ	Z	32.48	30.03	27.80	27.82	26.06	26.15	26.17	:	:	•	•	:	•			:		•	•		•	:
	10 Prove	H H	4.72	5.47	5.99	6.26	6.68	6.68	6.63	6.98	7.93	8.26	9.08	6.28	4.84	5.17	5.68	6.31	6.28	6.87	6.80	6.85	4.38	4.85
	l Analysis	C	34.80	38.69	41.96	41.82	44.97	44.78	44.84	47.28	51.05	54.68	57.46	47.98	35.79	42.49	45.54	47.89	47.91	50.05	50.21	50.45	51.38	53.09
	Elementa	° Z	32.53	30.08	27.98	27.98	26.15	26.15	26.15	:	:	:		•	:	:	:	:	:	:				:
	Colonio to Colonio de	H	4.68	5.41	6.04	6.04	6.60	6.60	6.60	7.06	7.86	8.15	9.03	6.24	4.98	5.08	5.70	6.24	6.24	6.71	6.71	6.71	4.30	4.87
	:	C	34.87	38.69	41.98	41.98	44.84	44.84	44.84	47.35	51.54	54.86	57.66	47.77	35.64	42.41	45.27	47.77	47.77	49.98	49.98	49.98	51.27	53.21
		()°C) (°C)	248	178	155	155	155	154–156	208–210	134	132-137	112	127-128	163-165	172	205	162-163	136	159-160	138-139	146	117-119	224	212
	0 HCNH-R	R ′ =	Methyl	Methyl	Methyl	Methyl	Methyl	Methyl	Methyl	Methyl	Methyl	Methyl	Methyl	Methyl	Methyl	Allyl	Allyl	Allyl	Allyl	Allyl	Allyl	Allyl	Methyl	Methyl
	z z z z z s z z	R =	Methyl	Ethyl	n-Propyl	iso-Propyl	n-Butyl	iso-Butyl	tert-Butyl	<i>n</i> -Pentyl	n-Heptyl	<i>n</i> -Nonyl	n-Undecyl	Cyclopentyl	Methoxymethyl	Methyl	Ethyl	n-Propyl	iso-Propyl	<i>n</i> -Butyl	iso-Butyl	tert-Butyl	Phenyl	Benzyl





Figure 1. Related compounds with 1,3,4-thiadiazole nucleus

2-amino-5-*tert*-butyl-1,3,4-thiadiazole and 0.03 mole of alkyl- or aryl-isothiocyanate in 25 ml. of ethanol was refluxed for 24 hours. The mixture was concentrated and diluted with ether to give the 1-alkyl- or 1-aryl-3-(5-*tert*-butyl-1,3,4-thiadiazol-2-yl)-2-thiourea (Table II).

2-Acylamido - 5 - substituted - 1,3,4 - thiadiazoles (Type IV). Various 5-substituted derivatives of 2-acetamido-1,3,4-thiadiazoles and 2-propionamido-1,3,4-thiadiazoles were prepared by treating 2-amino-5-substituted-1,3,4-thiadiazoles (I) with acetic anhydride and propionic anhydride, respectively, according to the method of Ueda *et al.* (1959). 2-Chloro-acetamido-5-substituted-1,3,4-thiadiazoles were prepared by the method of Gogiu and Mavrodin (1967).

2-Methanesulfamido-5-substituted-1,3,4-thiadiazoles (Type V). Three grams (0.026 mole) of methanesulfonyl chloride was added to a suspension of 3.14 grams (0.02 mole) of 2-amino-5-*tert*-butyl-1,3,4-thiadiazole in 10 ml. of pyridine. The mixture was mixed well, heated on a steam bath for 2 hours, and concentrated under vacuum. The residue was mixed with water and acidified by the addition of 10% hydrochloric acid. 2 - Methanesulfamido - 5 - *tert*-butyl-1,3,4-thiadiazole, which melts at 170–172° C., was isolated on workup with a yield of 43%. A series of 2-methanesulfamido-5-substituted-1,3,4-thiadiazoles were prepared in the same way.

