

microorganisms<sup>5,6</sup> and those of the present investigation, leave hardly any doubt that the formation of arginine in *Torulopsis utilis* involves a direct con-

version of  $\alpha$ -ketoglutarate *via* glutamate, proline, ornithine and citrulline.

PHILADELPHIA 11, PENNA.

RECEIVED OCTOBER 6, 1951

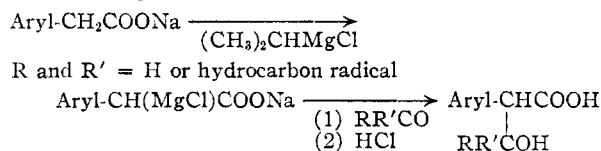
[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

## Antispasmodics. IX. $\beta$ -Diethylaminoethyl Esters of Substituted $\alpha$ -Aryl- $\beta$ -hydroxypropionic Acids

BY F. F. BLICKE AND HAROLD RAFFELSON<sup>1,2</sup>

A series of substituted  $\alpha$ -aryl- $\beta$ -hydroxypropionic acids has been prepared by interaction of an Ivanov reagent, such as aryl-CH<sub>2</sub>COONa or aryl-CH(R)COONa, with a carbonyl compound. The acids were converted into their  $\beta$ -diethylaminoethyl esters. A few of the esters exhibited high antispasmodic activity.

During the last few years we have prepared a variety of substituted  $\alpha$ -aryl- $\beta$ -hydroxypropionic acids by the interaction of an Ivanov reagent<sup>3,4</sup> with a compound which contains a carbonyl group<sup>5</sup>



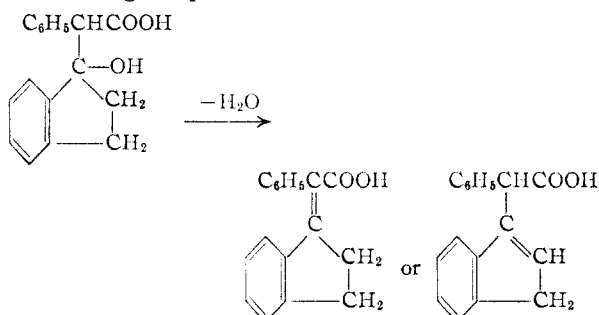
During this investigation Ivanov reagents were prepared from the sodium salts of phenyl-, 2-thienyl-, 3-thienyl- and *p*-xenylacetic acid and from the sodium salts of  $\alpha$ -substituted phenylacetic acids such as diphenyl-, benzylphenyl-, cyclohexylphenyl- and phenoxyphenylacetic and  $\alpha$ -phenylbutyric acid. These reagents were allowed to react with a variety of acyclic aldehydes and ketones and with cyclic ketones such as cyclopentanone, cyclohexanone, 3-thiophanone and 1- and 2-hydrindone. The acids which were produced are reported in Tables I and II.

Isobutyraldehyde and the chloromagnesium derivative of sodium phenylacetate reacted, according to Ivanov and Nicolov,<sup>6</sup> to produce two compounds which seemed to be isomeric  $\alpha$ -phenyl- $\beta$ -hydroxyisocaproic acids; one acid melted at 139–140°, the other at 171–172°. When we carried out this experiment, the only product isolated was an acid which melted at 126–127°, and the neutralization equivalent found corresponded to that calculated for  $\alpha$ -phenyl- $\beta$ -hydroxyisocaproic acid.

From the interaction of benzophenone with the chloromagnesium derivative of sodium phenylacetate, an acid (m.p. 206–207°) was obtained which, based on a neutralization equivalent, is  $\alpha, \beta, \beta$ -triphenyl- $\beta$ -hydroxypropionic acid. Paterno and Chieffi<sup>7</sup> stated that they isolated this acid (m.p.

205–208°) after exposure of a mixture of benzophenone and phenylacetic acid to sunlight. However, when Ivanov and Spassov,<sup>8</sup> and later Ivanov and Ivanov,<sup>9</sup> employed the same reaction used by us, they claimed that they obtained  $\alpha, \beta, \beta$ -triphenyl- $\beta$ -hydroxypropionic acid which melted at 186–187°. We are unable to explain this discrepancy.

The chloromagnesium derivative mentioned above reacted with 2-hydrindone in the expected manner to produce phenyl-(2-hydroxy-2-hydrindyl)-acetic acid. When 1-hydrindone was used, an unsaturated acid was obtained. Apparently, the hydroxy acid, formed initially, underwent dehydration during the process of isolation.



