

## CONCLUSIONS

At rates of application ranging from 1.5 to 3.0 kg of ai/ha, PH 40-51 proved to be an effective and safe black grass herbicide in autumn-sown wheat. At these dosages, a number of important broad-leaved weeds are also satisfactorily controlled. The apparent effectiveness against wild oats in cereals merits further evaluation. Studies on the synthesis of PH 40-51 have so far not resulted in a process which is economically acceptable.

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Homeosterically Related Plant Growth Regulators.<sup>1</sup> I. Synthesis

Charles G. Skinner\* and Dale R. Sargent

Four structurally related series of potential plant growth-regulating compounds have been synthesized containing  $-\text{OCH}_2-$ ,  $-\text{NHCH}_2-$ ,  $-\text{CH}_2\text{CH}_2-$ ,

and  $-\text{S}-$  in the same relative structural position in the molecules.

In conjunction with the biological response produced by synthetic plant growth regulators, considerable efforts have been made to correlate these activities with the chemical structures of the compounds (Wain and Fawcett, 1969); the published data have often been concerned with correlations using the aryl and aryloxy acids and their derivatives as model compounds (Osborne and Wain, 1951; Wain, 1958). In addition to studies concerning the overall structure, attempts have also been made to correlate biological activity with variations in benzene ring substituents, including the number and position of the substituents (Fawcett *et al.*, 1953). It has generally been observed that biological activity of the compounds may be increased by the addition of halogen (usually chlorine) on the aromatic nucleus. However, even with the vast amount of information collected concerning structure-activity relationships, the molecular basis of their mode of action has been indicated in only a few instances (Barth and Michel, 1969; Overbeek, 1961; Wain and Wightman, 1957).

Attempts to correlate chemical structure with plant growth activity were made by Koepfli *et al.* (1938) and were subsequently modified by Went (1949) to the effect that an unsaturated ring system and a side chain adjacent to the ring double bond containing at least two carbon atoms ending in a carboxyl group were all that was necessary for plant growth-regulating activity. While there are many exceptions, it is of interest to note that many synthetic compounds which are active in affecting plant growth still meet these criteria.

A recent compilation of organic herbicidal compounds which are presently in commercial use included 75 structures, of which 9% possessed a carbamate linkage, 5% a thiolcarbamate, 17% a ureido, and 12% contained an

amide function (Ashton and Crafts, 1973). Assuming all other structural features to be equivalent in an analogous series of derivatives, the indicated moieties are homeosterically related, *i.e.*,  $-\text{OCH}_2-$ ,  $-\text{NHCH}_2-$ ,  $-\text{CH}_2\text{CH}_2-$ , and  $-\text{S}-$  with relative mass units of 30, 29, 28, and 32, respectively. Since few systematic attempts have been made to correlate physiological activity of plant growth-regulating compounds on the basis of homeosteric relationships, four types of derivatives have been synthesized which incorporate these functional groups into a series of analogous compounds. Their relative biological activities have been determined in several plant systems using both physical and chemical assay procedures, and some biochemical results are presented in an accompanying paper.

## EXPERIMENTAL SECTION

**Organic Synthesis.** *O*-[(*Substituted*)carbamoyl]-3-hydroxypropionitriles (Table I). All of these derivatives were prepared in a similar manner using the method of Beaver *et al.* (1963). A mixture consisting of 0.033 m of the appropriate isocyanate and 0.033 m of 3-hydroxypropionitrile was heated in an oil bath at 80° for 6 hr under anhydrous conditions. Upon cooling to room temperature the reaction mixture solidified and was then recrystallized from the solvent system indicated in Table I. The products were dried in a vacuum desiccator over calcium chloride prior to elemental analysis.

