

Synthesis of Hydrazine Derivatives as Plant Growth Inhibitors

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Varied hydrazines were alkylated with lactones and unsaturated compounds. Under all reaction conditions, initial addition to methylhydrazine occurred at the *N*-methyl site. Results differ appreciably from those in recent publications. Twenty-two hydrazine derivatives were applied to rye grass and tomato plant foliage and growth inhibition and phytotoxicities were recorded. Among the compounds

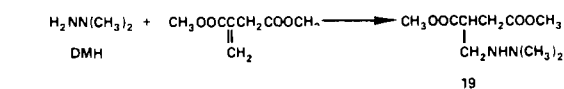
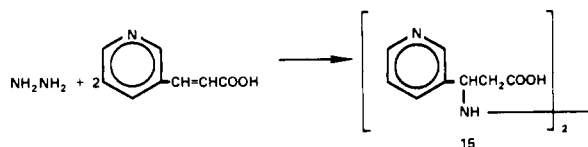
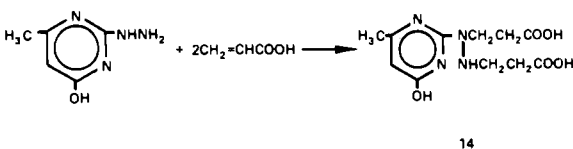
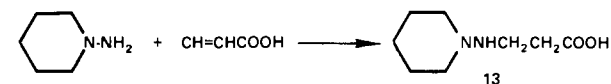
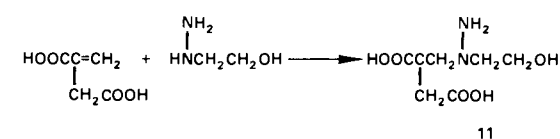
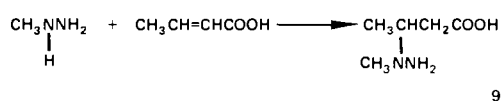
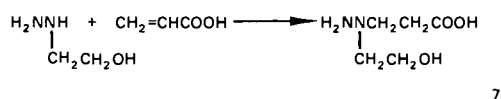
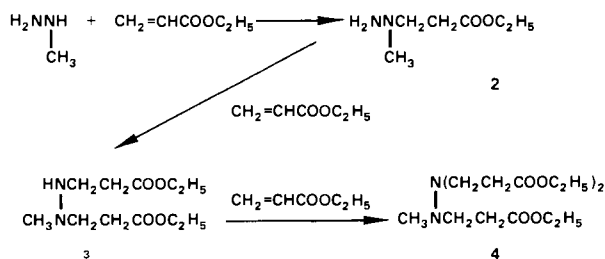
tested, the inhibition of grass growth by *N*-amino-*N*-methyl- β -alanine was comparable to the inhibition observed with maleic hydrazide (MH-30). This is the only example of a hydrazino acid with significant inhibitory activity. Five related compounds also gave appreciable inhibition of tomato plant growth, but had decreased activity on grasses.

MALEIC hydrazide (MH-30), B-Nine (*N*-dimethylaminosuccinamic acid), and beta-hydroxyethylhydrazine are useful plant growth regulators derived from hydrazine. The first two are classified as inhibitors and retardants, respectively. They cause a variety of desirable effects on plants. Maleic hydrazide inhibits sucker growth on tobacco plants, delays the sprouting of stored potatoes and onions, and reduces grass growth (Tate, 1965). B-Nine delays the fruit drop of apples (Edgerton and Hoffman, 1966) and beta-hydroxyethylhydrazine promotes flowering of pineapples (Gowing and Leeper, 1955).

The authors' investigation of hydrazines as growth inhibitors was initiated to find more effective materials. A better inhibitor with decreased phytotoxicity might prove useful as a "chemical lawnmower" or as an antilodging agent for grains such as rice or wheat. To this end, a series of new hydrazine derivatives, obtained by the Michael addition of varied hydrazines to compounds containing activated double bonds, were prepared and tested. Several articles appeared after this work had been completed which claimed synthesis results at variance with this report. The reproducible procedures described below will aid others in the preparation of related compounds.

The following equations illustrate the preparation of some of the compounds listed in Table I.