When  $\text{C}_6\text{H}_5\text{CH(MgCl)COONa}$  was allowed to react with ethylene oxide, and the reaction mixture acidified at 0°, the product isolated was  $\alpha$ -phenyl- $\gamma$ -hydroxybutyric acid. However, when the reaction mixture was acidified at room temperature, an oily, alkali-insoluble product, undoubtedly  $\alpha$ -phenyl- $\gamma$ -butyrolactone, was obtained.

Formaldehyde and the chloromagnesium derivative of sodium diphenylacetate reacted to form  $\alpha, \alpha$ -diphenyl- $\beta$ -hydroxypropionic acid. Treatment of the acid with lithium aluminum hydride converted it into 2,2-diphenyl-1,3-propanediol which was identical with the diol obtained by reduction of diethyl diphenylmalonate with lithium aluminum hydride.

In some instances, as in the preparation of tropic acid,<sup>10</sup> it may be more convenient to employ the chloromagnesium instead of the sodium salt. The former salt was used recently by Weston and

(1) This paper represents part of a dissertation submitted by Harold Raffelson in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan.

(2) Sterling-Winthrop Fellow.

(3) D. Ivanov and A. Spassov, *Bull. soc. chim.*, [4] **49**, 19 (1931).

(4) This term may be used to designate a compound of the type aryl-CH(MgCl)COONa or aryl-CH(MgCl)COOMgCl.

(5) A paper which described the preparation of a number of acids by the use of an Ivanov reagent, as well as the preparation of basic esters of the acids, was read before the Medicinal Chemistry Division of the American Chemical Society at the Cleveland meeting, April, 1951.

(6) D. Ivanov and N. I. Nicolov, *Bull. soc. chim.*, [4] **51**, 1325 (1932).

(7) E. Paterno and C. Chieffi, *Gazz. chim. ital.*, **40**, II, 321 (1910).

(8) D. Ivanov and A. Spassov, *Bull. soc. chim.*, [4] **49**, 377 (1931).

(9) D. Ivanov and Ch. Ivanov, *Compt. rend.*, **226**, 1199 (1948).

(10) F. F. Blicke, Harold Raffelson and Bohdan Barna, *THIS JOURNAL*, **74**, in press (1952).

TABLE I  
 SUBSTITUTED  $\alpha$ -ARYL- $\beta$ -HYDROXYPROPIONIC ACIDS  $\text{RCHCOOH}$ 

Compounds 1, 3, 15 and 17 were recrystallized from benzene; 2, 7 and 13 from carbon tetrachloride; 4 and 12 from toluene; 5 from toluene-petroleum ether; 6, 8, 10, 11, 21 and 22 from benzene-petroleum ether; 9 from alcohol; 14 and 18 from isopropyl alcohol; 16 and 19 from dioxane; 20 from carbon tetrachloride and petroleum ether.