*O*-[(*Substituted*)carbamoyl]-3-hydroxypropionic Acids. These derivatives were prepared in a comparable fashion. A suspension of 0.01 m of the appropriate hydroxypropionitrile derivative in 50 ml of 6 *N* hydrochloric acid was magnetically stirred and heated under reflux for 2-4 hr. Upon cooling to room temperature, a precipitate formed which was filtered, washed with water, and air dried. This material was dissolved in a dilute solution of sodium hydroxide and extracted twice with 10-15-ml portions of ether. The aqueous phase was adjusted to pH 2 with a dilute solution of hydrochloric acid to produce a precipitate which was filtered, washed with water, air dried, and recrystallized from either water or 95% ethanol, as indicated in Table II. These products were dried in a vacuum desiccator heated to 50-60°.

3-[*N*<sup>3</sup>-(*Substituted*)ureido]propionic Acids. Using the general procedure of Runti and Ulian (1963), a sample of

\*Department of Chemistry, North Texas State University, Denton, Texas 76203.

<sup>1</sup>In view of the confusion which exists between the concepts of classical and nonclassical isosteric replacements in chemical analogs, the authors suggest the term "homeosteric," homoios (Gr) meaning similar. The term homeosteric would thus be defined as two or more chemical moieties which are similar in mass or shape and valence bond angles.

**Table I. O-[(Substituted)carbamoyl]-3-hydroxypropionitriles**

$$\text{RNHC(=O)CH}_2\text{CH}_2\text{CN}$$

R group	Mp or (bp/mm), °C	% yield	Empirical formula	Calculated			Found		
				C	H	N	C	H	N
n-Propyl	(119/0.9) <sup>a</sup>	70	C <sub>7</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	53.83	7.75	17.94	54.08	8.22	17.81
Allyl	(120/0.7) <sup>a</sup>	39	C <sub>7</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	54.53	6.54	18.17	54.22	6.68	18.02
Cyclohexyl	63–64 <sup>b</sup>	81	C <sub>10</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	61.20	8.22	14.28	61.34	8.55	14.22
4-Fluorophenyl	73–74 <sup>c</sup>	38	C <sub>10</sub> H <sub>9</sub> FN <sub>2</sub> O <sub>2</sub>	57.69	4.36	13.46	57.82	4.36	13.34
4-Bromophenyl	110–111 <sup>c</sup>	57	C <sub>10</sub> H <sub>9</sub> BrN <sub>2</sub> O <sub>2</sub>	44.63	3.37	10.41	44.38	3.45	10.27
4-Methylphenyl	84–85 <sup>c</sup>	52	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	64.69	5.92	13.72	64.59	5.80	13.82
4-Methoxyphenyl	100–101 <sup>c</sup>	60	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	59.99	5.49	12.72	59.53	5.52	12.49
4-Nitrophenyl	161–162 <sup>c,d</sup>	22	C <sub>10</sub> H <sub>9</sub> N <sub>3</sub> O <sub>4</sub>	51.06	3.86	17.87	50.75	4.15	18.03
2-Chlorophenyl	56–57 <sup>e</sup>	54	C <sub>10</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>2</sub>	53.46	4.04	12.47	53.82	4.28	12.24
3-Chlorophenyl	54–55 <sup>f</sup>	53	C <sub>10</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>2</sub>	53.46	4.04	12.47	53.97	4.03	12.64
4-Chlorophenyl	101–102 <sup>e</sup>	57	C <sub>10</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>2</sub>	53.46	4.04	12.47	53.79	4.02	12.37
2,4-Dichlorophenyl	98–99 <sup>e</sup>	53	C <sub>10</sub> H <sub>8</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	46.35	3.11	10.81	46.64	3.36	10.42
2,5-Dichlorophenyl	82–83 <sup>g</sup>	29	C <sub>10</sub> H <sub>8</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	46.35	3.11	10.81	45.49	3.28	10.81

<sup>a</sup> Heated under reflux for 5 hr, then fractionally distilled. <sup>b</sup> Recrystallized from ether–petroleum ether. <sup>c</sup> Recrystallized from ethanol. <sup>d</sup> Heated at 160° for 8 hr. <sup>e</sup> Recrystallized from ethanol–hexane. <sup>f</sup> Recrystallized from ethyl acetate–hexane. <sup>g</sup> Recrystallized from heptane.