Scheme I
ALKYLATION OF HYDRAZINES




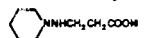
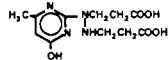
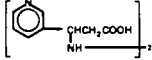
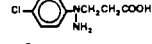
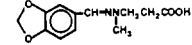
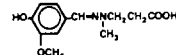

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Zapevalova *et al.* (1966) have summarized their work with unsymmetrical dimethylhydrazine (DMH) which differs from the results reported here. They showed that DMH reacted with α,β -unsaturated acid anhydrides and chlorides to give a mixture of the expected hydrazide acylation product (not shown) along with a cyclized pyrazolidi-

Table I. Inhibition of Plant Growth

Compound No.	Formula	Structure	M.P. or B.P. (Mm.)	Yield, %	Method	N (Calcd.)
1	C ₄ H ₁₀ N ₂ O ₂	$\text{H}_2\text{NNCH}_2\text{CH}_2\text{COOH}$ CH ₃	133-135	92 50	A B	23.72
2	C ₆ H ₁₄ N ₂ O ₂	$\text{H}_2\text{NNCH}_2\text{CH}_2\text{COOC}_2\text{H}_5$ CH ₃	(50) _{0.2}	96	C	19.17
3	C ₁₁ H ₂₂ N ₂ O ₄	$\text{H}_2\text{NNCH}_2\text{COOC}_2\text{H}_5$ CH ₃ NCH ₂ CH ₂ COOC ₂ H ₅	(115) _{0.5}	66	C ^a	11.38
4	C ₁₆ H ₃₀ N ₂ O ₆	$\text{N}(\text{CH}_2\text{CH}_2\text{COOC}_2\text{H}_5)_2$ CH ₃ NCH ₂ CH ₂ COOC ₂ H ₅	(140) _{0.3}	30	C ^a	8.09
5	C ₃ H ₈ N ₂ O ₂	$\text{H}_2\text{NNHCH}_2\text{CH}_2\text{COOH}$	118-120	78	A	26.91
6	C ₃ H ₁₂ N ₂ O ₂	$(\text{CH}_3)_2\text{NNHCH}_2\text{CH}_2\text{COOH}$	165-167	76 64	A B	21.20
7	C ₃ H ₁₂ N ₂ O ₃	$\text{H}_2\text{NNCH}_2\text{CH}_2\text{COOH}$ CH ₂ CH ₂ OH	125-127	72	A	18.91
8	C ₄ H ₁₀ N ₂ O ₂	$\text{CH}_3\text{CHCH}_2\text{COOH}$ NHNH ₂	120-122	85	A	23.72
9	C ₃ H ₁₂ N ₂ O ₂	$\text{CH}_3\text{CHCH}_2\text{COOH}$ CH ₃ NNH ₂	42-44	63 86	B A	21.20
10	C ₆ H ₁₄ N ₂ O ₂	$(\text{CH}_3)_2\text{NNHCHCH}_2\text{COOH}$ CH ₃	143-145	96	B	18.05
11	C ₇ H ₁₄ N ₂ O ₅	$\text{HOOCCHCH}_2\text{N}(\text{NH}_2)\text{CH}_2\text{CH}_2\text{OH}$ CH ₂ COOH	87-89	35	A	13.59
12	C ₃ H ₁₁ N ₃ O ₂		182-183	89	A	22.09
13	C ₃ H ₁₆ N ₂ O ₂		121-121.5	96	A	16.27
14	C ₁₁ H ₁₆ N ₄ O ₅		216-217	80	A	19.10
15	C ₁₆ H ₁₅ N ₄ O ₄		144 dec.	60	A	16.96
16	C ₄ H ₉ N ₃	$\text{H}_2\text{NNCH}_2\text{CH}_2\text{CN}$ CH ₃	(56-58) _{0.1}	91	D	42.39
17	C ₃ H ₇ N ₃	$\text{H}_2\text{NNHCH}_2\text{CH}_2\text{CN}$	(65) _{0.2} ^d	94	D	
18	C ₃ H ₁₁ N ₃	$(\text{CH}_3)_2\text{NNHCH}_2\text{CH}_2\text{CN}$	(60) _{0.2}	70 ^e	D	
19	C ₉ H ₁₈ N ₂ O ₄	$\text{CH}_3\text{OOCCH}_2\text{COOCH}_2$ $\text{CH}_2\text{NHN}(\text{CH}_3)_2$	(97) _{0.2}	96	B	12.84
20	C ₄ H ₁₁ ClN ₂ O ₂		154-155	48	A	13.05
21	C ₁₂ H ₁₄ N ₂ O ₄		116-117	51	E	11.20
22	C ₁₂ H ₁₆ N ₂ O ₄		107-108.5	46	E	11.11
	MH-30 (Standard)					

