

# Derivatives of 3-(2-Hydroxyethyl)-2-benzothiazolinone and Related Compounds

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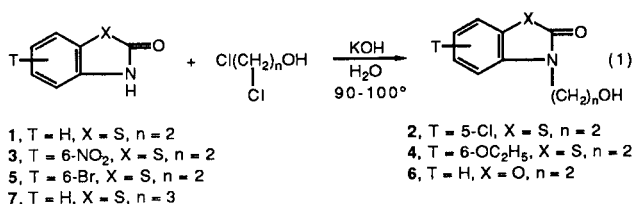
The reaction of the appropriate 2-benzothiazolinone with 2-chloroethanol or 3-chloropropanol under basic conditions afforded 3-(2-hydroxyethyl or 3-hydroxypropyl)-2-benzothiazolinone and related compounds **1-7**. The reaction of the alcohols **1**, **4**, **5** or **7** with potassium hydroxide and excess carbon disulfide furnished the potassium salts of xanthic acid **8-11** which upon oxidation gave the disulfides **12-15**. Esters of xanthic acid **16-23** were prepared by the reaction of **8** or **11** with various halogen compounds. Esters of acetic acid **24-28** were prepared by the reaction of the appropriate 2-benzothiazolinone with 2-bromoethyl acetate under basic conditions. Esterification of **1** with various acids afforded the esters **25, 29-32**.

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Since heterocycles containing nitrogen and sulfur and especially derivatives of 2-benzothiazolinone and benzothiazoline-2-thione [1-5] exhibited biological activity, it appeared desirable to continue our research efforts in this area of chemistry.

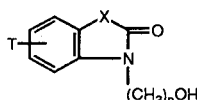
The purpose of this investigation was to synthesize 3-(2-hydroxyethyl)-2-benzothiazolinone and related compounds and to react these hydroxy-compounds with various electrophiles.

The key intermediates 3-(2-hydroxyethyl)-2-benzothiazolinone and related compounds **1-7** (Table 1) were prepared by the reaction of the appropriate 2-benzothiazolinone or 2-benzoxazolinone with 2-chloroethanol or 3-chloropropanol under basic conditions.



The reaction of **1**, **4**, **5** or **7** with potassium hydroxide and excess carbon disulfide afforded S-potassium O-[2-(oxobenzothiazolin-3-yl)ethyl]-xanthic acid and related compounds **8-11** (Table 2) in 89 to 99% yields.

Table 1



No.	T	X	n	Mp °C (N <sub>2</sub> )	% Yield	Empirical formula	Chemical Analysis							
							%C		%H		%N		%S	
						Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
<b>1</b>	H	S	2	94-95 [a]	98	C <sub>9</sub> H <sub>9</sub> NO <sub>2</sub> S	55.36	55.21	4.65	4.52	7.17	7.11	16.42	16.12
<b>2</b> [c]	5-Cl	S	2	157-158 [b]	90	C <sub>9</sub> H <sub>8</sub> ClNO <sub>2</sub> S [f]	47.06	46.84	3.51	3.50	6.10	6.01	13.96	14.04
<b>3</b>	6-NO <sub>2</sub>	S	2	161-163 [d]	93	C <sub>9</sub> H <sub>8</sub> N <sub>2</sub> O <sub>4</sub> S	45.00	45.17	3.36	3.38	11.66	11.73	13.35	13.32
<b>4</b>	6-OC <sub>2</sub> H <sub>5</sub>	S	2	viscous liquid	66	C <sub>11</sub> H <sub>13</sub> NO <sub>2</sub> S	55.21	54.94	5.48	5.29	5.85	5.95	13.40	13.58
<b>5</b> [e]	6-Br	S	2	133-134 [a]	96	C <sub>9</sub> H <sub>8</sub> BrNO <sub>2</sub> S	39.43	39.34	2.94	2.72	5.11	5.19	11.70	12.00
<b>6</b>	H	O	2	110-111 [b]	95	C <sub>9</sub> H <sub>9</sub> NO <sub>3</sub>	60.32	60.50	5.06	5.11	7.81	7.25	---	---
<b>7</b>	H	S	3	viscous liquid (1.6105)	94	C <sub>10</sub> H <sub>11</sub> NO <sub>2</sub> S	57.37	57.22	5.30	5.19	6.69	6.72	15.32	15.14