Other Related Compounds with 1,3,4-Thiadiazole Nucleus. A series of related compounds, as shown in Figure 1, were prepared by using conventional methods. 2-Amino-5hydroxy-1,3,4-thiadiazole(VI), m.p. 177° C., was synthesized by the method of Freund and Schander (1896). 1,3,4-Thiadiazol-2,5-dithiol(VII), m.p. 163° C., was prepared from hydrazine and carbondisulfide by Losanitch's method (1922). 2-Amino-5-mercapto-1,3,4-thiadiazole(VIII), m.p. 232° C., was prepared according to Guha (1922). A treatment of VIII with dimethyl sulfate in 20% aqueous sodium hydroxide gave 2-amino-5-methylthio-1,3,4-thiadiazole(IX), m.p. 178° C. A treatment of VIII with monochloroacetic acid, ethylmonochloroacetate, allyl chloride, benzyl chloride, and 2,4-dinitrochlorobenzene in 20% aqueous alkali solution gave 5-carboxymethylthio-isomer(X), m.p. 244-245° C., 5-ethoxycarbonylmethylthio-isomer(XI), m.p. 89-90° C., 5-allylthio-isomer(XII), m.p. 75° C., 5-benzylthio-isomer

			F	re-eme	rgence	Metho	d	Post-emergence Method						Water Method				
N-N R-S-NH-X			30	heat	adish	lover	rchardgrass	ice	heat	adish	lover	rchardgrass	arnyardgrass	lender spikerush	icc			
R =	Type	X =	¥	×	R	C	0	¥	2	¥	0	0	æ	S	~			
Methyl	lV V	$\left. \begin{array}{c} \mathbf{Acyl} \\ \mathbf{SO}_{2}\mathbf{CH}_{3} \end{array} \right)$		(I	nactive	:)			()	(nactive)			(Inactive)				
Ethyl	IV V	$\left. \begin{array}{c} \mathbf{Acyl} \\ \mathbf{SO}_{2}\mathbf{CH}_{3} \end{array} \right\rangle$		(I	nactive	:)			(1	(nactive)		(Inactive)						
<i>n</i> -Propyl	IV V	$\left. \begin{array}{c} \mathbf{Acyl} \\ \mathbf{SO}_{2}\mathbf{CH}_{3} \end{array} \right\}$		(1	nactive	e)			(Inactive)	(Inactive)							
iso-Propyl	IV V	Acyl SO ₂ CH ₃		(1	nactive	e)			((Inactive)								
<i>n</i> -Butyl	IV V	$\left. \begin{array}{c} \mathbf{Acyl} \\ \mathbf{SO}_{2}\mathbf{CH}_{3} \end{array} \right\}$		(1	nactive	e)			((Inactive)								
<i>iso</i> -Butyl	IV V	$\left. \begin{array}{c} \mathbf{Acyl} \\ \mathbf{SO}_{2}\mathbf{CH}_{3} \end{array} \right\}$		(1	nactive	e)			(Inactive)		(Inactive)						
<i>tert</i> -Butyl	IV	COCH ₃ COC₂H₅	0 1	0 1	030	0 5 0	020	0 2 0	020	1 3	020	020	0 1 0	0 0	0 0 0			
	V	SO ₂ CH ₃	0	0	0	0	0	0	0	0	0	0	0	0	0			

 Table III. Structural Relationship of 2-Acyl- or 2-Methanesulfamido-1,3,4-thiadiazoles with Herbicidal Activity on Plants Treated at a Dosage of 5 kg./ha.

(XIII), m.p. 156° C., and 5-(2,4-dinitrophenylthio)-isomer (XIV), m.p. above 250° C. Some of the compounds in Figure 1 (IX, XI, XII, and XIII) were further treated with an excess of methylisocyanate in dioxane in the presence of a few drops of triethylamine, and were synthesized to the S-substituted 1-methyl-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-ureas (XV, XVI, XVII, and XVIII). The melting points, and analytical data of these ureas are listed in Table IV.

1-Methyl-3-(thiazol-2-yl)ureas. 2-Amino-4-methylthiazole was prepared from chloroacetone and thiourea (Byer and Dickey, 1939). Similarly, some 4- or 5-substituted 2-amino-thiazoles were synthesized from α -chloroketones and thiourea. These 2-aminothiazoles were then treated with methyliso-cyanate in dioxane and the corresponding 1-methyl-3-(thiazol-2-yl)ureas were obtained (Table V).

HERBICIDAL TESTS

The following three methods were used for evaluating herbicidal activity:

(A) **Pre-emergence treatment.** Seeds of rice, wheat, radish, clover, and orchardgrass were sown, and covered with soil. A solution or homogeneous suspension of the candidate herbicide was sprayed on the soil.

