give N-(2-cyanoethyl)-bicyclo[2.2.1]-5-heptene-2,3-carboximide as colorless crystals, melting at 113-115°, in 75% yield.

Anal. Caled. for  $C_{12}H_{12}N_2O_2$ : C, 66.62; H, 5.56; N, 12.96. Found: C, 66.83; H, 5.41; N, 13.05.

A mixed melting point with the product obtained from the attempted esterifications above showed no depression. N,N,N',N'-Tetra-(2-cyanoethyl)-succinamide.—A small

N,N,N',N'-l'etra-(2-cyanoethyl)-succinamide.—A small amount of solid filtered from several different alkyl N,N-bis-(2-cyanoethyl)-succinamates proved in each case to be the same material. It was flammable, neutral to litmus, very slightly soluble in organic solvents but could be crystallized from hot water to give a nicely crystalline solid, melting from  $175-176^\circ$ .

Anal. Calcd. for  $C_{16}H_{20}N_6O_2$ : C, 58.50; H, 6.19; N, 25.60. Found: C, 58.41; H, 6.27; N, 25.44.

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# The Synthesis of Several Acid Analogs of 2-Mercaptobenzimidazole<sup>1,2</sup>

By Theodore L. Rebstock, Charles D. Ball, Charles L. Hamner and Harold M. Sell

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Twenty-three acid analogs of 2-mercaptobenzimidazoles were prepared by treating substituted 2-mercaptobenzimidazoles with monochloroacetic,  $\alpha$ -bromopropionic or  $\beta$ -bromopropionic acid.

Several workers have reported that benzimidazole is an antagonist of purine compounds. Woolley<sup>3</sup> observed that benzimidazole inhibited the growth of several yeasts and bacteria and that the inhibition could be completely removed by the addition of aminopurines. Klotz and Mellody<sup>4</sup> demonstrated that yeast nucleic acid reversed the inhibitory effect of benzimidazole on the growth of the bacterium, Escherichiacoli. Gillespie, et al.,5 showed that 4-methoxy-6-methylbenzimidazole inhibited growth of Tetrahymena gelii, a guanine-requiring protozoan and also of developing embryos of Rani pipiens. By using peas as the test plant, Galston, et al.,6 noted that benzimidazole was a metabolic antagonist of adenine and hindered cell elongation. Recently Rebstock, et al., reported that several acid analogs of 2-mercaptobenzimidazole arrested leaf and stem growth of Cranberry bean plants and root formation of cucumber seedlings.7

In the present work several new acid analogs of 2-mercaptobenzimidazole were synthesized to study the effect of chemical structure of derivatives of 2-mercaptobenzimidazole on growth inhibition of plants. Different chemical groups were substituted in the benzene ring of the benzimidazole nucleus and the thioether acid side chains were varied.

The acids were prepared by the Williamson synthesis by treating the appropriately substituted 2-mercaptobenzimidazoles with monochloroacetic,  $\alpha$ -bromopropionic or  $\beta$ -bromopropionic acids. The 2-mercaptobenzimidazoles were synthesized from

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(2) Journal Article No. 1932, Michigan Agricultural Experiment Station, East Lansing. Supported in part by the Horace H. Rackham Research Endowment of Michigan State University.

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suitably substituted *o*-phenylenediamines by the method described by Van Allan and Deacon<sup>8</sup> using a mixture of potassium hydroxide dissolved in aqueous ethanol and carbon disulfide. Where the *o*-phenylenediamines were commercially unavailable, these compounds were prepared from the corresponding *o*-nitroaniline or *o*-dinitrobenzene derivative by either reducing the nitro compound with stannous chloride or tin in concentrated hydrochloric acid. The melting points, neutralization equivalents, yields and analyses for the (2-benzimidazolylthio) acid derivatives are summarized in Table I.

The results of the biological assay of these compounds will be reported elsewhere.