[a] Recrystallization from toluene. [b] Recrystallization from isopropyl alcohol. [c] <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 3.60 (t, 2, CH<sub>2</sub>O), 3.90 (t, 2, NCH<sub>2</sub>), 4.90 (br, s, 1, OH), 6.90-7.70 (m, 3, ArH). [d] Recrystallization from ethyl acetate. [e] <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 3.60 (t, 2, CH<sub>2</sub>O), 3.90 (t, 2, NCH<sub>2</sub>), 4.80 (br s, 1, OH), 6.90-7.90 (m, 3, ArH). [f] Calcd. Cl, 15.44. Found: Cl, 15.48.

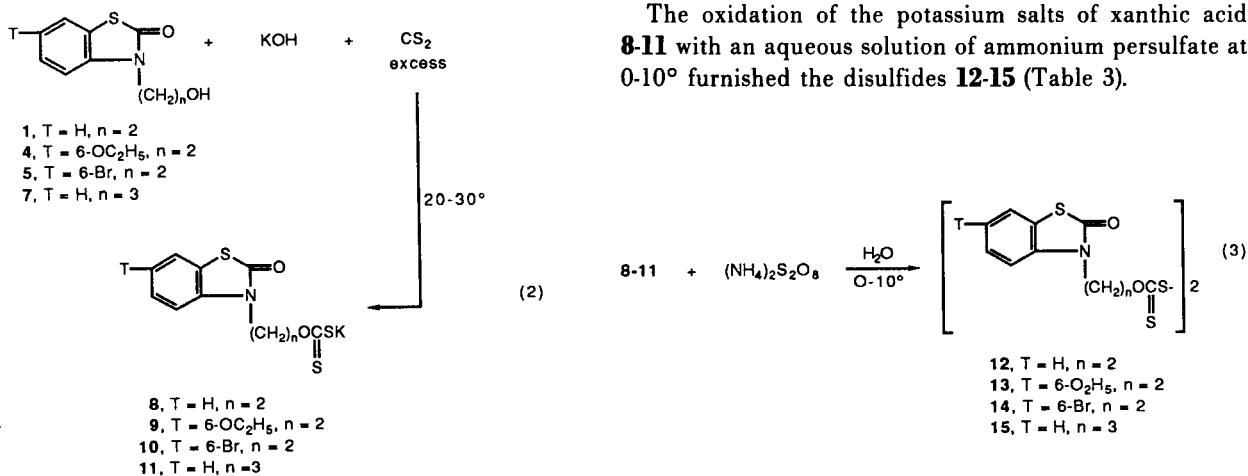
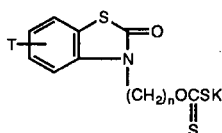
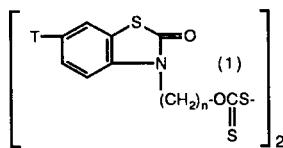


Table 2



No.	T	n	% Yield	Empirical formula	Chemical Analysis							
					%C		%H		%N		%S	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
8	H	2	99	C <sub>10</sub> H <sub>8</sub> KNO <sub>2</sub> S <sub>3</sub>	46.57	40.48	2.61	2.60	4.52	4.47	31.08	31.20
9	6-OC <sub>2</sub> H <sub>5</sub>	2	95	C <sub>12</sub> H <sub>12</sub> KNO <sub>2</sub> S <sub>3</sub>	40.77	40.55	3.42	3.46	3.96	3.69	27.21	27.10
10	6-Br	2	93	C <sub>10</sub> H <sub>7</sub> BrKNO <sub>2</sub> S <sub>3</sub>	30.88	30.70	1.82	2.03	3.61	3.75	24.83	24.60
11	H	3	89	C <sub>10</sub> H <sub>10</sub> KNO <sub>2</sub> S <sub>3</sub> ·2H <sub>2</sub> O	36.76	36.60	2.80	2.65	3.90	3.76	26.75	26.50