^a Phytotoxicity rating key
 1 = No injury.
 2 = Slight injury.
 3 = Moderate injury.
 4 = Severe injury.
 5 = All plants killed.

by Hydrazine Derivatives

N (Found)	Phytotoxicity ^a								Inhibition ^b							
	Rye Grass				Tomato				Rye Grass				Tomato			
	100	500	1000	5000	100	500	1000	5000	100	500	1000	5000	100	500	1000	5000
23.60	1	1	1	2	1	1	3	5	1	3	3	4	2	3	3	...
19.15			1	4			1	2		1	3			1	5	
11.56			1	4			1	2		1	3			3	5	
8.05			1	1			1	1		1	1			1	1	
26.91			1	1			1	5		1	1			3	...	
21.20			1	1			1	1		1	1			1	1	
18.95			1	4			1	1		1	...			1	1	
23.68			1	2			2	5		1	2			4	...	
21.40			1	1			1	1		1	1			1	1	
17.89			1	1			1	1		1	1			1	1	
13.48			1	1			1	1		1	1			1	1	
22.08			1	3			1	3		1	3			1	1	
16.32			1	2			1	1		1	2			1	1	
19.23			1	1			1	1		1	1			1	1	
17.00			1	1			1	1		1	1			1	1	
41.73			1	1			1	1		1	1			1	1	
			1	1			1	2		1	1			1	4	
			1	1			1	1		1	1			1	1	
12.78			1	1			1	1		1	1			1	1	
12.97			1	1			1	1		1	1			1	1	
11.00			1	1	1	1	1	2		1	1		2	3	3	4
11.15			1	1			1	1		1	1			1	2	
			1	2	3		2	3	1	3	3	5		3	4	

Growth inhibition rating key

1 = Equal to control.

2 = Slight to 1/4 inhibition of growth.

3 = 1/4 to 1/2 inhibition of growth.

4 = 1/2 to 3/4 inhibition of growth.

5 = 3/4 to complete inhibition of growth.

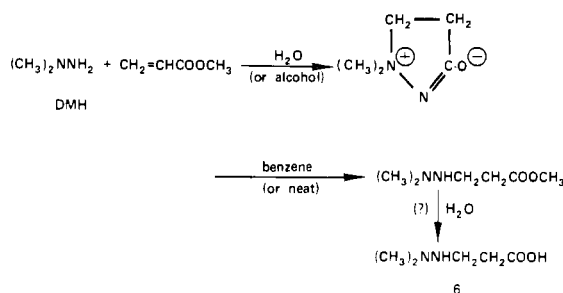
^a Solution heated to reflux for 1 hour before removing solvent. Compounds 3 and 4 are from the same preparation. Two equivalents of ethyl acrylate were used to one of methylhydrazine.

^b Hoffman and Jacobi (1935) report b.p. 65° C. at 0.2 mm.

^c Reaction required 1 hour of refluxing before work-up. Hinman and Rosene (1956) report b.p. 80-90° C. at 3 mm.

none. They claimed that the course of the reaction depends on the polarity of the medium and the activity of the double bond. Methyl acrylate and DMH in aqueous solution were reported to give almost quantitative yields (alcohol gave lower yields) of 1,1-dimethylpyrazolin-3-ium oxide, m.p. 90–1° C. In the absence of solvent or in benzene they obtained a 70% yield of the linear Michael addition product, b.p. 74° C. (11 mm.). Hydrolysis of this ester should give the hydrazino acid (6). Acrylamide,

