

hydrolyzed without recrystallization by heating for four hours on the steam-bath in the presence of 500 ml. of 5% aqueous hydrochloric acid. In the case of compounds containing two nitrophenyl groups which were consequently quite insoluble in water, aqueous ethanol was used as the solvent. When the hydrolysis was complete, the reaction mixture was chilled and extracted once with ether and once with ethyl acetate. The aqueous residue containing the amine hydrochloride was evaporated at reduced pressure. The crystalline salt was then dissolved in 100 ml. of water and the free base liberated with ammonia. After standing overnight in the refrigerator a yield of 9.6 g. of base was isolated by filtration, the product melting at 137–140°. A

sample recrystallized for analysis from water melted at 144–145°

**Dichloroacetamides of *p*-Nitrophenyl Amino Alcohols.**—Dichloroacetamides of all bases were prepared by the method described recently for the preparation of  $\alpha,\alpha$ -dihaloacetamides of *dl*-threo-*p*-nitrophenyl-2-amino-1,3-propanediol.<sup>15</sup> In bases where the benzyl hydroxyl group had been replaced by hydrogen it was necessary to reflux for at least two hours for the reaction to go to completion.

(15) Rebstock, *THIS JOURNAL*, **72**, 4800 (1950).

DETROIT, MICH.

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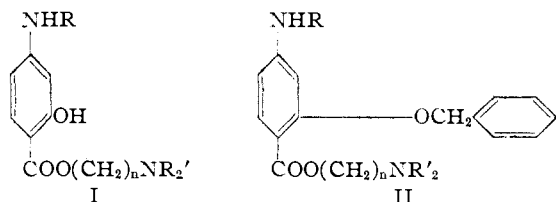
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## Derivatives of 4-Amino-2-hydroxybenzoic Acid. I

BY R. O. CLINTON, S. C. LASKOWSKI, U. J. SALVADOR AND MARY WILSON

There is described the preparation of several series of new local anesthetics derived from the 4-aminosalicylic acid (PAS) nucleus. The majority of these compounds are very active, both topically and by infiltration procedures.

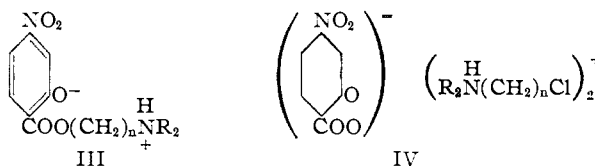
As part of a continuing investigation of new local anesthetics in these laboratories we have prepared several series of compounds derived from the 4-amino-2-hydroxybenzoic acid nucleus. The present communication describes a number of dialkylaminoalkyl 4-amino- and 4-alkylamino-2-hydroxybenzoates, I, and dialkylaminoalkyl 4-amino- and 4-alkylamino-2-benzyloxybenzoates, II.



Although no compounds of the type presently discussed have appeared in the literature,<sup>1</sup> a few dialkylaminoalkyl salicylates have been described by McElvain.<sup>2</sup> The latter compounds did not show outstanding anesthetic properties. It would be expected, by analogy with other series, that the inclusion of a 4-amino group in this type of compound would greatly increase the local anesthetic activity, but no conclusions as to toxicity or irritation would be warranted.

Considerable experimental work was carried out in the determination of a suitable procedure for the preparation of the intermediate  $\omega$ -dialkylaminoalkyl 2-hydroxy-4-nitrobenzoates. The direct Fischer esterification of 2-hydroxy-4-nitrobenzoic acid by means of a dialkylaminoalkanol and dry hydrogen chloride gave very poor results, as did the preparation of the basic esters *via* an intermediate  $\omega$ -haloalkyl 2-hydroxy-4-nitrobenzoate. Transesterification between a dialkylaminoalkanol and an alkyl 2-hydroxy-4-nitrobenzoate gave fair yields with dialkylaminopropanols and poor yields with dialkylaminoethanols. The Hörenstein-Pählicke<sup>3</sup> reac-

tion between 2-hydroxy-4-nitrobenzoic acid and a dialkylaminoalkyl chloride gave poor to excellent yields of the dialkylaminoalkyl 2-hydroxy-4-nitrobenzoate hydrochlorides, the best results being obtained from 2-dialkylaminoethyl chlorides. The products were somewhat difficult to purify, due to the properties inherent in the dialkylaminoalkyl 2-hydroxy-4-nitrobenzoate bases. Because of the high "acidity" of the free phenolic group, it is probable that the bases exist in the form of the salts indicated by III. The bases are highly colored, high melting, and water soluble, although their solubility in non-polar solvents is very slight. Judging from



the experimental results, it seems likely that the "acidity" of the phenolic group could also interfere with the course of the Hörenstein-Pählicke reaction through the formation of semi-stable intermediates of the type shown in IV, although no evidence was obtained that alkylation of the phenolic group occurred to an appreciable extent.<sup>4</sup>

Because of the difficulties encountered in the above procedures, attention was turned to the utilization of a "blocked" 2-hydroxy-4-nitrobenzoic acid. Since it had been found in preliminary work that the catalytic reduction of an alkyl 2-acetoxy-4-nitrobenzoate in alcohol gave as sole product the alkyl 4-amino-2-hydroxybenzoate, due to acetyl group transference to the solvent, this route offered a possible source of the desired products. The Hörenstein-Pählicke reaction between 2-acetoxy-4-nitrobenzoic acid and a dialkylaminoalkyl chloride in isopropyl alcohol solution gave a mixture of compounds, the major product proving to be the

(1) Since the completion of this manuscript Drain, *et al.*, *J. Pharm. Pharmacol.*, **1**, 784 (1949), have indicated their preparation of 2-diethylaminoethyl 4-amino-2-hydroxybenzoate. No experimental data or properties were recorded.