**Table II. O-[(Substituted)carbamoyl]-3-hydroxypropionic Acids**

$$\text{RNHC(=O)CH}_2\text{CH}_2\text{COOH}$$

R group	Mp, °C	% yield	Empirical formula	Calculated			Found		
				C	H	N	C	H	N
Cyclohexyl	125–127 <sup>a</sup>	30	C <sub>10</sub> H <sub>17</sub> NO <sub>4</sub>	55.80	7.96		55.97	8.18	
Phenyl	117–118 <sup>a</sup>	54	C <sub>10</sub> H <sub>11</sub> NO <sub>4</sub>	57.41	5.30	6.70	57.29	5.36	6.72
4-Fluorophenyl	113–114 <sup>a</sup>	63	C <sub>10</sub> H <sub>9</sub> FO <sub>4</sub>	52.86	4.44	6.17	52.71	4.42	6.24
2-Chlorophenyl	106–107 <sup>a</sup>	28	C <sub>10</sub> H <sub>9</sub> ClNO <sub>4</sub>	49.29	4.14	5.75	49.03	4.23	5.86
3-Chlorophenyl	125–126 <sup>a</sup>	14	C <sub>10</sub> H <sub>9</sub> ClNO <sub>4</sub>	49.29	4.14	5.75	49.18	4.24	5.73
4-Chlorophenyl	127–128 <sup>c</sup>	25	C <sub>10</sub> H <sub>9</sub> ClNO <sub>4</sub>	49.29	4.14	5.75	48.75	4.19	5.51
2,4-Dichlorophenyl	126–128 <sup>a</sup>	29	C <sub>10</sub> H <sub>7</sub> Cl <sub>2</sub> NO <sub>4</sub>	43.19	3.26	5.04	43.23	3.24	5.34
3,4-Dichlorophenyl	106–107 <sup>a</sup>	9	C <sub>10</sub> H <sub>8</sub> Cl <sub>2</sub> NO <sub>4</sub>	43.19	3.26	5.04	43.26	3.19	5.08
2,5-Dichlorophenyl	140–141 <sup>a</sup>	31	C <sub>10</sub> H <sub>8</sub> Cl <sub>2</sub> NO <sub>4</sub>	43.19	3.26	5.04	43.61	3.15	5.53
4-Bromophenyl	149–150 <sup>a</sup>	17	C <sub>10</sub> H <sub>9</sub> BrNO <sub>4</sub>	41.69	3.50	4.86	41.44	3.68	4.58
4-Methylphenyl	146–147 <sup>a</sup>	41	C <sub>11</sub> H <sub>13</sub> NO <sub>4</sub>	59.18	5.87	6.28	58.92	5.89	6.46
4-Methoxyphenyl	137–138 <sup>b</sup>	33	C <sub>11</sub> H <sub>13</sub> NO <sub>5</sub>	55.23	5.48	5.86	54.91	5.43	6.04
N-Nitrophenyl	182–183 <sup>b</sup>	8	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> O <sub>5</sub>	47.25	3.97	11.02	47.07	3.95	11.07

<sup>a</sup> Recrystallized from water. <sup>b</sup> Recrystallized from 95% ethanol.