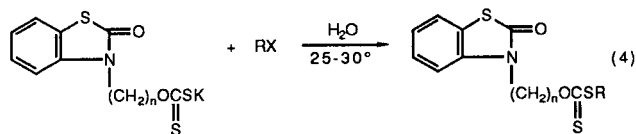
Table 3



No.	T	n	Mp °C w/dec	% Yield	Empirical formula	Chemical Analysis							
						%C		%H		%N		%S	
						Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
12	H	2	158-160 [a]	67	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> S <sub>6</sub>	44.42	44.30	2.98	2.86	5.18	5.24	35.58	35.44
13	-OC <sub>2</sub> H <sub>5</sub>	2	164-165 [b]	73	C <sub>24</sub> H <sub>24</sub> N <sub>2</sub> O <sub>6</sub> S <sub>6</sub>	45.84	45.96	3.85	3.90	4.45	4.48	30.59	30.47
14	-Br	2	166-167 [a]	86	C <sub>20</sub> H <sub>14</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S <sub>6</sub>	34.39	34.46	2.02	2.03	4.01	4.30	27.54	27.49
15	H	3	128-129 [b]	91	C <sub>22</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> S <sub>6</sub>	46.45	46.49	3.54	3.70	4.93	4.86	33.82	33.73

[a] Recrystallization from dimethylformamide. [b] Recrystallization from toluene.

The reaction of **8** or **11** with methyl iodide, *O*-fluorobenzyl chloride, *p*-fluorobenzyl chloride, chloroacetonitrile or *m*-trifluoromethylbenzyl chloride in an aqueous medium at 25-30° afforded the esters of xanthic acid **16-23** (Table 4).



**8**, n = 2  
**11**, n = 3

**16**, n = 2, R = -CH<sub>3</sub>  
**17**, n = 3, R = -CH<sub>3</sub>

**18**, n = 2, R = -CH<sub>2</sub>-

**19**, n = 2, R = -CH<sub>2</sub>-

**20**, n = 3, R = -CH<sub>2</sub>-

**21**, n = 3, R = -CH<sub>2</sub>-

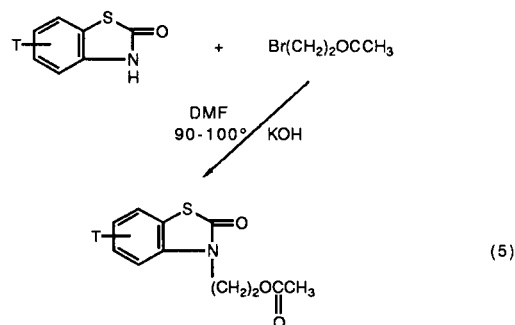
**22**, n = 3, R = -CH<sub>2</sub>CN

**23**, n = 3, R = -CH<sub>2</sub>-

In Method 1, the reaction of the appropriate 2-benzothiazolinone with 2-bromoethyl acetate in dimethylform-

amide at 90-100° under basic conditions afforded the substituted esters of acetic acid **24-28** (Table 5).

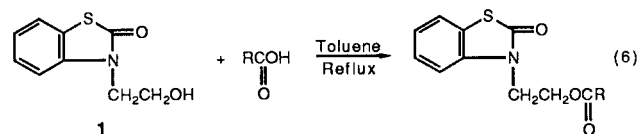
Method 1



**24**, T = -6Br; **25**, T = H; **26**, T = 5-Cl; **27**, T = 6-OC<sub>2</sub>H<sub>5</sub>; **28**, T = 6-NO<sub>2</sub>

In Method 2, the substituted esters of acetic, propionic, isobutyric, isovaleric or valeric acid **25, 29-32** (Table 6) were synthesized by the reaction of **1** with the appropriate acid containing catalytic amount of *p*-toluenesulfonic acid in refluxing toluene.