Scheme II
DIMETHYLHYDRAZINE REACTIONS
(Zapevalova et al., 1966)



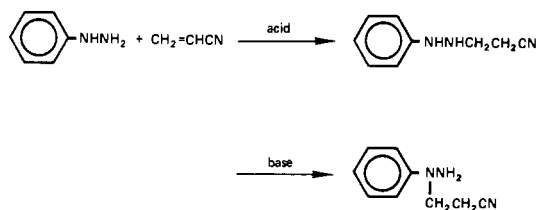
a weak acylating agent, gave the Michael addition product irrespective of the polarity of the reaction solvent and did not form a cyclic product. Zapevalova *et al.* claimed that the Michael addition product from methyl acrylate, and DMH, after hydrolysis in water for 1 month, gave the hydrazino acid (6) with a m.p. 90–1° C.

Acid (6) had m.p. 165–7° C. when made directly from DMH and acrylic acid in an alcoholic solvent, or from DMH and β -propiolactone without solvent. Apparently the Zapevalova *et al.* (1966) hydrolysis product was not 6 but was the cyclic pyrazolidinone shown above.

The authors had no difficulty in preparing the Michael addition products shown in Table I. However, these products gradually decompose during prolonged storage in air. Zapevalova *et al.* (1966) showed that their esters polymerized when heated in water. Strong acids or bases cause rapid cyclization to pyrazolidinones, which had no desirable effects on plants.

Pietra (1953) reported that phenylhydrazine cyanoethylates principally on the primary nitrogen in acid and on the secondary nitrogen in basic solution. Pietra hydro-

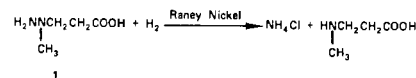
Scheme III
CYANOETHYLATION OF HYDRAZINE
(Pietra 1953)



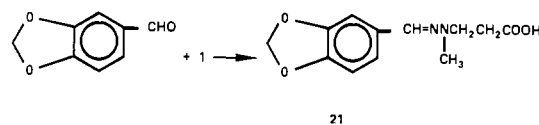
lyzed the acid-catalyzed product to secure *N*-anilino- β -alanine, m.p. 137–8° C. In this report phenylhydrazine was added to acrylic acid to furnish a 50% yield of *N*-anilino- β -alanine, m.p. 136–7° C., as the only crystalline product.

The structures of the methylhydrazine adducts were verified by hydrogenolysis of the N–N bond. Reduction

of the adducts by hydrogen and Raney nickel catalyst gave the theoretical yield of ammonium chloride. This proved that the initial alkylation occurred on the *N*-methyl nitrogen.



Aldehyde derivatives such as 21 were prepared from 1 and piperonal as further confirmation of the structure.



The reaction site of methylhydrazine was the *N*-methyl under all reaction conditions. The products obtained were not salts, hydrazides, or pyrazolidinones.

MATERIALS AND METHODS

The procedures A, B, C, D, and E given below outline the techniques used to make the compounds listed in Table I. The reagents used were purchased from Aldrich Chemical Co.; Matheson, Coleman and Bell; or Distillation Products Industries (Eastman); or were commercial samples. The ethyl acrylate was a commercial sample from Rohm and Haas, the β -propiolactone from Celanese Corp., and the β -butyrolactone from Eastman Chemical Products. All reagents were used as received. All melting and boiling points are uncorrected. Analyses were by Micro-Tech Laboratories, Skokie, Ill., or by the analytical group of International Minerals & Chemical Corp., Libertyville, Ill.

(A) *N*-Amino-*N*-methyl- β -alanine (No. 1). Acrylic acid (45 grams, 0.625 mole) was dissolved in a mixture of 450 ml. of 2-propanol and 50 ml. of methanol. The solution was cooled to 10° C. and methylhydrazine (28.8 grams, 0.625 mole) was added slowly, maintaining the temperature below 25° C. The product precipitated from the solution within 2 hours and was filtered, yielding 67 grams (91%) of product, m.p. 125–30° C. Recrystallization from methanol–2-propanol raised the m.p. to 133–5° C.