(2) McElvain and Caruey, *THIS JOURNAL*, **68**, 2595 (1946).

(3) Hörenstein and Pählicke, *Ber.*, **71**, 1644 (1938).

(4) In the case of the related compound, 2-hydroxy-4-nitrobenzotrinitrile, phenolic alkylation does occur under the conditions of the Hörenstein-Pählicke reaction. Further, experiments in other series (unpublished) have indicated that phenolic alkylation can also be made to take place with the alkyl 2-hydroxy-4-nitrobenzoates.

TABLE I

DIALKYLAMINOALKYL 2-HYDROXY-4-NITROBENZOATE HYDROCHLORIDES

n	R <sub>2</sub>	M.p., °C.	Formula	Analyses, %			
				N, <sup>a</sup> calcd.	N, <sup>a</sup> found	Cl, calcd.	Cl, found
2	(CH <sub>3</sub> ) <sub>2</sub>	174.0-175.0	C <sub>11</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>5</sub>	4.82	5.08	12.20	11.92
2	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> <sup>b</sup>	179.6-180.4	C <sub>13</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>5</sub>	4.39	4.37	11.12	11.12
2	C <sub>5</sub> H <sub>10</sub> <sup>c</sup>	183.8-184.8	C <sub>14</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>5</sub>	4.23	4.24	10.72	10.65
2	C <sub>6</sub> H <sub>12</sub> <sup>d,e</sup>	181.5-182.2	C <sub>15</sub> H <sub>21</sub> N <sub>2</sub> O <sub>5</sub>	8.13 <sup>f</sup>	8.33 <sup>f</sup>	10.28	10.23
2	C <sub>7</sub> H <sub>14</sub> <sup>g</sup>	181.5-182.1	C <sub>16</sub> H <sub>23</sub> ClN <sub>2</sub> O <sub>5</sub>	3.90	3.94	9.88	9.64
2	C <sub>4</sub> H <sub>8</sub> O <sup>h</sup>	195.2-197.6	C <sub>13</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>5</sub>	8.42 <sup>f</sup>	8.59 <sup>f</sup>	10.65	10.78
3	C <sub>5</sub> H <sub>10</sub> <sup>c,i</sup>	183.0-184.0	C <sub>15</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>5</sub>	4.07	4.04	10.28	10.26
3	C <sub>6</sub> H <sub>12</sub> <sup>d</sup>	173.0-173.8	C <sub>16</sub> H <sub>23</sub> ClN <sub>2</sub> O <sub>5</sub>	7.80 <sup>f</sup>	8.09 <sup>f</sup>	9.88	9.79
3	C <sub>4</sub> H <sub>8</sub> O <sup>h</sup>	210.0-210.6	C <sub>14</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>5</sub>	4.04	3.97	10.22	10.22

<sup>a</sup> See ref. 11. <sup>b</sup> Calcd.: C, 48.98; H, 6.01. Found: C, 48.97; H, 5.88. <sup>c</sup> 1-Piperidyl. <sup>d</sup> 2-Methyl-1-piperidyl. <sup>e</sup> Calcd.: C, 52.25; H, 6.14. Found: C, 52.35; H, 6.07. <sup>f</sup> Total nitrogen (Dumas). <sup>g</sup> 2,6-Dimethyl-1-piperidyl. <sup>h</sup> 4-Morpholinyl. <sup>i</sup> Calcd.: C, 52.25; H, 6.14. Found: C, 52.16; H, 6.17.

TABLE II

DIALKYLAMINOALKYL 2-BENZYLOXY-4-NITROBENZOATES

n	R <sub>2</sub>	M.p., °C.	Formula	Hydrochloride				Picrate				
				Nitrogen, %		Chlorine, %		M.p., °C.	Nitrogen, % <sup>b</sup>		Nitrogen, % <sup>a</sup>	
				Calcd.	Found	Calcd.	Found			Calcd.	Found	Calcd.
2	(CH <sub>3</sub> ) <sub>2</sub> <sup>c,d</sup>	180.2-181.3	C <sub>18</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>5</sub>	3.68	3.80	9.31	9.13	182.0-183.6	2.44	2.47	9.76	9.75
3	(CH <sub>3</sub> ) <sub>2</sub> <sup>e</sup>	163.6-164.1	C <sub>19</sub> H <sub>23</sub> ClN <sub>2</sub> O <sub>5</sub>	3.55	3.58	8.98	8.86	210.6-211.7	2.38	2.43	9.52	9.20
<sup>f</sup>	(CH <sub>2</sub> ) <sub>2</sub>	158.2-159.4	C <sub>19</sub> H <sub>23</sub> ClN <sub>2</sub> O <sub>5</sub>	3.55	3.53	8.98	8.84	205.0-206.0	2.38	2.45	9.52	9.10
2	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	181.0-181.8	C <sub>20</sub> H <sub>25</sub> ClN <sub>2</sub> O <sub>5</sub>	..	..	8.67	8.63	139.0-140.0	2.33	2.44	9.32	9.06
3	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	133.9-134.7	C <sub>21</sub> H <sub>27</sub> ClN <sub>2</sub> O <sub>5</sub>	3.31	3.33	8.38	8.25	140.8-141.6	2.28	2.33	9.12	8.85
3	C <sub>5</sub> H <sub>10</sub> <sup>g,h,i</sup>	161.4-162.5	C <sub>22</sub> H <sub>27</sub> ClN <sub>2</sub> O <sub>5</sub>	3.22	3.28	8.15	7.95	182.6-183.4	2.23	2.28	8.92	8.85
2	C <sub>6</sub> H <sub>12</sub> <sup>j</sup>	184.4-185.0	C <sub>22</sub> H <sub>27</sub> ClN <sub>2</sub> O <sub>5</sub>	..	..	8.15	8.29	129.3-131.1	2.23	2.38	8.92	8.67