Method 2



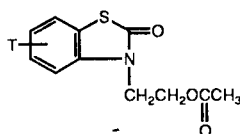
**25**, R = -CH<sub>3</sub> **29**, R = -C<sub>2</sub>H<sub>5</sub> **30**, R = -CH(CH<sub>3</sub>)<sub>2</sub>  
**31**, R = -C<sub>4</sub>H<sub>9</sub> **32**, R = -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>

Table 4

R =															
-CH <sub>3</sub>		-CH <sub>3</sub>										-CH <sub>2</sub> CN			
<b>16</b>		<b>17</b>		<b>18</b>		<b>19</b>		<b>20</b>		<b>21</b>		<b>22</b>		<b>23</b>	
No.	n	Mp °C	% Yield	Empirical formula	Chemical Analysis										
					%C		%H		%N		%S				
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
<b>16</b>	2	63-65 [a]	83	C <sub>11</sub> H <sub>11</sub> NO <sub>2</sub> S <sub>3</sub>	46.28	46.10	3.88	3.78	4.91	4.58	33.71	33.51			
<b>17</b>	3	viscous liquid	98	C <sub>12</sub> H <sub>13</sub> NO <sub>2</sub> S <sub>3</sub>	48.13	48.20	4.38	4.20	4.68	4.30	32.12	31.98			
<b>18</b>	2	100-101 [b]	60	C <sub>17</sub> H <sub>14</sub> FNO <sub>2</sub> S <sub>3</sub>	53.80	53.76	3.72	3.75	3.69	3.76	25.35	25.36			
<b>19</b>	2	112-113 [b]	76	C <sub>17</sub> H <sub>14</sub> FNO <sub>2</sub> S <sub>3</sub>	53.80	53.69	3.72	3.72	3.69	3.73	25.35	25.18			
<b>20</b>	3	77-78 [c]	92	C <sub>18</sub> H <sub>16</sub> FNO <sub>2</sub> S <sub>3</sub> [d]	54.94	54.80	4.10	4.01	3.56	3.66	24.44	24.64			
<b>21</b>	3	58-59 [b]	89	C <sub>18</sub> H <sub>16</sub> FNO <sub>2</sub> S <sub>3</sub> [e]	54.94	54.79	4.10	3.98	3.56	3.45	24.44	24.20			
<b>22</b>	3	viscous liquid	99	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S <sub>3</sub>	48.13	48.10	3.73	3.60	8.63	8.69	29.65	29.45			
<b>23</b>	3	viscous liquid	92	C <sub>19</sub> H <sub>16</sub> F <sub>3</sub> NO <sub>2</sub> S <sub>3</sub> [f]	51.45	51.53	3.64	3.74	3.16	3.00	21.69	21.50			

[a] Recrystallization from heptane-isopropyl alcohol (4:1). [b] Recrystallization from isopropyl alcohol. [c] Recrystallization from heptane-ethyl acetate (4:1). [d] Calcd. F, 4.83. Found: F, 4.74. [e] Calcd. F, 4.83. Found: F, 4.76. [f] Calcd. F, 12.85. Found: F, 12.98.

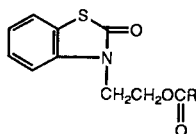
Table 5 (Method 1)



No.	T	Mp °C	Yield	Empirical formula	Chemical Analysis							
					%C		%H		%N		%S	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
24	6-Br	97-98 [a]	84	C <sub>11</sub> H <sub>10</sub> BrNO <sub>3</sub> S	41.79	41.70	3.19	3.07	4.43	4.74	10.14	10.55
25 [d]	H	viscous liquid N <sub>D</sub> <sup>25</sup> = 1.5900	84	C <sub>11</sub> H <sub>11</sub> NO <sub>3</sub> S	55.68	55.50	4.67	4.50	5.90	6.05	13.51	13.59
26 [e]	5-Cl	63-65 [a]	79	C <sub>11</sub> H <sub>10</sub> ClNO <sub>3</sub> S [b]	48.62	48.66	3.71	3.72	5.15	5.19	11.80	11.94
27	6-OC <sub>2</sub> H <sub>5</sub>	viscous liquid	87	C <sub>13</sub> H <sub>15</sub> NO <sub>4</sub> S	58.84	58.60	5.70	5.50	5.28	5.29	12.08	12.11
28	6-NO <sub>2</sub>	130-131 [c]	78	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>5</sub> S	46.80	46.60	3.57	3.45	9.92	10.14	11.36	11.46