(B) **Post-emergence treatment.** Seeds of the above selected crops were sown, and reared for about two weeks. Then the candidate herbicide was sprayed onto the seedlings.

(C) Irrigated-water treatment. Ceramic pots were packed with soil and watered to make paddy conditions. Four sheaves of rice seedlings and slender spikerush (*Eleocharis acicularis* R. Br.) were transplanted into each pot. After one week, seeds of barnyardgrass (*Echinochloa Crusgalli* L.) were sown into the paddy soil, and a solution or homogeneous suspension of the candidate herbicide was added to the irrigation water.

Usually the primary screening tests were carried out at the dosage of 5 kg./ha. (4.45 lb./acre) and 2.5 kg./ha. (2.23 lb./acre). The treated plants were kept in a greenhouse to ob-

serve any phytotoxicity up to about a month. The phytotoxicity ratings range from 0 to 5 with 0 meaning no phytotoxicity and 5 indicating complete kill of the plant.

- 5-Plant dead
- 4--Heavy damage
- 3-Moderate damage
- 2-Small damage
- 1-Slight damage
- 0--None (Healthy)

RESULTS

The first biological experiments on 2-amino-5-substituted-1,3,4-thiaciazoles (Type I) were in vain. All the compounds belonging to Type I were inactive and failed to kill any of the test plants.

The introduction of a urea bond at position-2 brought about an interesting response. In Table I, it can be seen that some of compounds belonging to Type II show good herbicidal activity. It is interesting to note that this herbicidal activity is dependent on the molecular structure of the R radical at position 5 in the general type II. When R' is fixed as methyl and R" as hydrogen, the activity of the homologue of Type II can be arranged as follows:

$$CH_3 < C_2H_5 < n-C_3H_7 < iso-C_3H_7 < tert-C_4H_9 >$$

 $iso-C_4H_9 > n-C_{4-11}H_{9-23}$

This depends upon the molecular length as well as the degree of branching. This activity is maximized when R is the tertiary butyl radical.

The 1-methyl-3-(5-tert-butyl-1,3,4-thiadiazol-2-yl)urea is, indeed, a strikingly phytotoxic compound. This new herbicide is effective enough at a dosage of one or two kg./ha. for the control of a broad range of weeds when sprayed onto the foliage of the seedlings or on the surface of soil. Recent experiments in a potato field and in a barley field revealed that weeds can be controlled perfectly with pre-emergence treat-



ments of this herbicide at a dosage of one or two kg./ha., while potato or barley can survive because of a difference of susceptibility.

In Table II, such a series of 5-*tert*-butyl-1,3,4-thiadiazoles are presented to show how the various changes in the urea moiety affect herbicidal activity. The compound with a dimethylureyl group in position 2 is very herbicidal, and its activity can compare favorably with a methylureyl compound. But replacement of an oxygen atom in urea moiety with a sulfur atom, like compounds belonging to Type III, causes a decrease in herbicidal activity. Another interesting point in Table II is the fact that with the introduction of bulky molecules into the R' or R'' radical or Type II, herbicidal activity was lost almost completely.

In order to study further the importance of the urea bond, the ureyl radical at position 2 was varied to a 2-acetamido-, 2-propionamido-, or a 2-chloroacetamido radical, all of which represent compounds belonging to Type IV, and to the methanesulfamido radical, which represents Type V. But all the compounds of these types demonstrated marginal phytotoxicity or were essentially nonherbicidal as shown in Table III.

In order to obtain more information, many other structurally related compounds, which possess a 1,3,4-thiadiazole nucleus and are given in Figure 1, were tested for herbicidal activity. Generally they were not any more active than the compounds of Type II. Only several compounds (XVII or XVIII), which have the methylureyl group at position 2, showed some activity, Table IV. However, this activity was weak and limited.

DISCUSSION

In order to resolve the question as to what role the 1,3,4thiadiazole ring plays in herbicidal activity, some of thiazole compounds bearing a 3-methylureyl radical at position 2 were prepared by the conventional method from 2-aminothiazoles and methylisocyanate. The herbicidal activity of the thiazole derivatives was compared with that of the 1,3,4-thiadiazole derivatives. As shown in Table V, all these 2-(3-methylureyl)thiazoles are less toxic to the plants than the 5-*tert*-butyl-1,3,4-thiadiazoles. From these results, it can be concluded that the 5-*tert*-butyl-1,3,4-thiadiazole nucleus is an essential factor which contributes to the severe phytotoxicity or herbicidal activity.