Carbonyl compound employed	R	R'	R''	M.p., °C.	Yield, %	Formula	Neut. equiv. Calcd.	Neut. equiv. Found
1 Formaldehyde	C <sub>6</sub> H <sub>5</sub>	H	H	116-117 <sup>b</sup>	66			
2 Acetaldehyde	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	135-136 <sup>c</sup>	50			
3 Propionaldehyde	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	H	141-142	61	C <sub>11</sub> H <sub>14</sub> O <sub>3</sub>	194.2	195.0
4 Isobutyraldehyde	C <sub>6</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>2</sub> CH	H	126-127 <sup>d</sup>	63	C <sub>12</sub> H <sub>16</sub> O <sub>3</sub>	208.3	208.8
5 2-Ethylbutyraldehyde	C <sub>6</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH	H	98-100	74	C <sub>14</sub> H <sub>20</sub> O <sub>3</sub>	236.3	235.6
6 Benzaldehyde	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	H	173-174 <sup>e</sup>	80			
7 Acetone	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	CH <sub>3</sub>	91-93 <sup>f</sup>	77	C <sub>11</sub> H <sub>14</sub> O <sub>3</sub>	194.2	193.0
8 Methyl ethyl ketone	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	89-91	73	C <sub>12</sub> H <sub>16</sub> O <sub>3</sub>	208.3	210.0
9 Diethyl ketone	C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	151-152 <sup>g</sup>	82	C <sub>13</sub> H <sub>18</sub> O <sub>3</sub>	222.3	223.1
10 Diisopropyl ketone	C <sub>6</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>2</sub> CH	(CH <sub>3</sub> ) <sub>2</sub> CH	156-157	45	C <sub>15</sub> H <sub>22</sub> O <sub>3</sub>	250.3	249.0
11 Cyclopentanone	C <sub>6</sub> H <sub>5</sub>	-(CH <sub>2</sub> ) <sub>4</sub> -		99-100 <sup>h</sup>	61	C <sub>13</sub> H <sub>16</sub> O <sub>3</sub>	220.3	220.0
12 Cyclohexanone	C <sub>6</sub> H <sub>5</sub>	-(CH <sub>2</sub> ) <sub>5</sub> -		139-140 <sup>i</sup>	84	C <sub>14</sub> H <sub>18</sub> O <sub>3</sub>	234.3	234.1
13 3-Thiophanone	C <sub>6</sub> H <sub>5</sub>	-CH <sub>2</sub> SCH <sub>2</sub> CH <sub>2</sub> -		89-91	47	C <sub>12</sub> H <sub>14</sub> O <sub>3</sub> S	238.3	236.1
14 Acetophenone	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	184-186 <sup>j</sup>	73	C <sub>16</sub> H <sub>16</sub> O <sub>3</sub>	256.3	255.0
15 2-Hydrindone	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>4</sub> $\begin{cases} \text{CH}_2- (1) \\ \text{CH}_2- (2) \end{cases}$		159-161	70	C <sub>17</sub> H <sub>16</sub> O <sub>3</sub>	268.3	269.6
16 Benzophenone	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	206-207 <sup>k</sup>	35	C <sub>21</sub> H <sub>18</sub> O <sub>3</sub>	318.4	316.3
17 Formaldehyde	2-C <sub>4</sub> H <sub>9</sub> S <sup>l</sup>	H	H	95-96 <sup>m</sup>	69			
18 Formaldehyde	4-C <sub>6</sub> H <sub>5</sub> -C <sub>6</sub> H <sub>4</sub>	H	H	207-209 (dec.)	78	C <sub>15</sub> H <sub>14</sub> O <sub>3</sub>	242.3	242.2
19 Cyclohexanone	4-C <sub>6</sub> H <sub>5</sub> -C <sub>6</sub> H <sub>4</sub>	-(CH <sub>2</sub> ) <sub>5</sub> -		215-216	83	C <sub>20</sub> H <sub>22</sub> O <sub>3</sub>	310.4	310.0
20 Cyclopentanone	2-C <sub>4</sub> H <sub>9</sub> S	-(CH <sub>2</sub> ) <sub>4</sub> -		73-75	87	C <sub>11</sub> H <sub>14</sub> O <sub>3</sub> S	226.3	225.1
21 Cyclohexanone	2-C <sub>4</sub> H <sub>9</sub> S	-(CH <sub>2</sub> ) <sub>5</sub> -		108-110	77	C <sub>12</sub> H <sub>16</sub> O <sub>3</sub> S	240.3	240.3
22 Cyclohexanone	3-C <sub>4</sub> H <sub>9</sub> S	-(CH <sub>2</sub> ) <sub>5</sub> -		131-132	74	C <sub>12</sub> H <sub>16</sub> O <sub>3</sub> S	240.3	241.3

<sup>a</sup> The crude acid was washed with petroleum ether (60-75°) to free it from phenylacetic acid. <sup>b</sup> A. Ladenburg and L. Rügheimer (*Ber.*, 13, 373 (1880)) found 117-118°. <sup>c</sup> Otto Hromatka (*ibid.*, 75, 814 (1942)) reported 136°; ref. 11, m.p. 133-134°. <sup>d</sup> See ref. 6. <sup>e</sup> Ref. 6, m.p. 175°. <sup>f</sup> Reference 11, m.p. 93-94°. <sup>g</sup> Reference 11, m.p. 154-155°. <sup>h</sup> Reference 11, m.p. 96-97°. <sup>i</sup> Reference 8, m.p. 135°; ref. 11, m.p. 134-136°. <sup>j</sup> Reference 8, m.p. 182-183°. <sup>k</sup> Reference 7, m.p. 205-208°; ref. 8 and ref. 9, m.p. 186-187°. <sup>l</sup> Thienyl. <sup>m</sup> Wilhelm Steinkopf and Arthur Wolfram (*Ann.*, 437, 22 (1924)) found 95.5-96°.