<sup>a</sup> See ref. 11. <sup>b</sup> See ref. 12. <sup>c</sup> The crystalline base had m.p. 60.0-60.7°. Calcd.: N, <sup>12</sup> 4.07. Found: N, <sup>12</sup> 3.96. <sup>d</sup> The hemiflavianate had m.p. 145° (liquefies) -185°. Calcd.: S, 3.20. Found: S, 3.12. <sup>e</sup> The crystalline base had m.p. 57.8-59.0°. Calcd.: N, <sup>12</sup> 3.91. Found: N, <sup>12</sup> 3.89. <sup>f</sup> 3-Dimethylamino-2-propyl. <sup>g</sup> 1-Piperidyl. <sup>h</sup> The crystalline base had m.p. 77.7-78.6°. Calcd.: N, <sup>12</sup> 3.52; N, <sup>11</sup> 3.52. Found: N, <sup>12</sup> 3.52; N, <sup>11</sup> 3.42. <sup>i</sup> The hemiflavianate had m.p. 110.0 (liquefies) but not clear at 150°. Calcd.: S, 2.89. Found: S, 2.85. <sup>j</sup> 2-Methyl-1-piperidyl.

dialkylaminoalkyl 2-acetoxy-4-nitrobenzoate. Since, however, the dialkylaminoalkyl 2-acetoxy-4-nitrobenzoates could be isolated only in relatively poor yields, it was apparent that acetyl group transference to the solvent had occurred during the course of this reaction.

A suitable "blocking" agent was found in the labile benzyl group. 2-Benzyloxy-4-nitrobenzoic acid proved quite suitable for the Hörenstein-Pählicke reaction, and high yields of easily purified products could be readily obtained. Further, it was found possible to prepare 2-benzyloxy-4-nitrobenzoyl chloride in excellent yield under mild conditions, thus making possible the direct preparation of the esters from a dialkylaminoalkanol.

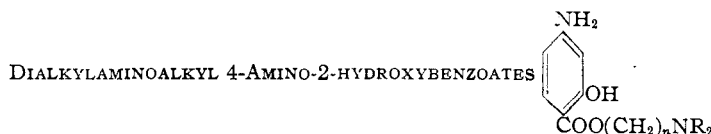
The dialkylaminoalkyl 2-hydroxy-4-nitrobenzoate hydrochlorides, prepared by the above procedures, are listed in Table I. In Table II are listed the dialkylaminoalkyl 2-benzyloxy-4-nitrobenzoate hydrochlorides and picrates. The latter derivatives proved more suitable than the flavianates, since only hemiflavianates were formed with these compounds, and these did not possess a sharp melting point.

The dialkylaminoalkyl 2-hydroxy-4-nitrobenzoate hydrochlorides were readily reduced to the corresponding 4-amino compounds either by catalytic reduction with platinum oxide or by a modified iron-hydrochloric acid procedure. The same compounds were obtained by the direct catalytic reduction of the dialkylaminoalkyl 2-benzyloxy-4-nitrobenzoates using a palladium-charcoal catalyst (four moles uptake of hydrogen), while iron-hydrochloric acid reduction gave the dialkylaminoalkyl 4-amino-2-benzyloxybenzoates in high yields. These compounds are listed in Tables III and IV.

The catalytic reduction of a dialkylaminoalkyl 2-acetoxy-4-nitrobenzoate hydrochloride with platinum oxide in alcoholic solution gave the expected deacetylated product, although the yield of the purified dialkylaminoalkyl 4-amino-2-hydroxybenzoate was only 60-70%. The direct transesterification of, e. g., methyl 4-amino-2-hydroxybenzoate with a dialkylaminoalkanol gave little or no product.

The dialkylaminoalkyl 4-alkylamino-2-hydroxybenzoates were prepared by several routes. The reductive alkylation of a dialkylaminoalkyl 4-am-