#### Experimental

Preparation of (2-Benzimidazolylthio) Acid Derivatives.— The acetic,  $\alpha$ -propionic and  $\beta$ -propionic acid derivatives were synthesized by treating the appropriately substituted 2-mercaptobenzimidazole with monochloroacetic,  $\alpha$ -bromopropionic or  $\beta$ -bromopropionic acids. Equal molar quantities of the monohalogenated acid and the 2-mercaptobenzimidazole were refluxed two hours in a 2 N aqueous sodium hydroxide solution. After cooling, the solution was filtered and made acid to congo red with dilute hydrochloric acid. The precipitated acid was collected on a filter, dissolved in a minimum volume of boiling ethanol and decolorized with Norite. The filtered hot alcohol solution was diluted with water until a permanent cloudiness was obtained and then placed in the refrigerator for crystallization. The acid derivatives were recrystallized until the melting points were constant.

**Preparation of 2-Mercaptobenzimidazoles.**—These compounds were prepared by the procedure of Van Allan and Deacon<sup>8</sup> using as the reactants the appropriately substituted *o*-phenylenediamine and a mixture of aqueous ethanolic potassium hydroxide and carbon disulfide.

Preparation of o-Phenylenediamines.—4-Chloro- and 4nitro-o-phenylenediamine were secured from Distillation Products Industries. 4-Methoxy-1,2-diaminobenzene,<sup>9</sup> 4phenyl-1,2-diaminobenzene,<sup>10</sup> 4-methyl-1,2-diaminobenzene<sup>11</sup> and 3,5-dimethyl-1,2-diaminobenzene<sup>12</sup> were prepared from

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### TABLE I PROPERTIES OF 2-BENZIMIDAZOLVLTHIO ACIDS



Ring substitu- tion	Acid side chain	M.p.,ª °C.	Formula	Vield, ه %	Neut. equiv. Calcd. Found		Carbon, % Caled. Found		Hydrogen, % Calcd. Found		Nitrogen, % Calco Found	
	a-Propionic	181-182	CieHieOsNoS	41	222 3	218 8	54 04	53 87	4 54	4 48	12.60	12 79
5-Chloro-	Acetic	193 - 194	CoH7OoNoSCI	68	242.7	245 5	44 54	44 67	2.91	3 25	11 54	11 23
5-Chloro-	8-Propionie	103-108	CioHoOoNoSCI	60	256 7	259 0	46 78	46 58	3 53	3 73	10 01	10.88
5-Chloro-	a-Propionic	166-167	CinHaO2N2SC1	39	256.7	253.0	46.78	46 55	3 53	3 43	10.91	10.00
4.6-Dichloro-	Acetic	222 - 224	CoHsO2N2SC12	25	277.1	277.3	39.00	39 34	2 18	2 36	10.11	10.09
5.6-Dichloro-	Acetic	219 - 221	C <sub>9</sub> H <sub>6</sub> O <sub>2</sub> N <sub>2</sub> SCl <sub>2</sub>	81	277.1	274.1	39.00	39.38	2.18	2.41	10.11	10.08
5,6-Dichloro-	$\alpha$ -Propionic	230 - 231	C10H6O2N2SCl2	69	291.2	292.3	41.25	41.28	2.77	3.02	9.62	9.69
4,5,6-Trichloro-	Acetic	205 - 207	C <sub>9</sub> H <sub>5</sub> O <sub>2</sub> N <sub>2</sub> SCl <sub>3</sub>	42	311.6	310.2	34.69	34.75	1.62	1.89	8.99	9.33
4,5,6-Trichloro-	a-Propionic	222 - 224	C10H7O2N2SCl3	80	325.6	324.4	36.88	37.09	2.17	2.11	8.60	8.84
5-Bromo-	Acetic	194 - 196	C <sub>9</sub> H <sub>7</sub> O <sub>2</sub> N <sub>2</sub> SBr	70	287.1	288.1	37.64	37.86	2.46	2.68	9.76	9.84
5-Bromo-	a Propionic	180-181	C10H9O2N2SBr	43	301.2	302.4	39.88	39.43	3.01	2.89	9.30	9.45
5-Nitro-	Acetic	191 - 192	C9H7O4N3S	69	253.2	250.5	42.68	42.54	2.79	2.96	16.59	16.34
5-Nitro-	a-Propionic	186 - 188	$C_{10}H_7O_4N_3S$	52	267.3	271.0	44.94	45.03	3.39	3.15	15.72	15.99
5-Methoxyl-	Acetic	194 - 196	C10H10O3N2S	50	238.3	235.7	50.41	50.79	4.23	4.21	11.76	11.77
5-Methoxyl-	α-Propionic	151 - 152	$C_{11}H_{12}O_3N_2S$	71	252.3	255.1	52.36	52.63	4.79	4.85	11.10	11.07
5-Methyl-	Acetic	197 - 200	$C_{10}H_{10}O_2N_2S$	47	222.3	226.4	54.04	54.00	4.54	4.62	12.60	12.61
5-Methyl-	α-Propionic	160 - 162	$C_{11}H_{12}O_2N_2S$	55	236.3	240.3	55.91	56.09	5.12	5.47	11.86	11.71
4,6-Dimethyl-	Acetíc	247 - 249	$C_{11}H_{12}O_2N_2S$	55	236.3	231.7	55.91	56.01	5.12	4.92	11.86	11.85
4,6-Dimethyl-	$\alpha$ -Propionic	160-161	$C_{12}H_{14}O_2N_2S$	64	250.3	248.2	57.58	57.68	5.64	5.99	11.19	10.98
5,6-Dimethyl-	Acetic	207 - 209	$C_{11}H_{12}O_2N_2S$	85	236.3	234.9	55.91	55.74	5.12	5.33	11.86	12.11
5,6-Dimethyl-	$\alpha$ -Propionic	208 - 210	$C_{12}H_{14}O_2N_2S$	64	250.3	253.7	57.58	57.97	5.64	5.91	11.19	11.32
5-Phenyl-	Acetic	215 - 216	$C_{13}H_{12}O_2N_2S$	74	284.3	282.8	63.36	63.40	4.25	4.21	9.85	9.79
5-Phenyl-	a-Propionic	200 - 202	$C_{16}H_{14}O_2N_2S$	87	298.4	299.4	64.41	64.16	4.73	4.52	9.39	9.35
a The molting	- nointe more -	determined	on a Diahum Io	1	+	int hlad	- and a.		for out	itan at a		:

<sup>a</sup> The melting points were determined on a Fisher-Johus melting point block and corrected for calibration of the instrument. <sup>b</sup> Yields are calculated on the basis of the once-recrystallized acid.

2 - Nitro - 4 - methoxyaniline, 4 - amino - 3 - nitrobiphenyl, 4methyl-2-nitroaniline and 2,4-dimethyl-6-nitroaniline, respectively, by reduction with stannous chloride in concentrated hydrochloric acid. 1,3-Dichloro-2,5-diaminobenzene,<sup>13</sup> 4bromo-1,2-diaminobenzene<sup>14</sup> and 4,5-dimethyl-1,2-diaminobenzene<sup>15</sup> were synthesized from 2,4-dichloroaniline, *m*bromoaniline and 3,4-dimethylaniline, respectively, by nitrating the acetylated aniline derivative with concentrated nitric acid and reducing the nitro compound after hydrolysis with

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stannous chloride. 1,2-Dichloro-4,5-diaminobenzene<sup>16</sup> was made from 1,2-dichloro-2-nitrobenzene by nitration and reduction of the dinitro compound<sup>17</sup> with mossy tin in concentrated hydrochloric acid. 1,2,3-Trichloro-5,6-diaminobenzene was prepared by the reduction of 1,2,3-trichloro-5,6-dinitrobenzene<sup>18</sup> which in turn was synthesized by the nitration of 1,2,3-trichloro-5-nitrobenzene.<sup>19</sup>

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[A CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

## Metabolite Analogs. VI. Preparation of Some Analogs of 4-Amino-5-imidazolecarboxamide<sup>1</sup>

### By John R. E. Hoover<sup>2</sup> and Allan R. Day

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1,2,3-Triazole analogs of the imidazole intermediates of *de novo* purine synthesis have been prepared as potential modifiers of nucleic acid metabolism. The 1-benzyl-1,2,3-triazoles were formed readily by condensing benzyl azide with esters and nitriles containing an active methylene group and the benzyl group was removed by reduction with sodium in liquid ammonia.

The use of drugs which affect nucleic acid metabolism, especially certain analogs of the natural purines, has been one of the more fertile fields of cancer

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chemotherapy to date. In view of this, an investigation of the possibility of interfering with purine metabolism by the use of analogs of the recently elucidated natural purine precursors,<sup>3</sup> especially of

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