 TABLE II  
 SUBSTITUTED  $\alpha$ -PHENYL- $\beta$ -HYDROXYPROPIONIC ACIDS C<sub>6</sub>H<sub>5</sub>C(R)COOH

Compounds 1 and 3 were recrystallized from isopropyl alcohol; 2 from toluene; 4 from ethyl acetate; 5 from benzene-petroleum ether.

R	R'	R''	M.p., °C.	Yield, %	Formula	Neut. equiv. Calcd.	Neut. equiv. Found
1 C <sub>6</sub> H <sub>5</sub>	H	H	158-159 <sup>a</sup>	91	C <sub>16</sub> H <sub>14</sub> O <sub>3</sub>	242.3	242.0
2 C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	H	H	188-189	22	C <sub>16</sub> H <sub>16</sub> O <sub>3</sub>	256.3	254.9
3 C <sub>6</sub> H <sub>5</sub> O	H	H	160-161	26	C <sub>15</sub> H <sub>14</sub> O <sub>4</sub>	258.3	260.0
4 C <sub>6</sub> H <sub>11</sub>	H	H	146-148	94	C <sub>16</sub> H <sub>20</sub> O <sub>3</sub>	248.3	250.2
5 C <sub>2</sub> H <sub>5</sub>	-(CH <sub>2</sub> ) <sub>4</sub> -		108-109	57	C <sub>16</sub> H <sub>20</sub> O <sub>3</sub>	248.3	247.0

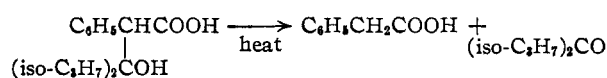
<sup>a</sup> Harold E. Zaugg (*THIS JOURNAL*, 72, 3001 (1950)) found 157-158°.

DeNet<sup>11</sup> to obtain  $\beta$ -alkyltropic acids which were converted into basic-alkyl esters.

The  $\beta$ -diethylaminoethyl esters (Tables III and IV) were obtained from the acids and  $\beta$ -diethylaminoethyl chloride by the Horenstein and Pählicke procedure.<sup>12</sup>

After  $\alpha$ -phenyl- $\beta$ , $\beta$ -diisopropyl- $\beta$ -hydroxypropionic acid had been heated with  $\beta$ -diethylaminoethyl chloride, an oily hydrochloride was obtained which would not crystallize. In the hope that the product could be converted into a crystalline methobromide, the hydrochloride was treated with sodium bicarbonate solution, and the liberated

base allowed to react with methyl bromide. A crystalline methobromide (m.p. 107°) was isolated but, by analysis and mixed melting point, this substance was shown to be identical with the methobromide which we synthesized from methyl bromide and  $\beta$ -diethylaminoethyl phenylacetate. It is evident, therefore, that the original hydroxy acid underwent a decomposition, which is characteristic of  $\beta$ -hydroxypropionic acids, during the esterification



(11) Arthur W. Weston and Robert W. DeNet, *THIS JOURNAL*, 73, 4221 (1951).

(12) H. Horenstein and H. Pählicke, *Ber.*, 71, 1644 (1938).

Some of the esters exhibited high antispasmodic activity when tested against acetylcholine-induced

TABLE III  
HYDROCHLORIDES OF  $\beta$ -DIETHYLAMINOETHYL ESTERS OF SUBSTITUTED  $\alpha$ -ARYL- $\beta$ -HYDROXYPROPIONIC ACIDS  
 $\text{RCHCOOCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2\cdot\text{HCl}$

$\text{R}'\text{R}''\text{COH}$

Compound 2 was recrystallized from ethyl acetate-ether; compounds 3, 4 and 7 from butanol-isopropyl ether; 5, 6, 8, 16 and 18 from acetone; 9 from ethanol-ether; 10 from ethyl acetate; 11 from isopropyl alcohol-isopropyl ether; 12, 20 and 21 from methyl ethyl ketone; 13, 15, 19 and 22 from isopropyl alcohol.