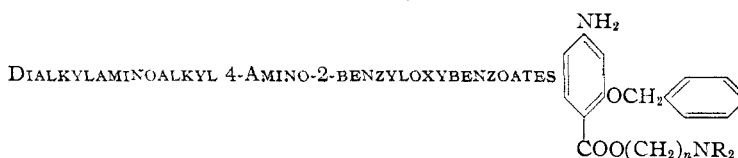
TABLE III



n	R <sub>2</sub>	M.p., °C.	Base Formula	Nitrogen, %		M.p., °C.	Phosphate H <sub>3</sub> PO <sub>4</sub> , %		Nitrogen, %		M.p., °C.	Flavianate Sulfur, %	
				Calcd.	Found		Calcd.	Found	Calcd.	Found		Calcd.	Found
2	(CH <sub>3</sub> ) <sub>2</sub>	136.1-137.2	C <sub>11</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	6.25 <sup>a</sup>	6.36 <sup>a</sup>	219.7-220.0 <sup>b,c</sup>	30.42	30.60	8.69	8.63	230.8-231.3 <sup>b</sup>	5.95	5.86
2	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Cil	C <sub>13</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	.....	.....	.....	d	d	d	d	207.5-209.2	5.66	5.74
2	C <sub>6</sub> H <sub>10</sub> <sup>e</sup>	79.0-80.6	C <sub>14</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	10.60 <sup>f</sup>	10.97	223.5-223.8 <sup>b</sup>	27.06	27.14	7.73	7.86	229.0-229.9 <sup>b</sup>	5.54	5.53
2	C <sub>6</sub> H <sub>12</sub> <sup>g</sup>	60.0-62.0	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub>	10.07	10.18	203.5-204.0	26.05	26.22	7.44	7.20	199.8-201.2	5.41	5.38
2	C <sub>6</sub> H <sub>14</sub> <sup>h</sup>	111.0-111.6	C <sub>16</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub>	9.58	9.44	197.7-200.0	25.11	25.35	7.18	7.00	224.5-225.5	5.29	5.35
2	C <sub>6</sub> H <sub>16</sub> <sup>i</sup>	64.2-65.6 <sup>j</sup>	C <sub>17</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub>	5.27 <sup>a</sup>	5.25 <sup>a</sup>	200.7-201.2	26.91	27.17	7.69	7.90	.....	5.52	5.52
3	(CH <sub>3</sub> ) <sub>2</sub>	Oil	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	.....	.....	209.6-210.7 <sup>b</sup>	29.15	29.22	8.33	8.08	227.0-227.7 <sup>b</sup>	5.80	5.74
3	(CH <sub>3</sub> ) <sub>2</sub>	Oil	C <sub>12</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	.....	.....	203.2-204.2 <sup>b</sup>	29.15	29.45	8.33	8.12	199.0-199.3 <sup>b</sup>	5.80	5.91
3	C <sub>6</sub> H <sub>10</sub> <sup>e</sup>	57.5-58.5	C <sub>13</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub>	5.04 <sup>a</sup>	5.08 <sup>a</sup>	204.7-205.0 <sup>b,m</sup>	26.05	26.00	7.44	7.29	230.0-230.5 <sup>b</sup>	5.41	5.34
3	C <sub>6</sub> H <sub>12</sub> <sup>g</sup>	Oil	C <sub>14</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub>	.....	.....	201.0-201.5	25.11	25.00	7.18	7.08	.....	.....	.....
3	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	Oil	C <sub>14</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub>	.....	.....	212.3 <sup>b</sup>	26.91	26.88	7.69	7.61	209.9-210.3	5.52	5.38
3	C <sub>6</sub> H <sub>10</sub> <sup>i</sup>	146.4-147.2	C <sub>14</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	10.00	10.09	185.2-186.7	25.91	25.89	7.41	7.41	219.0-220.0 <sup>b</sup>	5.39	5.42

<sup>a</sup> Primary aromatic amino nitrogen, by titration with nitrous acid. <sup>b</sup> With decomposition. <sup>c</sup> The monohydrochloride melted at 225.0-225.5°. Calcd. for C<sub>11</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>3</sub>: N, 10.75; Cl, 13.60. Found: N, 10.80; Cl, 13.60. <sup>d</sup> The monohydrochloride melted at 154.0-154.8°. Calcd. for C<sub>13</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>3</sub>: C, 54.07; H, 7.33; N, 9.70. Found: C, 53.80; H, 7.42; N, 9.65. <sup>e</sup> 1-Piperidyl. <sup>f</sup> Calcd.: C, 64.61; H, 7.63. Found: C, 63.34; H, 7.69. <sup>g</sup> 2-Methyl-1-piperidyl. <sup>h</sup> 2,6-Dimethyl-1-piperidyl. <sup>i</sup> 4-Morpholinyl. <sup>j</sup> The base crystallized from dilute alcohol as a hydrate, m.p. 87-90°. <sup>k</sup> Blackens from 270°, not melted at 300°. <sup>l</sup> 3-Dimethylamino-2-propyl. <sup>m</sup> The monohydrochloride melted at 239.5-240.2°. Calcd. for C<sub>14</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>3</sub>: N, 8.90; Cl, 11.26. Found: N, 8.99; Cl, 10.98. <sup>n</sup> The monopicrate melted at 146.3-148.2°. Calcd. for C<sub>22</sub>H<sub>27</sub>N<sub>5</sub>O<sub>10</sub>: N, 12.53. Found: N, 12.53.

TABLE IV



n	R <sub>2</sub>	Type <sup>a</sup>	M.p., °C.	Formula	Salt		Nitrogen, %		Type <sup>b</sup>	M.p., °C.	Derivative Sulfur, %		
					Calcd.	Found	Calcd.	Found			Calcd.	Found	
2	(CH <sub>3</sub> ) <sub>2</sub>	B	84.5-86.0	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub>	N, <sup>c</sup>	4.46	4.46	8.91	8.89	F	173.7-176.2	5.10	4.95
2	(CH <sub>3</sub> ) <sub>2</sub>	P	135.5-137.5	C <sub>18</sub> H <sub>25</sub> N <sub>2</sub> O <sub>7</sub> P	H <sub>3</sub> PO <sub>4</sub> ,	23.77	23.89	6.79	6.60	.....	.....	.....	.....
2	(CH <sub>3</sub> ) <sub>2</sub>	DH	169.6 <sup>d</sup>	C <sub>18</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	Cl,	18.31	18.02	.....	.....	.....	.....	.....	.....
3	(CH <sub>3</sub> ) <sub>2</sub>	B	76.0-77.0	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub>	.....	.....	.....	8.53	8.47	F	181.0-182.5 <sup>m</sup>	4.99	4.96
3	(CH <sub>3</sub> ) <sub>2</sub>	P	150.0-154.0	C <sub>19</sub> H <sub>27</sub> N <sub>2</sub> O <sub>7</sub> P	H <sub>3</sub> PO <sub>4</sub> ,	22.99	23.12	6.57	6.35	.....	.....	.....	.....
3	(CH <sub>3</sub> ) <sub>2</sub>	B	103.0-103.8	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub>	.....	.....	.....	8.53	8.47	DF	199.0-199.5 <sup>d</sup>	6.70	6.70
3	(CH <sub>3</sub> ) <sub>2</sub>	P	151.0-155.0	C <sub>19</sub> H <sub>27</sub> N <sub>2</sub> O <sub>7</sub> P	H <sub>3</sub> PO <sub>4</sub> ,	22.99	23.22	6.57	6.54	.....	.....	.....	.....
2	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	B	86.2-87.6	C <sub>20</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub>	.....	.....	.....	8.18	8.23	DF	191.6-194.0 <sup>d</sup>	6.59	6.47
2	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	H	125.4-126.2	C <sub>20</sub> H <sub>27</sub> ClN <sub>2</sub> O <sub>3</sub>	Cl,	9.36	9.13	7.39	7.25	.....	.....	.....	.....
3	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	B	85.4-86.4	C <sub>21</sub> H <sub>28</sub> N <sub>2</sub> O <sub>3</sub>	.....	.....	.....	7.86	7.89	F	157.7-159.6 <sup>i</sup>	4.78	4.70
3	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	DH	166.5-167.5	C <sub>21</sub> H <sub>30</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	Cl,	16.51	16.38	.....	.....	.....	.....	.....	.....
3	C <sub>6</sub> H <sub>10</sub> <sup>i</sup>	B	103.0-104.0	C <sub>22</sub> H <sub>28</sub> N <sub>2</sub> O <sub>3</sub>	N, <sup>c</sup>	3.80	3.90	7.60	7.50	F	192.0-192.5 <sup>n</sup>	4.70	4.70
3	C <sub>6</sub> H <sub>10</sub> <sup>i</sup>	P	117.0-121.0	C <sub>22</sub> H <sub>31</sub> N <sub>2</sub> O <sub>7</sub> P	H <sub>3</sub> PO <sub>4</sub> ,	21.02	21.22	6.01	5.85	.....	.....	.....	.....
2	C <sub>6</sub> H <sub>12</sub> <sup>j</sup>	B	97.8-99.2	C <sub>22</sub> H <sub>28</sub> N <sub>2</sub> O <sub>3</sub>	.....	.....	.....	7.60	7.90	DF	196.6-197.0 <sup>d</sup>	6.43	6.44