(B) *N*-Amino-*N*-methyl- β -alanine (No. 1). Methylhydrazine (46 grams, 1 mole) was cooled to –20° C. β -Propiolactone (72 grams, 1 mole) was added slowly with stirring and continued cooling, maintaining the temperature below 0° C. The solution was allowed to reach room temperature overnight. The material, which crystallized very slowly, yielded 59 grams (50%), m.p. 123–7.5° C. Recrystallization from a mixture of methanol and 2-propanol raised the melting point to 133–5° C. Both spectral analyses and a mixture melting point showed that compound 1 was obtained by this procedure and A.

(C) Ethyl 3-(1-Methylhydrazino)propionate (No. 2). Methylhydrazine (100 grams, 2.18 moles) was added to 400 ml. of methanol. The solution was cooled to –20° C. and ethyl acrylate (218 grams, 2.18 moles) was added slowly to maintain the temperature below 0° C. The solution was stirred for an additional hour. The methanol was removed at aspirator pressure. Distillation yielded 304 grams (96%) of product, b.p. 50° C. at 0.2 mm.

(D) **3-(1-Methylhydrazino)propionitrile (No. 16).** Methylhydrazine (46 grams, 1.0 mole) was added to 400 ml. of methanol and cooled to -20°C . Acrylonitrile (53 grams, 1.0 mole) was added slowly, maintaining the temperature below 10°C . The solution was stirred until room temperature was reached. The methanol was removed under aspirator pressure. The product was distilled yielding 89 grams (91%) of material, b.p. $56-8^{\circ}\text{C}$. at 0.1 mm.

(E) **3',4'; -Dioxymethylenebenzylidene - 2 - methyl - 2-carboxyethylhydrazone (No. 21).** A solution of *N*-amino-*N*-methyl- β -alanine (1) (11.8 grams, 0.1 mole) in 15 ml. of water was added to a solution of piperonal (15 grams, 0.1 mole) in 100 ml. of tetrahydrofuran. The solution was stirred for 16 hours. The precipitate was filtered from the solution and recrystallized from benzene, m.p. $116-17^{\circ}\text{C}$., yield 13.5 grams (51%).

Plant Culture. The preliminary biological evaluations with tomatoes and rye grass were made at Boyce Thompson Institute, Yonkers, N. Y., using the procedure of Huffman *et al.* (1967).

Subsequent evaluations of *N*-amino-*N*-methyl- β -alanine were made at the International Minerals & Chemical Corp. greenhouses. Kentucky bluegrass (*Poa pratensis*), Merion bluegrass (*Poa pratensis*, var. Merion), and perennial rye grass (*Lolium perenne*) seeds were planted at a rate of 0.5, 0.25, and 0.5 gram per container, respectively. A soil medium consisting of soil, sand, and peat moss at 2:1:1 ratio was placed uniformly into No. 10 containers (15.5-cm. diameter \times 17.5 cm. high) provided with four drainage holes. The seeds and plants were watered as required with one-half Hoagland nutrient solution. During the pretreatment period, the plants developed under normal care in the greenhouse with periodic clipping as needed.

The chemicals used were *N*-amino-*N*-methyl- β -alanine (1) dissolved in water or dilute acetic acid and MH-30 in water at 0, 500, 1000, and 5000 p.p.m. All solutions contained 500 p.p.m. Triton X-100. Fifteen milliliters of each concentration was sprayed on the foliage of 3-month-old grass which had been clipped to 3 cm. This spray volume was more than adequate to wet the foliage completely.

The grass was clipped to 3 cm. high on the 14th and 28th day after treatment. Fresh and dry weights of clipped grass, average height, and phytotoxicity rating were recorded.

RESULTS AND DISCUSSION

The amino acid, *N*-amino-*N*-methyl- β -alanine (1), was the only compound in the series which demonstrated significant grass growth inhibiting effects (Table I). Preliminary comparisons of the growth inhibiting effects of 1 and MH-30 showed them to be about equal for perennial rye grass. The activity varied markedly with minor changes in chemical structure (Table I). Replacement of the carboxylic acid moiety by ester (2) or nitrile (16) reduced the growth inhibiting effect. Removal of the methyl group from the hydrazine portion of the molecule (5) resulted in complete loss of activity on rye grass. The Schiff base (21) of 1 and piperonal was prepared as a potential slow release, stable form of the active compound. It showed decreased phytotoxicity but the growth retardant effect on grass was eliminated. Its inhibitory effect on tomato plants was slightly enhanced.