R	R'	R''	M.p., °C.	Yield, %	Formula	Analyses, %		Effective dilution against acetylcholine	
						Nitrogen Calcd. Found	Halogen Calcd. Found		
1 $\text{C}_6\text{H}_5$	H	H	<sup>a</sup>	..	.....	..	..	..	.....
2 $\text{C}_6\text{H}_5$	$\text{CH}_3$	H	127-128	77	$\text{C}_{16}\text{H}_{26}\text{O}_3\text{NCl}$	4.44 4.30	11.22 11.27	1:6,166,000	
3 $\text{C}_6\text{H}_5$	$\text{C}_2\text{H}_5$	H	107-108	81	$\text{C}_{17}\text{H}_{28}\text{O}_3\text{NCl}$	4.24 4.13	10.75 10.76	1:27,550,000	
4 $\text{C}_6\text{H}_5$	$(\text{CH}_3)_2\text{CH}$	H	117-121	94	$\text{C}_{18}\text{H}_{30}\text{O}_3\text{NCl}$	4.07 4.06	10.31 10.30	1:10,000,000	
5 $\text{C}_6\text{H}_5$	$(\text{CH}_3)_2\text{CH}$	H	162-163	..	$\text{C}_{19}\text{H}_{32}\text{O}_3\text{NBr}^b$	3.48 3.46	19.86 19.80	.....	
6 $\text{C}_6\text{H}_5$	$(\text{C}_2\text{H}_5)_2\text{CH}$	H	143-144	87	$\text{C}_{20}\text{H}_{34}\text{O}_3\text{NCl}$	3.77 3.72	9.53 9.54	1:4,336,000	
7 $\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$	H	129-133	82	$\text{C}_{21}\text{H}_{26}\text{O}_3\text{NCl}$	3.71 3.70	9.38 9.58	1:5,496,000	
8 $\text{C}_6\text{H}_5$	$\text{CH}_3$	$\text{CH}_3$	128-130 <sup>c</sup>	91	$\text{C}_{17}\text{H}_{28}\text{O}_3\text{NCl}$	4.25 4.18	10.75 10.86	1:21,880,000	
9 $\text{C}_6\text{H}_5$	$\text{CH}_3$	$\text{C}_2\text{H}_5$	96-98	79	$\text{C}_{18}\text{H}_{30}\text{O}_3\text{NCl}$	4.07 4.09	10.31 10.26	1:7,245,000	
10 $\text{C}_6\text{H}_5$	$\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5$	120-121 <sup>d</sup>	85	$\text{C}_{19}\text{H}_{32}\text{O}_3\text{NCl}$	3.91 3.88	9.91 9.94	.....	
11 $\text{C}_6\text{H}_5$	$-(\text{CH}_2)_4-$		133-135 <sup>e</sup>	89	$\text{C}_{19}\text{H}_{30}\text{O}_3\text{NCl}$	3.94 3.89	9.96 10.05	1:13,190,000	
12 $\text{C}_6\text{H}_5$	$-(\text{CH}_2)_5-$		137-138 <sup>f</sup>	77	$\text{C}_{20}\text{H}_{32}\text{O}_3\text{NCl}$	3.79 3.77	9.59 9.66	1:87,000,000	
13 $\text{C}_6\text{H}_5$	$-(\text{CH}_2)_5-$		192-193	79	$\text{C}_{21}\text{H}_{34}\text{O}_3\text{NBr}^b$	3.27 3.22	18.66 18.64	.....	
14 $\text{C}_6\text{H}_5$	$-\text{CH}_2\text{SCH}_2\text{CH}_2-$		Oil						
15 $\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_4$ $\begin{cases} \text{CH}_2- \\ \text{CH}_2- \end{cases}$		151-153	86	$\text{C}_{23}\text{H}_{30}\text{O}_3\text{NCl}$	3.47 3.46	8.78 8.71	1:1,289,000	
16 $\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$	139-141	39	$\text{C}_{27}\text{H}_{32}\text{O}_3\text{NCl}$	3.09 3.01	7.81 7.69	.....	
17 $2\text{-C}_4\text{H}_9\text{S}^g$	H	H	Oil						
18 $4\text{-C}_6\text{H}_5\text{-C}_6\text{H}_4$	H	H	108-109	89	$\text{C}_{21}\text{H}_{28}\text{O}_3\text{NCl}$	3.71 3.68	9.38 9.48	1:<1,000,000	
19 $4\text{-C}_6\text{H}_5\text{-C}_6\text{H}_5$	$-(\text{CH}_2)_5-$		168-170	85	$\text{C}_{26}\text{H}_{36}\text{O}_3\text{NCl}$	3.14 3.10	7.95 8.00	.....	
20 $2\text{-C}_4\text{H}_9\text{S}$	$-(\text{CH}_2)_4-$		102-104	88	$\text{C}_{17}\text{H}_{28}\text{O}_3\text{NCIS}$	3.87 3.90	9.80 9.71	1:17,000,000	
21 $2\text{-C}_4\text{H}_9\text{S}$	$-(\text{CH}_2)_5-$		123-125	80	$\text{C}_{18}\text{H}_{30}\text{O}_3\text{NCIS}$	3.73 3.66	9.43 9.53	1:27,000,000	
22 $3\text{-C}_4\text{H}_9\text{S}$	$-(\text{CH}_2)_5-$		143-145	87	$\text{C}_{18}\text{H}_{30}\text{O}_3\text{NCIS}$	3.73 3.69	9.43 9.55	1:22,390,000	