<sup>a</sup> B = base, P = phosphate, H = monohydrochloride, DH = dihydrochloride. <sup>b</sup> F = flavianate, DF = diflavianate. <sup>c</sup> Aromatic primary amine, by titration with nitrous acid. <sup>d</sup> With decomposition. <sup>e</sup> Calcd.: C, 55.82; H, 6.25. Found: C, 55.93; H, 6.06. <sup>f</sup> 3-Dimethylamino-2-propyl. <sup>g</sup> Calcd.: C, 70.75; H, 7.86. Found: C, 70.80; H, 7.96. <sup>h</sup> Calcd.: C, 58.74; H, 7.04. Found: C, 58.45; H, 7.39. <sup>i</sup> 1-Piperidyl. <sup>j</sup> 2-Methyl-1-piperidyl. <sup>k</sup> Calcd.: C, 71.71; H, 7.66. Found: C, 71.87; H, 7.90. <sup>l</sup> Calcd.: C, 55.51; H, 5.11. Found: C, 55.52; H, 4.90. <sup>m</sup> Calcd.: C, 54.19; H, 4.71. Found: C, 54.14; H, 4.82. <sup>n</sup> Calcd.: C, 56.29; H, 5.02. Found: C, 56.18; H, 4.92.

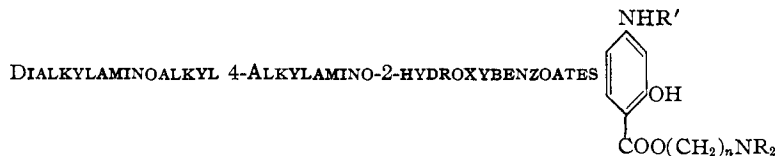
ino-2-hydroxybenzoate by means of an aldehyde, zinc dust and acetic acid, or by catalytic reductive alkylation by means of an aldehyde using platinum oxide catalyst, gave satisfactory yields of products. A somewhat more attractive procedure, from a purification viewpoint, was the reductive alkylation of a dialkylaminoalkyl 4-amino-2-benzyloxybenzoate by means of an aldehyde, zinc dust and acetic acid, followed by catalytic debenzoylation with hydrogen and palladium-charcoal. The routes via a 2-hydroxy compound were complicated by the tendency of the phenolic group to complex with metals, and

by the instability of the *m*-aminophenol grouping toward air oxidation in the presence of a base. The direct reaction of a 4-alkylamino-2-benzyloxybenzoyl chloride hydrochloride with a dialkylaminoalkanol gave poor yields, and the products were quite difficult to purify.

The dialkylaminoalkyl 4-alkylamino-2-hydroxybenzoates prepared in the present work are listed in Table V, and the intermediate dialkylaminoalkyl 4-alkylamino-2-benzyloxybenzoates (characterized as the flavianates) are listed in Table VI.