[a] Recrystallization from heptane-isopropyl alcohol (4:1). [b] Calcd. Cl, 13.05. Found: Cl, 13.28. [c] Recrystallization from methyl alcohol-ethyl acetate (4:1). [d] <sup>1</sup>H-nmr (deuteriochloroform): δ 1.98 (s, 3, OCCH<sub>3</sub>), 4.24 (t, 2, CH<sub>2</sub>O), 4.42 (t, 2, NCH<sub>2</sub>), 7.03-7.53 (m, 4, ArH). [e] <sup>1</sup>H-nmr (deuteriochloroform): δ 1.62 (s, 3, OCH<sub>3</sub>), 4.16 (t, 2, CH<sub>2</sub>O), 4.32 (t, 2, NCH<sub>2</sub>), 7.01-7.43 (m, 3, ArH).

Table 6



No.	R	N <sub>D</sub> <sup>25</sup>	Yield	Empirical formula	Chemical Analysis							
					%C		%H		%N		%S	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
25 [a]	-CH <sub>3</sub>	1.5895	84	C <sub>11</sub> H <sub>11</sub> NO <sub>3</sub> S	55.68	55.48	4.67	4.60	5.90	6.04	13.51	13.37
29	-C <sub>2</sub> H <sub>5</sub>	1.5744	78	C <sub>12</sub> H <sub>13</sub> NO <sub>3</sub> S	57.35	57.20	5.21	5.10	5.57	5.70	12.76	12.94
30 [b]	-CH(CH <sub>3</sub> ) <sub>2</sub>	1.5642	91	C <sub>13</sub> H <sub>15</sub> NO <sub>3</sub> S	58.85	58.70	5.70	5.51	5.27	5.33	12.08	12.19
31	-C <sub>4</sub> H <sub>9</sub>	1.5620	70	C <sub>14</sub> H <sub>17</sub> NO <sub>3</sub> S	60.19	60.10	6.13	6.01	5.01	5.16	11.47	11.63
32	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	1.5555	84	C <sub>14</sub> H <sub>17</sub> NO <sub>3</sub> S	60.19	60.01	6.13	6.05	5.01	4.90	11.47	11.56

[a] The index of refraction and nmr spectral data for **25** derived by Methods 1 and 2 were comparable. [b] <sup>1</sup>H nmr (deuteriochloroform): δ 1.09 (d, 6, C-(CH<sub>3</sub>)<sub>2</sub>) J = 7 Hz, 2.48 (heptet, 1, CH) J = 7 Hz, 4.20 (t, 2, CH<sub>2</sub>O), 4.40 (t, 2, NCH<sub>2</sub>), 6.90-7.50 (m, 4, ArH).

The index of refraction and NMR spectral data [Tables 5 and 6] for **25** derived by Methods 1 and 2 were comparable.

#### EXPERIMENTAL

The nmr spectra were obtained with a Varian T-60 nmr spectrometer. The chemical shifts are reported in δ, using tetramethylsilane as reference. All melting points were taken upon a Fisher-Johns block and are uncorrected.

#### 3-(2-Hydroxyethyl)-2-benzothiazolinone and Related Compounds 1-7.

To a stirred solution containing 1 mole of the appropriate 2-benzothiazolinone or 2-benzoxazolinone, 66 g (1.0 mole) of 85% potassium hydrox-

ide, and 400 ml of water, 1.1 mole of 2-chloroethanol or 3-chloropropanol was added in one portion. The stirred reaction mixture was heated at 90-100° for 24 hours and then at 25-30° for 18 hours. For all compounds except **4** and **7** of Table 1, the stirred reaction mixture was cooled to 5°. After stirring at 0-10° for 1 hour, the product was collected by filtration, washed with 200 ml of cold water and air-dried at 25-30°. For **4** and **7** of Table 1, after cooling to 25° the stirred reaction mixture was extracted with 500-600 ml of ethyl ether and chloroform, respectively. The separated solvent layers were washed with water until neutral and dried over sodium sulfate. The ethyl ether and chloroform were removed *in vacuo* at a maximum temperature of 80-90° at 1-2 mm. The data are summarized in Table 1.

S-Potassium O-[2-(2-Oxobenzothiazolin-3-yl)ethyl]xanthic Acid and Related Compounds **8-11**.