<sup>a</sup> Julius von Braun, Otto Braunsdorf and Kurt R  th (*Ber.*, 55, 1666 (1922)), as well as Robert R. Burtner and John W. Cusic (*THIS JOURNAL*, 65, 262 (1943)), obtained this compound as an oil. <sup>b</sup> Methobromide. <sup>c</sup> Reference 11, m.p. 1.25-126.5°. <sup>d</sup> Reference 11, m.p. 119-120°. <sup>e</sup> Reference 11, m.p. 135-136°. <sup>f</sup> Reference 11, m.p. 138-139°. <sup>g</sup> Thienyl.

TABLE IV  
HYDROCHLORIDES OF  $\beta$ -DIETHYLAMINOETHYL ESTERS OF  
SUBSTITUTED  $\alpha$ -PHENYL- $\beta$ -HYDROXYPROPIONIC ACIDS  
 $\text{C}_6\text{H}_5\text{C(R)COOCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2\cdot\text{HCl}$

$\text{CH}_2\text{OH}$

Compound 1 was recrystallized from isopropyl alcohol; 2 from isopropyl alcohol-ether; 3 from acetone-ether; 4 from acetone. The effective dilution of the above compounds against acetylcholine was in each instance less than 1:1,000,000. The hydrochloride of the  $\beta$ -diethylaminoethyl ester of  $\alpha$ -phenyl- $\alpha$ -(1-hydroxy-1-cyclopentyl)-butyric acid was obtained as an oil.

R	M.p., °C.	Formula	Analyses, %		Chlorine	
			Nitrogen Calcd. Found	Calcd. Found	Calcd. Found	Calcd. Found
1 $\text{C}_6\text{H}_5$	156-157 <sup>a</sup>	$\text{C}_{21}\text{H}_{28}\text{O}_3\text{NCl}$	3.71 3.77	9.38 9.35		
2 $\text{C}_6\text{H}_5\text{CH}_2$	130-131	$\text{C}_{22}\text{H}_{30}\text{O}_3\text{NCl}$	3.57 3.66	9.05 8.98		
3 $\text{C}_6\text{H}_5\text{O}$	115-116	$\text{C}_{21}\text{H}_{28}\text{O}_4\text{NCl}$	3.56 3.62	9.00 9.06		
4 $\text{C}_6\text{H}_{11}$	144-146	$\text{C}_{21}\text{H}_{34}\text{O}_3\text{NCl}$	3.65 3.73	9.24 9.21		

<sup>a</sup> Harold E. Zaugg (*THIS JOURNAL*, 72, 3001 (1950)) found 155-156°.

spasm in the isolated strip of intestine. The compounds were evaluated under the supervision of Dr. A. N. Lands in the Sterling-Winthrop Research Institute.

### Experimental Part

In reactions in which formaldehyde was used, it was introduced in the manner described previously.<sup>10</sup>

**$\alpha$ -Phenyl- $\beta$ -hydroxybutyric Acid.**—Magnesium (4.8 g., 0.2 mole) and enough absolute ether to cover the metal were placed in a dry, 500-cc., three-necked flask equipped with a