Results from growth inhibition studies with Kentucky blue-, Merion blue-, and rye grass by compound 1 and MH-30 under greenhouse conditions are summarized in Table II and Figure 1. The addition of acetic acid to solutions of 1 had little effect on the growth inhibition

Table II. Inhibition of Grass Growth by *N*-Amino-*N*-methyl- β -alanine (1)

Grass	Treatment	Clipping Time, Days	Phytotoxicity ^a				Grass Height Increase, Cm.			
			Chem. Concentration, P.P.M.				Chem. Concentration, P.P.M.			
			0	500	1000	5000	0	500	1000	5000
Kentucky blue	1 + CH ₃ COOH	14	1.5	1.8	2.5	5.0	9.8	5.3	4.1	5.1
	1 ^b		1.0	1.0	1.0	3.0	5.0	3.5	3.5	
	MH 30, standard		1.5	2.0	3.0	5.5	4.8	4.3		
	1 + CH ₃ COOH	28	1.0	1.0	1.0	1.0	12.1	12.5	11.6	9.8
	1 ^b		1.0	1.0	1.0	12.0	11.0	0.0		
	MH 30, standard		1.0	3.0	3.3	4.1	0.2	0.0		
Merion blue	1 + CH ₃ COOH	14	1.0	1.0	1.8	5.0	9.3	4.5	3.6	3.8
	1 ^b		1.0	1.0	3.0	4.5	4.0	2.5		
	MH 30, standard		1.0	2.0	3.0	5.4	4.8	4.0		
	1 + CH ₃ COOH	28	1.0	1.0	1.0	1.0	10.6	10.1	8.6	5.8
	1 ^b		1.0	1.0	2.0	10.5	9.5	0.0		
	MH 30		1.0	3.0	4.8	5.6	0.0	0.1		
Perennial rye	1 + CH ₃ COOH	14	1.0	1.0	2.0	5.0	9.5	6.6	5.3	4.9
	1 ^c		1.0	1.0	2.0	6.3	5.8	5.8		
	MH 30		2.8	2.8	3.5	4.9	4.6	4.3		
	1 + CH ₃ COOH	28	1.0	1.0	1.0	1.0	10.5	10.6	10.3	11.0
	1 ^c		1.0	1.0	1.0	11.3	11.5	10.3		
	MH 30		3.3	4.3	5.0	0.8	0.0	0.1		

^a Phytotoxicity ratings (see Table I footnotes).

^b One replication.

^c Two replications. All others four replications.

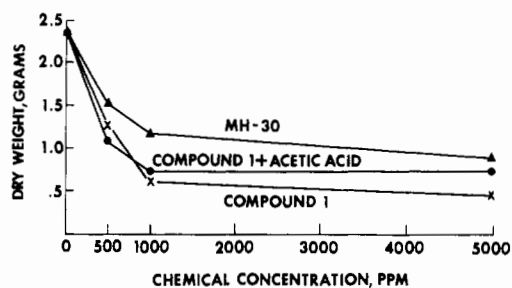


Figure 1. Effect of compound 1 and MH-30 on the dry weight of Kentucky bluegrass, 14 days after treatment

caused by 1. The standard MH-30 treatment reduced the grass growth for more than 28 days, while compound 1 was effective for only 14 days. Compound 1 was less phytotoxic than MH-30 and reduced the dry weight slightly more than MH-30. Maximum growth inhibition was obtained with 1000 p.p.m. of either compound 1 or MH-30

as shown by Figure 1 for the effect on the dry weight of Kentucky bluegrass, 14 days after treatment. Response by Merion bluegrass was similar to that for Kentucky bluegrass, while rye grass was less sensitive to 1 and more sensitive to MH-30.

ACKNOWLEDGMENT

The authors thank Gordon James, Brigitte Haugk, and Carl Quasthoff for technical assistance.

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Received for review March 25, 1968. Accepted August 30, 1968.