In order to extend the pharmacological investiga-

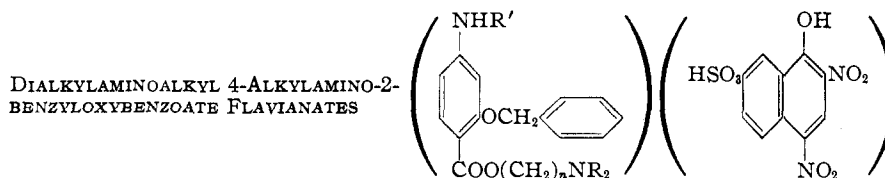
TABLE V



n	R <sub>2</sub>	R' <sup>b</sup>	Type <sup>a</sup>	M.p., °C.	Formula	Carbon, %		Base or salt Hydrogen, %		Nitrogen, %		M.p., °C.	Flavianate Sulfur, %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found		Calcd.	Found
2	(CH <sub>3</sub> ) <sub>2</sub>	C <sub>3</sub> H <sub>7</sub>	B	Oil	C <sub>14</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub>	63.13	63.17	8.33	8.24	10.52	10.36	192.4-193.2	5.52	5.56
2	(CH <sub>3</sub> ) <sub>2</sub>	C <sub>4</sub> H <sub>9</sub>	B	Oil	C <sub>15</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub>	64.26	64.28	8.63	8.57	9.99	9.86	174.0-177.8	5.39	5.40
2	(CH <sub>3</sub> ) <sub>2</sub>	C <sub>5</sub> H <sub>11</sub>	B	Oil	C <sub>16</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub>	65.27	65.31	8.90	8.93	9.52	9.37	183.1-184.0 <sup>c</sup>	5.27	5.32
2	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	C <sub>4</sub> H <sub>9</sub>	DH	162.0-166.0	C <sub>17</sub> H <sub>26</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	53.54	53.54	7.93	7.71	18.59 <sup>d</sup>	18.70 <sup>d</sup>	186.0-187.5 <sup>e</sup>	5.15	5.12
2	C <sub>6</sub> H <sub>10</sub> <sup>f</sup>	C <sub>4</sub> H <sub>9</sub>	DH	171.7 <sup>c</sup>	C <sub>18</sub> H <sub>30</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	54.96	54.83	7.69	7.89	18.03 <sup>d</sup>	17.89 <sup>d</sup>	214.7-215.0 <sup>e</sup>	5.05	5.10
2	C <sub>8</sub> H <sub>12</sub> <sup>g</sup>	C <sub>4</sub> H <sub>9</sub>	B	Oil	C <sub>19</sub> H <sub>30</sub> N <sub>2</sub> O <sub>3</sub>	68.23	67.99	9.04	8.93	8.38	8.17	185.6-186.8 <sup>g</sup>	4.94	5.02
2	C <sub>8</sub> H <sub>14</sub> <sup>h</sup>	C <sub>4</sub> H <sub>9</sub>	B	62.8-64.0	C <sub>20</sub> H <sub>32</sub> N <sub>2</sub> O <sub>3</sub>	68.93	69.20	9.26	9.32	8.04	8.23	168.0-170.0 <sup>g</sup>	4.84	4.88
2	C <sub>8</sub> H <sub>16</sub> <sup>k</sup>	C <sub>4</sub> H <sub>9</sub>	B	Oil	C <sub>17</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	63.33	63.60	8.13	8.33	8.69	8.73	226.6-228.4 <sup>c</sup>	5.04	5.10
3	(CH <sub>3</sub> ) <sub>2</sub>	C <sub>3</sub> H <sub>7</sub>	B	Oil	C <sub>18</sub> H <sub>28</sub> N <sub>2</sub> O <sub>3</sub>	65.27	65.15	8.90	8.95	9.52	9.50	179.7-180.8 <sup>g</sup>	6.95	6.95
3	(CH <sub>3</sub> ) <sub>2</sub>	C <sub>4</sub> H <sub>9</sub>	B	67.5-68.4	C <sub>18</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub>	65.27	65.12	8.90	9.16	9.52	9.45	158.6-159.4	5.27	5.23
3	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	C <sub>4</sub> H <sub>9</sub>	B	Oil	C <sub>18</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub>	...	...	...	...	8.69	8.54	147.6-149.3	5.04	5.12
3	C <sub>3</sub> H <sub>7</sub> <sup>f</sup>	C <sub>4</sub> H <sub>9</sub>	DH	115.8-118.6 <sup>l</sup>	C <sub>19</sub> H <sub>34</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	53.64	53.63	8.06	7.83	16.67 <sup>d</sup>	16.67 <sup>d</sup>	198.0-199.4 <sup>c, m, r</sup>	4.94	4.96
3	C <sub>3</sub> H <sub>7</sub> <sup>f</sup>	C <sub>5</sub> H <sub>11</sub>	B	Oil	C <sub>20</sub> H <sub>32</sub> N <sub>2</sub> O <sub>3</sub>	68.93	69.04	9.26	9.07	8.04	8.04	184.2-185.6 <sup>p</sup>	4.84	4.98
3	C <sub>6</sub> H <sub>10</sub> <sup>q</sup>	C <sub>4</sub> H <sub>9</sub>	B	Oil	C <sub>20</sub> H <sub>32</sub> N <sub>2</sub> O <sub>3</sub>	68.93	69.04	9.26	9.29	8.04	7.91	176.0-178.0 <sup>l</sup>	4.84	4.86
3	C <sub>8</sub> H <sub>12</sub> <sup>g</sup>	C <sub>5</sub> H <sub>11</sub>	B	Oil	C <sub>21</sub> H <sub>34</sub> N <sub>2</sub> O <sub>3</sub>	69.57	69.84	9.45	9.56	7.73	7.76	157.0-159.2 <sup>q</sup>	4.74	4.70
3	C <sub>8</sub> H <sub>16</sub> <sup>k</sup>	C <sub>4</sub> H <sub>9</sub>	DH	117.0-120.2 <sup>n</sup>	C <sub>18</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub>	50.59	50.73	7.55	7.72	6.56	6.40	194.8-197.0 <sup>c, u</sup>	4.93	4.98