**Table III. 3-[N<sup>3</sup>-(Substituted)ureido]propionic Acids**

$$\text{RNHC(=O)NHCH}_2\text{CH}_2\text{COOH}$$

R group	Mp, °C	% yield	Empirical formula	Calculated			Found		
				C	H	N	C	H	N
Cyclohexyl	163–164 <sup>a</sup>	42	C <sub>10</sub> H <sub>15</sub> N <sub>2</sub> O <sub>3</sub>	56.06	8.47	13.08	55.88	8.77	13.09
Phenyl	173–174 <sup>b</sup>	64							
4-Fluorophenyl	177–178 <sup>c</sup>	63	C <sub>10</sub> H <sub>11</sub> FN <sub>2</sub> O <sub>3</sub>	53.09	4.90	12.36	52.94	4.92	12.24
2-Chlorophenyl	160–161 <sup>c</sup>	53	C <sub>10</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>3</sub>	49.49	4.57	11.55	49.48	4.72	11.29
3-Chlorophenyl	161–162 <sup>c</sup>	39	C <sub>10</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>3</sub>	49.49	4.57	11.55	49.41	4.56	11.39
4-Chlorophenyl	226–227 <sup>d</sup>	51							
2,4-Dichlorophenyl	202–203 <sup>c</sup>	67	C <sub>10</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	43.34	3.64	10.11	43.16	3.71	9.71
3,4-Dichlorophenyl	162–163 <sup>c</sup>	61	C <sub>10</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	43.34	3.64	10.11	43.75	3.51	9.92
2,5-Dichlorophenyl	223–224 <sup>c</sup>	52	C <sub>10</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	43.34	3.64	10.11	43.24	3.70	9.96
4-Bromophenyl	233–234 <sup>e</sup>	63							
4-Methylphenyl	186–187 <sup>c</sup>	73	C <sub>11</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	59.44	6.35	12.61	59.57	6.33	12.32
4-Methoxyphenyl	172–173 <sup>c</sup>	75	C <sub>11</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub>	55.45	5.92	11.76	55.06	6.14	11.67

<sup>a</sup> Recrystallized from water. <sup>b</sup> Hoogewerff and Van Dorp (1890), mp 174°. <sup>c</sup> Recrystallized from 95% ethyl alcohol. <sup>d</sup> Runti and Ulian (1965), mp 225°. <sup>e</sup> Runti and Ulian (1965), mp 229°. <sup>f</sup> Petersen and Muller (1948), mp 188°.

**Table IV. S-[(Substituted)carbamoyl]mercaptoacetic Acids**

R group	Mp, °C	% yield	Empirical formula	Calculated			Found		
				C	H	N	C	H	N
Cyclohexyl	125-126 <sup>a</sup>	42	C <sub>9</sub> H <sub>15</sub> NO <sub>3</sub> S	49.74	6.96	6.45	47.79	7.34	6.22
Phenyl	147-148 <sup>b</sup>	17	C <sub>9</sub> H <sub>9</sub> NO <sub>3</sub> S	51.17	4.29	6.63	50.76	4.17	6.30
2-Chlorophenyl	148-149 <sup>b</sup>	59	C <sub>9</sub> H <sub>8</sub> ClNO <sub>3</sub> S	43.99	3.28	5.70	43.99	3.26	5.61
3-Chlorophenyl	127-128 <sup>b</sup>	29	C <sub>9</sub> H <sub>8</sub> ClNO <sub>3</sub> S	43.99	3.28	5.70	43.25	3.31	5.49
4-Chlorophenyl	136-138	4 <sup>c</sup>	C <sub>9</sub> H <sub>8</sub> ClNO <sub>3</sub> S	43.99	3.28	5.70	43.63	3.06	5.55

<sup>a</sup> Recrystallized from ether-petroleum ether. <sup>b</sup> Recrystallized from 95% ethanol. <sup>c</sup> Low yields were obtained on repeated attempts and with different methods.