No reasonable theoretical explanation for these experimental conclusions can be given at this time. It may be said, however, that the substances found to be active, have dimensions of molecular size which closely resemble monuron or diuron. Probably these compounds are absorbed by the roots, transported upward in the transpiration stream and act by inhibiting the release of oxygen in the process of photosynthesis.

To better determine practical utility, the most promising 1-methyl-3-(5-*tert*-butyl-1,3,4-thiadiazol-2-yl)urea was sprayed on twelve sorts of common weeds and cultivated plants using pre-emergence application. The phytotoxicity was compared with monuron, diuron, buturon, and simazine. Table VI demonstrates the phytotoxicity of the test compounds on Large crabgrass (*Digitaria adsendes*), clover, rye-grass, cabbage, tomato, beet, radish, carrot, cucumber, redbean, and soybean. This new 1,3,4-thiadiazole herbicide has broad spectrum activity and its toxicity appears to be on the same level as that of other commercial herbicides.

There is not much data about how the stage of development may influence the susceptibility of weeds. But, in general, it

Table V. Physical and Herbicidal Properties of 2-(3-Methylureyl)thiazole Derivatives

						Herl	oicidal A	ctivity	at a Do	osage o	f 5 kg.,	/ha.			
				Pre-emergence Method						ergence	I wa	Irrigated- water Method			
	N O ⊢NHĊ R′=	NHCH ₃ M.P. (°C)	Rice	Wheat	Radish	Clover	Orchardgrass	Rice	Wheat	Radish	Clover	Orchardgrass	Barnyardgrass	Slender spikerush	Rice
CH ₃ C ₂ H ₅ CH ₅ (CH ₃) ₂ CH (CH ₃) ₃ C	H H CH ₃ H H	218 214 176 156–158 232–236	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	1 0 1 0 0	1 1 0 0	3 4 5 2 0	2 1 3 0 0	3 1 2 0 0	1 2 0 0	0 0 0 0 0	0 0 0 0

Table VI. Herbicidal Activity of Selected Urea Herbicides and Simazine

Compound	Dosage (kg./ha.)	Large crabgrass	Clover	Ryegrass	Cabbage	Chinese cabbage	Tomato	Beet	Radish	Carrot	Cucumber	Redbean	Soybean
1-Methyl-3-(5-tert-butyl-	2.0	5	5	5	5	5	5	5	5	5	5	5	4
1,3,4-thiadiazol-2-yl)urea	$\begin{array}{c}1.0\\0.5\end{array}$	5 5–4	5 5	5 5-4	5 5	5 5	5 0	5 5	5 1	5 1	5 0	5 0	3 1
3-(p-Chlorophenyl)-	2.0	4	5	5–4	5	5	2	5	5	0	5	0	0
1,1-dimethylurea (monuron)	$\begin{array}{c}1.0\\0.5\end{array}$	4 3	5 4	4 4	5 5	5 1	0 0	0 0	5 0	0 0	1 0	0 0	0 0
3-(3,4-Dichlorophenyl)- 1,1-dimethylurea	2.0 1.0	5	5 5	5 5	5 5	5 5	5 5	5 5	5 5	5 5	5 5	5 5	1 0
(diuron)	0.5	5-4	5	5-4		5	5	5	5	5	4	4	0
3-(<i>p</i> -Chlorophenyl)-1-methyl- 1-(1-methyl-2-propynyl)urea (buturon)	2.0 1.0 0.5	4 3 3	5 5 4	5-4 4 3	5 5 5	5 5 5	5 5 5	5 5 5	5 5 5	2 1 0	5 5 5	2 1 1	1 0 0
Simazine	2.0 1.0 0.5	5 5–4 3	5 5 5	5 5-4 3	5 5 5	5 5 5	5 5 4	5 5 5	5 5 5	5 4 2	5 5 4	5 3 2	3 0 0

can be said that peak effectiveness of the herbicides is obtained when they are applied using pre-emergence or postemergence treatments onto the weeds in the early stages of growth.

New herbicides are currently under investigation for the purpose of developing practical usages. Any cooperative efforts in the study of herbicidal physiology or herbicidal development would be most welcome and are hereby solicited.

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