<sup>a</sup> B = base, DH = dihydrochloride. <sup>b</sup> C<sub>3</sub>H<sub>7</sub> = *n*-propyl, C<sub>4</sub>H<sub>9</sub> = *n*-butyl, C<sub>5</sub>H<sub>11</sub> = *n*-amyl. <sup>c</sup> With decomposition. <sup>d</sup> Chlorine analysis. <sup>e</sup> The picrate melted at 143.5-145.5°. Calcd.: N, 12.521. Found: N, 12.500. <sup>f</sup> 1-Piperidyl. <sup>g</sup> 2-Methyl-1-piperidyl. <sup>h</sup> 2,6-Dimethyl-1-piperidyl. <sup>i</sup> 3-Dimethylamino-2-propyl. <sup>j</sup> Diflavianate. <sup>k</sup> 4-Morpholinyl. <sup>l</sup> Monohydrate. Calcd.: H<sub>2</sub>O, 4.24. Found: H<sub>2</sub>O, 4.21. <sup>m</sup> The monopicrate melted at 134.2-136.2°. Calcd.: N, 11.745. Found: N, 11.743. <sup>n</sup> Monohydrate. Calcd.: H<sub>2</sub>O, 4.21. Found: H<sub>2</sub>O, 3.88. <sup>o</sup> The picrate had m.p. 164.2-165.8°. Calcd. N, 11.745. Found: N, 11.735. <sup>p</sup> Calcd.: C, 54.36; H, 5.78. Found: C, 53.95; H, 5.76. <sup>q</sup> Calcd.: C, 53.69; H, 5.59. Found: C, 53.81; H, 5.36. <sup>r</sup> Calcd.: C, 53.69; H, 5.59; Found: C, 53.63; H, 5.60. <sup>s</sup> Calcd.: C, 55.02; H, 5.96. Found: C, 55.12; H, 6.04. <sup>t</sup> Calcd.: C, 54.36; H, 5.78. Found: C, 54.40; H, 5.98. <sup>u</sup> Calcd.: C, 51.68; H, 5.27. Found: C, 51.63; H, 5.15. <sup>v</sup> Calcd.: C, 54.36; H, 5.78. Found: C, 54.31; H, 5.93.

TABLE VI



n	R <sub>2</sub>	R'	M.p., °C.	Formula	Sulfur, %		Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
2	(CH <sub>3</sub> ) <sub>2</sub>	C <sub>3</sub> H <sub>7</sub> <sup>a, b</sup>	168.6-170.0 <sup>c</sup>	C <sub>31</sub> H <sub>34</sub> N <sub>4</sub> O <sub>11</sub> S	4.78	4.72	55.51	55.62	5.11	5.12
2	(CH <sub>3</sub> ) <sub>2</sub>	C <sub>4</sub> H <sub>9</sub> <sup>d, e</sup>	178.0-178.5 <sup>c</sup>	C <sub>32</sub> H <sub>38</sub> N <sub>4</sub> O <sub>11</sub> S	4.68	4.74	56.12	56.02	5.30	5.51
2	(CH <sub>3</sub> ) <sub>2</sub>	C <sub>5</sub> H <sub>11</sub> <sup>f</sup>	168.8-170.0	C <sub>33</sub> H <sub>38</sub> N <sub>4</sub> O <sub>11</sub> S	4.59	4.73	56.72	56.55	5.48	5.31
3	(CH <sub>3</sub> ) <sub>2</sub>	C <sub>4</sub> H <sub>9</sub> <sup>d</sup>	182.4-183.4	C <sub>33</sub> H <sub>38</sub> N <sub>4</sub> O <sub>11</sub> S	4.59	4.72	56.72	56.82	5.48	5.26
<sup>g</sup>	(CH <sub>3</sub> ) <sub>2</sub>	C <sub>4</sub> H <sub>9</sub> <sup>d</sup>	148.5-151.5	.....	4.59	4.28	...	...	...	...
3	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> <sup>h</sup>	C <sub>4</sub> H <sub>9</sub> <sup>d</sup>	139.2-141.0	C <sub>45</sub> H <sub>48</sub> N <sub>4</sub> O <sub>19</sub> S <sub>2</sub>	6.15	6.12	51.92	52.10	4.65	4.62
3	C <sub>6</sub> H <sub>10</sub> <sup>i</sup>	C <sub>4</sub> H <sub>9</sub> <sup>d</sup>	196.6-198.0 <sup>c</sup>	C <sub>35</sub> H <sub>42</sub> N <sub>4</sub> O <sub>11</sub> S	4.34	4.41	58.52	58.72	5.73	5.64
3	C <sub>6</sub> H <sub>10</sub> <sup>i</sup>	C <sub>5</sub> H <sub>11</sub> <sup>f</sup>	189.8-190.3 <sup>c</sup>	C <sub>37</sub> H <sub>44</sub> N <sub>4</sub> O <sub>11</sub> S	4.26	4.33	59.02	58.96	5.89	5.96

<sup>a</sup> *n*-Propyl. <sup>b</sup> The crystalline base had m.p. 71.5-72.7°. Calcd. for C<sub>21</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>: N, 7.86. Found: N, 7.81. <sup>c</sup> With decomposition. <sup>d</sup> *n*-Butyl. <sup>e</sup> The crystalline base had m.p. 46.0-53.9°. Calcd. for C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.12; H, 8.02; N, 7.40. <sup>f</sup> *n*-Amyl. <sup>g</sup> 3-Dimethylamino-2-propyl. <sup>h</sup> Diflavianate. <sup>i</sup> 1-Piperidyl.

tion,<sup>5</sup> a number of related compounds were also prepared. Two basic esters were synthesized from 2-(3'-methylbenzyloxy)-4-nitrobenzoic acid in order to determine the effect of "weight increase" within this ring. However, when an attempt was made to extend this series by the utilization of 2-(4'-nitrobenzyloxy)-4-nitrobenzoic acid, the reactions failed at the stage of reduction to the 4,4'-diamino compounds, apparently due to cleavage of the labile 4'-aminobenzyloxy group. For the purpose of determining the effect on local anesthetic activity of the

4-amino group in a dialkylaminoalkyl 4-amino-2-benzyloxybenzoate, there were prepared two related dialkylaminoalkyl 2-benzyloxybenzoates. These compounds were readily obtained by means of the Hörenstein-Pählicke reaction, utilizing 2-benzyloxybenzoic acid.<sup>6</sup> For the determination of the influence of the 2-hydroxy group, there were prepared several simple 4-amino- and 4-alkylaminobenzoate esters of analogous types.