**Table V. N-(Substituted)glutaramic Acids**

R group	Mp, °C	% yield	Empirical formula	Calculated			Found		
				C	H	N	C	H	N
Cyclohexyl	137-139 <sup>a</sup>	51	C <sub>11</sub> H <sub>19</sub> NO <sub>3</sub>	61.94	8.98		62.20	9.04	
Phenyl	126-127 <sup>b,c</sup>	88	C <sub>11</sub> H <sub>13</sub> NO <sub>3</sub>						
2-Chlorophenyl	118-119 <sup>a</sup>	77	C <sub>11</sub> H <sub>12</sub> ClNO <sub>3</sub>	54.66	5.01	5.80	54.57	5.03	5.79
3-Chlorophenyl	125-126 <sup>a</sup>	81	C <sub>11</sub> H <sub>12</sub> ClNO <sub>3</sub>	54.66	5.01	5.80	54.33	5.05	5.79
4-Chlorophenyl	134-135 <sup>d</sup>	38	C <sub>11</sub> H <sub>12</sub> ClNO <sub>3</sub>						
2,4-Dichlorophenyl	153-154 <sup>a</sup>	55	C <sub>11</sub> H <sub>11</sub> Cl <sub>2</sub> NO <sub>3</sub>	47.85	4.02	5.07	47.49	4.13	5.07
4-Bromophenyl	155-157 <sup>a</sup>	71	C <sub>11</sub> H <sub>12</sub> BrNO <sub>3</sub>	46.17	4.23		46.38	4.51	
4-Methylphenyl	174-175 <sup>a</sup>	68	C <sub>12</sub> H <sub>15</sub> NO <sub>3</sub>	65.14	6.83		64.93	6.69	
4-Methoxyphenyl	140-141 <sup>a</sup>	47	C <sub>12</sub> H <sub>15</sub> NO <sub>4</sub>	60.74	6.37		60.82	6.53	

<sup>a</sup> Recrystallized from 95% ethanol. <sup>b</sup> Recrystallized from water. <sup>c</sup> Beilstein, 12, 297 (1929), mp 126-127° (ethanol). <sup>d</sup> Evans and Roberts (1957), mp 134°.

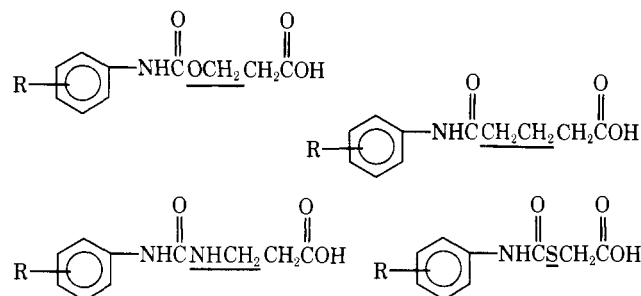
0.033 m of the appropriate isocyanate in 20 ml of chlorobenzene was added dropwise over a period of 2 hr to a magnetically stirred solution consisting of 0.033 m of  $\beta$ -alanine in 40 ml of 1 N sodium hydroxide. After addition was complete, the reaction mixture was allowed to stir for an additional 12 hr at room temperature. The solution was filtered, and the immiscible phases were separated using a separatory funnel. The aqueous phase was brought to pH 2-3 with a dilute solution of hydrochloric acid, at which time a precipitate formed which was filtered, washed with water, air dried, and recrystallized from either 95% ethanol or water, as indicated in Table III. These derivatives were dried in a vacuum desiccator heated to 50-60°.

S-[(Substituted)carbamoyl]mercaptoacetic Acids (Table IV). These compounds were prepared using the same general procedure as previously described for the preparation of the 3-[N<sup>3</sup>-(substituted)ureido]propionic acids. The products were recrystallized from 95% ethanol or ether-petroleum ether (bp 30-60°), as indicated in Table IV, and then dried overnight at 50-60° *in vacuo*.