reflux condenser, stirrer and a dropping funnel, and 2 cc. of isopropyl chloride added. After the reaction began, 150 cc. of dry ether was added, followed by 15.8 g. (0.1 mole) of pulverized sodium phenylacetate which had been dried at 130° for several hours. The material was stirred vigorously, and 15.7 g. (0.2 mole) of isopropyl chloride, dissolved in 50 cc. of dry ether, was introduced, dropwise, at such a rate that the mixture refluxed. The mixture was stirred and refluxed for 5 hours. The flask was cooled in an ice-bath, the material stirred, and 9.7 g. (0.22 mole) of acetaldehyde, dissolved in 50 cc. of ether, was added, dropwise. After the mixture had been refluxed for 3 hours, it was cooled in an ice-bath and 25 cc. of water was added slowly from the dropping funnel, followed by the addition of 30 cc. of concd. hydrochloric acid which had been dissolved in 100 cc. of water. The mixture was stirred for one-half hour, the two layers separated, and the aqueous layer extracted with ether. The combined ether solutions were stirred thoroughly with 250 cc. of 10% sodium carbonate solution. The aqueous layer was acidified (congo red) with dilute hydrochloric acid, the brown, oily precipitate extracted with ether, and the extracts dried with magnesium sulfate. The ether was removed by the use of a bath which was not heated higher than 55°. The solidified residue was washed with petroleum ether (60-75°); yield 9.9 g. (55%); m.p. 135-136°<sup>13</sup> after recrystallization from carbon tetrachloride.

**Phenyl-(1-hydrindylidene)-acetic or Phenyl-(3-indenyl)-acetic Acid and the  $\beta$ -Diethylaminoethyl Ester.**—1-Hydrindone (30.3 g.) was added, dropwise, to the Ivanov reagent which has been described above. After hydrolysis of the reaction mixture, 16.6 g. (62%) of the acid was obtained; m.p. 153-154.5° after recrystallization from methanol. The acid decolorized a bromine as well as a permanganate solution instantly. Calcd. for  $\text{C}_{17}\text{H}_{14}\text{O}_2$ : neut. equiv., 250.3. Found: neut. equiv., 251.0.

(13) Otto Hromatka (*Ber.*, 75, 814 (1942)) found 136°.

The  $\beta$ -diethylaminoethyl ester hydrochloride (86% yield) was recrystallized from acetone; m.p. 164–166°.

*Anal.* Calcd. for  $C_{22}H_{28}O_2NCl$ : N, 3.63; Cl, 9.19. Found: N, 3.63; Cl, 9.16.

**$\alpha$ -Phenyl- $\gamma$ -hydroxybutyric Acid and the  $\beta$ -Diethylaminoethyl Ester.**—After the preparation of the Ivanov reagent in the described manner, the mixture was cooled to about 10°, stirred, and a chilled, ethereal solution of 44 g. (1 mole) of ethylene oxide added. Dry benzene was then added through the dropping funnel while the ether was removed by distillation. This process was continued until the temperature of the mixture reached 65°. The mixture was refluxed for 5 hours, cooled to 5°, and hydrolyzed with dilute hydrochloric acid. The organic layer was separated and extracted with 10% sodium carbonate solution. Upon acidification of the alkaline layer at 5° with dil. hydrochloric acid, an oil precipitated which solidified after it had been kept at 0° for some time; yield 11.5 g. (64%); m.p. 100–101°<sup>14</sup> after recrystallization from isopropyl alcohol–petroleum ether.

The  $\beta$ -diethylaminoethyl ester hydrochloride (76% yield) was recrystallized from acetone–xylene; m.p. 94–96°.

*Anal.* Calcd. for  $C_{16}H_{24}O_2NCl$ : N, 4.44; Cl, 11.23. Found: N, 4.36; Cl, 11.29.

**2,2-Diphenyl-1,3-propanediol (a) From  $\alpha,\alpha$ -Diphenyl- $\beta$ -hydroxypropionic Acid.**—The propionic acid (26.2 g.) was

(14) P. Carré and D. Libermann (*Bull. soc. chim.*, [4] **53**, 264 (1933)) found 99–100°.

placed in the thimble of a modified<sup>15</sup> soxhlet apparatus connected to a 1-liter flask which contained 8.2 g. of lithium aluminum hydride and 600 cc. of dry ether. The mixture was refluxed until the acid had dissolved, cooled in an ice-bath, stirred and 50 cc. of water added, dropwise, followed by a mixture of 80 cc. of concd. hydrochloric acid and 100 cc. of water. The ether layer was extracted with sodium carbonate solution, dried over magnesium sulfate, and the solvent removed. The crystalline residue (23.7 g., 96%) was recrystallized from isopropyl alcohol–petroleum ether; m.p. 106–107°.<sup>16</sup>

(b) **From Diethyl Diphenylmalonate.**—Lithium aluminum hydride (1.7 g.) and 100 cc. of ether were placed in a flask equipped with a stirrer, dropping funnel and a reflux condenser. The mixture was stirred and 9.4 g. of the malonate in 20 cc. of ether was added slowly. The mixture was refluxed for 3 hours, and then treated in the manner described above; crude yield 6.6 g. (97%); m.p. 106–107°; mixed m.p. 106–107°.