To a stirred charge containing 0.25 mole of **1**, **4**, **5** or **7** in 500 ml of carbon disulfide, 16.5 g (0.25 mole) of 85% potassium hydroxide was added in small portions at 20-25° over a 10 minute period. After stirring at 25-30° for 24 hours, 600 ml of ethyl ether was added and stirring continued at 25-30° for 30 minutes. The solid was collected by filtration, washed with 200 ml of ethyl ether and air-dried at 25-30°. The data are summarized in Table 2.

Formic Acid, Thiono-bis-, 1,1'-Dithio-, bis[2-(2-Oxo-3-benzothiazolin-3-yl)ethyl] Ester and Related Products (**12-15**).

To a stirred solution at 0° containing 0.1 mole of **8**, **9**, **10** or **11** in 500 ml of water, a solution containing 12.6 g (0.055 mole) of ammonium persulfate in 100 ml of water was added dropwise at 0-10° over a 20 minute period. After stirring at 0-10° for 2 hours, the solid was collected by filtration, washed with water until neutral and air-dried at 20-30°. The data are summarized in Table 3.

O-[2 or 3-(2-Oxo-3-benzothiazolin-3-yl)ethyl or propyl] Ester S-substituted Ester Carbonodithioic Acids **16-23**.

To a stirred charge containing 0.2 mole of **8** or **11** and 600 ml of water, 0.2 mole of the appropriate halogen compound (methyl iodide, *o*-fluorobenzyl chloride, *p*-fluorobenzyl chloride, chloroacetonitrile or *m*-trifluoromethylbenzyl chloride) was added in one portion, and stirring was continued at 25-30° for 24 hours. For all solids, **16**, **18-21**, the stirred reaction mixture was cooled to 0°, and stirring continued at 0-5° for 1 hour. The solid was collected by filtration, washed with 500 ml of water and air-dried at 25-30°. For all liquids, **17**, **22-23** 600 ml of ethyl ether was added, and stirring continued at 25-30° for 30 minutes. The separated ether layer was washed with water until neutral and dried over sodium sulfate. The ether was removed *in vacuo* at a maximum temperature of 80-90° at 1-2 mm. The data are summarized in Table 4.

[2-(2-Oxo-3-benzothiazolin-3-yl)ethyl] Ester, Acetic Acid and Related Products **24-32**.

Method 1, **24-28**.

To a stirred solution containing 0.1 mole of the appropriate 2-benzo-

thiazolinone, 6.6 g (0.1 mole) of 85% potassium hydroxide, 150 ml of dimethylformamide and 10 ml of water, 18.4 g (0.11 mole) of 2-bromoethyl acetate was added in one portion. The reaction mixture was heated at 90-100° for 2 days and at 25-30° for 1 day. For compounds **24**, **26** and **28**, 800 g of ice water was added and stirring continued at 0-10° for one hour. The solid was collected by filtration, washed with water until neutral to litmus and air-dried at 25-30°. For compounds **25** and **27**, 600 ml of water and 500 ml of ethyl ether were added, and stirring continued at 25-30° for 15 minutes. The separated ether layer was washed with water until neutral and dried over sodium sulfate. The ether was removed *in vacuo* at maximum temperature of 80-90° at 1-2 mm. The data are summarized in Table 5.

Method 2, **25**, **29-32**.

A stirred mixture containing 0.2 mole of **1**, 0.25 mole of acetic, propionic, isobutyric, isovaleric or valeric acid, 4 g of *p*-toluenesulfonic acid and 200 ml of toluene was heated at reflux for 6 hours or until 3.6 ml of water was collected *via* a Dean-Stark Condenser. After stirring at 25-30° for 18 hours, 20 g (0.25 mole) of 50% sodium hydroxide and 300 ml of water were added. This was followed by the addition of 500 ml of ethyl ether and stirring was continued for 15 minutes. The separated top organic layer was washed with water until neutral and dried over sodium sulfate. The ether and toluene were removed *in vacuo* at a maximum temperature of 80-90° at 1-2 mm. The data are summarized in Table 6.

#### REFERENCES AND NOTES

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