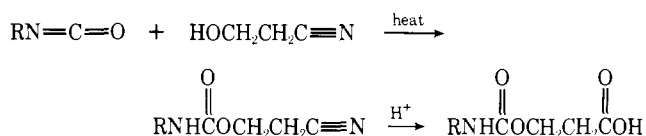
N-(Substituted)glutaramic Acids (Table V). Using a modification of the procedure of Evans and Roberts (1957), a mixture of 0.033 m of the appropriately substituted aniline (freshly distilled or recrystallized) and 0.033 m of glutaric anhydride was heated in an oil bath at 100° for 3 hr under anhydrous conditions. Upon cooling to room temperature, the material solidified and was then taken up in 95% ethanol, treated with Darco G-60, and filtered through a Celite pad. The products were recrystallized a second time from either 95% ethanol or water, as indicated in Table V, to yield a colorless derivative which was then dried overnight in a vacuum desiccator at 50-60°. Water was added to the alcoholic filtrate to obtain a second crop of crystals.

## RESULTS AND DISCUSSION

Four new series of plant growth-regulating compounds have been synthesized which are homeosterically related to each other as indicated in the accompanying formulas.



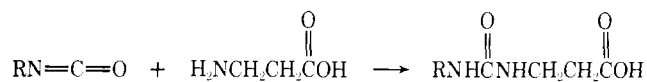
The syntheses of O-[(substituted)carbamoyl]-3-hydroxypropionic acids



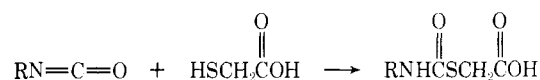
initially involved the condensation of 3-hydroxypropionitrile with the appropriately substituted isocyanate, which gave the anticipated products in good yields. Hydrolysis of the carbamoylpropionitrile produced the corresponding carboxylic acid.

The syntheses of 3-[N<sup>3</sup>-(substituted)ureido]propionic acids employed a one-step condensation reaction involving the addition of the appropriate isocyanate, contained in chlorobenzene, to an alkaline solution of  $\beta$ -alanine.

The preparation of the S-[(substituted)carbamoyl]mer-

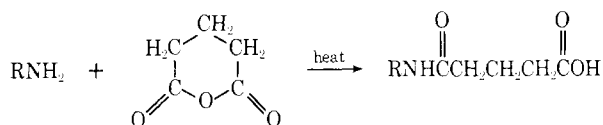


captoacetic acids was carried out by the addition of the appropriate isocyanate to a basic solution of mercaptoacetic acid in the same manner as just described for the 3-[N<sup>3</sup>-(substituted)ureido]propionic acid derivatives



Considerable difficulty was encountered in the isolation of most of these latter derivatives, which resulted in relatively low yields of products.

The syntheses of the *N*-(substituted)glutamic acids involved the condensation of equimolar amounts of the appropriate amine and glutaric anhydride.



These four series of compounds were subsequently studied in several biological systems, including coleoptile elongation and whole plant assays, and an attempt was made to elucidate structure-activity relationships. In the *Avena sativa* coleoptile assays, the RNHC=OOR' and RNHC=OSR' series of compounds were more inhibitory to segment elongation than were equivalently substituted derivatives in the RNHC=NHR' and RNHC=OCH<sub>2</sub>R' series. Within a given homeosteric series, a chloro or bromo substituent on the aryl portion of the analog usually increased the toxic properties of the compound.

Using a *Helianthus annuus* variety of sunflower plants, spray applications were made to the aerial portion of 10-day-old plants, and only the RNHC=OCH<sub>2</sub>R' series of derivatives were effective in inhibiting the increase in height of the test plants. These derivatives were also studied using hydroponic assay techniques and all the homeosters inhibited growth, as evidenced by a decrease in height of sunflower plants.

Based on the data obtained in these studies, three general observations may be made concerning the effect of molecular structural changes as they relate to plant growth activity. (a) Carbamate and/or thiolcarbamate structures are more effective in inducing plant growth inhibition than are analogous urea and amide moieties on exposed cut surfaces. (b) However, in whole plants (normal spray application to foliage), absorption problems appear to predominate, and the more lipophilic amide structures produce the most inhibitory activity. (c) Electronegative substituents (especially chlorine and bromine) on aromatic rings usually increase inhibitory activity over that of analogous unsubstituted phenyl derivatives.

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