*Anal.* Calcd. for  $C_{15}H_{16}O_2$ : C, 78.92; H, 7.07. Found: C, 78.78; H, 6.99.

(15) Modified in such a manner that it was not necessary for the thimble to become full before the dissolved acid could flow into the reaction flask.

(16) Dieter G. Markees and Alfred Burger (*THIS JOURNAL*, **71**, 2031 (1949)) found 102–104°.

ANN ARBOR, MICHIGAN

RECEIVED SEPTEMBER 26, 1951

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

## Antispasmodics. X. 1,3-Dioxolanes and 1,3-Dioxanes

By F. F. BLICKE AND FLOYD E. ANDERSON<sup>1,2</sup>

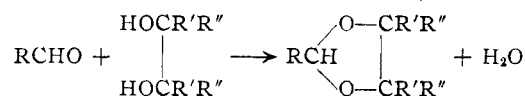
The preparation of a number of substituted 1,3-dioxolanes and 1,3-dioxanes has been described. The 1,3-dioxolanes, in which the substituents are basic-alkyl groups, exhibit antispasmodic and antihistaminic activity.

Since paraldehyde is an excellent hypnotic, it was decided to prepare a number of substances which would be analogous in their basic structure to the aldehyde, namely, 1,3-dioxolanes and 1,3-dioxanes. It had been shown by Knoefel<sup>3</sup> that certain alkyl derivatives of these parent compounds do exhibit hypnotic activity. However, except for 4,6,6-trimethyl-1,3-dioxane which was found to be active when administered orally to rats, all of the compounds reported in Tables I and II, which were prepared and tested for hypnotic activity<sup>4</sup> during this investigation, proved to be inactive or only slightly active.

Twelve basic dioxolanes (Table III) were then prepared. A typical example of this group, 2,2-diphenyl-4-dimethylaminomethyl-1,3-dioxolane, was found to be devoid of hypnotic activity but, in a detailed pharmacological study of this substance and other members of the group by Brown and Werner,<sup>5</sup> it was found that some of these compounds are potent spasmolytic agents; they also exhibit antihistaminic activity.

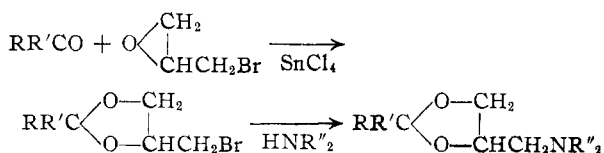
1,3-Dioxolanes were prepared from an aldehyde and a 1,2-glycol in the presence of 85% orthophos-

phoric acid. R, R' and R'' = hydrogen or alkyl,



and may be alike or different.

In order to obtain basic 1,3-dioxolanes, a ketone was allowed to react with epibromohydrin,<sup>6</sup> in the presence of stannic chloride, and the bromomethyl-1,3-dioxolane obtained was then aminated



Benzophenone and epibromohydrin condensed in the presence of stannic chloride to form the crystalline 2,2-diphenyl-4-bromomethyl-1,3-dioxolane. However, when other ketones such as 2,2-di-(*p*-methoxyphenyl) ketone, di-(2-thienyl) ketone and fluorenone were substituted for benzophenone, the dioxolane could neither be obtained in crystalline form nor could it be distilled without decomposition; in these instances the crude product was aminated.

Phenyl 2-thienyl ketone reacted with epibromohydrin and stannic chloride to yield an oily dioxolane which could be distilled. When cooled, the

(1) This paper represents part of a dissertation submitted by Floyd E. Anderson in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan.

(2) The Wm. S. Merrell Company Fellow.

(3) P. K. Knoefel, *J. Pharmacol. Exp. Therap.*, **50**, 88 (1934); *ibid.*, **53**, 440 (1935).

(4) Tested in the Wm. S. Merrell Company laboratories under the supervision of Dr. Harold W. Werner.

(5) Barbara B. Brown and Harold W. Werner, *J. Pharmacol. Exp. Therap.*, **97**, 157 (1949).

(6) When an attempt was made to aminate the corresponding chloromethyl compound (G. Willfang, *Ber.*, **74**, 145 (1945)) by the use of diethylamine, the chloromethyl compound was recovered unchanged.