Preliminary testing of the compounds herein discussed has indicated a high degree of local anesthetic activity, both topically and by infiltration, for the majority of the compounds.

(5) Preliminary pharmacological results have been published by Luduena and Hoppe, *Fed. Proc.*, **9**, 297 (1950). Complete data will be published at a later date.

(6) Cohen and Dudley, *J. Chem. Soc.*, **97**, 1745 (1910).

### Experimental<sup>7</sup>

**2-Hydroxy-4-nitrobenzoic Acid.**—To two hundred and sixty milliliters of hot (100°) 68% sulfuric acid was added 15 g. of crude (m.p. 174–176°) 2-methoxy-4-nitrobenzotrile. The mixture was heated rapidly (20 minutes) to the reflux point, and refluxing was continued for 15 minutes. The hot, highly colored mixture was poured onto ice, mixed well and allowed to stand for 20 minutes. The solid material was filtered off, washed thoroughly with water, and dissolved in a solution of one equivalent of sodium bicarbonate. After decolorization at 50°, the solution was acidified with concentrated hydrochloric acid, filtered and the resulting washed precipitate was recrystallized from dilute alcohol. There was thus obtained 12.2–13.9 g. (79–90% yields) of 2-hydroxy-4-nitrobenzoic acid as white needles, m.p. 236–238° (dec.).

A mixture of 89.0 g. (0.5 mole) of crude 2-methoxy-4-nitrobenzotrile (m.p. 174–176°), 200 ml. of glacial acetic acid, 28 ml. (0.5 mole) of concentrated sulfuric acid and 92 ml. of 55% hydrobromic acid (81 g. of hydrogen bromide, 1.0 mole) was refluxed and stirred for 24 hours. The internal temperature of the mixture was 114–115°, and methyl bromide was evolved steadily at the rate of 0.094 mole per hour. The mixture was poured into 2000 ml. of ice-water and the precipitate was filtered off, washed with water, and purified as above. There was thus obtained 72–78 g. (78–85% yields) of white 2-hydroxy-4-nitrobenzoic acid, m.p. 236–238° (dec.). For the 55% hydrobromic acid there could be substituted an equivalent quantity of 48% hydrobromic acid, the concentration then being adjusted by substitution of the calculated amount of acetic anhydride for a portion of the acetic acid.

**2-Bromoethyl 2-Hydroxy-4-nitrobenzoate.**—The esterification of 2-hydroxy-4-nitrobenzoic acid with 2-bromoethanol, when carried out by the ethylene dichloride procedure,<sup>8</sup> gave yields of 40–50% of product; the Fischer method was somewhat more satisfactory (65–75% yields). The product crystallized from alcohol in pale yellow cottony needles, m.p. 74.7–74.9°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>9</sub>BrNO<sub>3</sub>: C, 37.26; H, 2.78; Br, 27.55. Found: C, 37.48; H, 2.67; Br, 27.39.

**2-Chloroethyl 2-Hydroxy-4-nitrobenzoate.**—The Fischer method gave a 77% yield of product, forming pale yellow cottony needles from alcohol, m.p. 87.4–88.4°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>9</sub>ClNO<sub>3</sub>: C, 44.01; H, 3.28; Cl, 14.44. Found: C, 44.24; H, 3.56; Cl, 14.37.

**Dialkylaminoalkyl 2-Hydroxy-4-nitrobenzoate Hydrochlorides.** **A.**—To a stirred, refluxing solution of 137.5 g. (0.75 mole) of pure 2-hydroxy-4-nitrobenzoic acid in 800 ml. of isopropyl alcohol was added dropwise 110 g. (0.80 mole) of redistilled 2-diethylaminoethyl chloride. The addition required 90 minutes. The heterogeneous mixture (dense white precipitate present) was stirred and refluxed for an additional seven hours, cooled, filtered and the filtrate was evaporated to dryness *in vacuo*. The residual paste was triturated with acetone and the insoluble material was combined with the original precipitate. (The acetone solution was processed to recover 2-hydroxy-4-nitrobenzoic acid.) The combined insoluble precipitates were recrystallized from alcohol containing a small amount of anhydrous hydrogen chloride,<sup>9</sup> to yield 161.4 g. (67.7%) of material melting at 179–180°. For the 2-diethylaminoethyl chloride there could be substituted a proportionate quantity of the pure chloride hydrochloride (added in alcoholic solution) and one equivalent of sodium bicarbonate (added to the acid solution), without diminution in yield.

**B.**—A mixture of 30.0 g. (0.14 mole) of ethyl 2-hydroxy-4-nitrobenzoate, 28.6 g. (0.20 mole) of redistilled 3-(1-piperidyl)propanol and 350 ml. of dry toluene was distilled slowly through a 12" Vigreux column during eight hours. A total of 175 ml. of distillate was collected. The still residue was evaporated *in vacuo*, finally at 100° and 0.01 mm. The residual oil or paste was dissolved in 250 ml. of hot iso-

propyl alcohol and the deeply colored solution was treated with 20% ethereal hydrogen chloride solution until the color was discharged. After dilution with an equal volume of ethyl acetate the mixture was cooled, filtered, and the white crystalline product was washed thoroughly with ethyl acetate. Recrystallization from isopropyl alcohol gave 19.2 g. of white prisms, m.p. 183.0–184.0°. From the mother liquors was recovered an additional 6.0 g. of material melting at 179–181°.

**C.**—A stream of dry hydrogen chloride was passed through a refluxing mixture of 91.5 g. of 2-hydroxy-4-nitrobenzoic acid, 45 g. of redistilled 2-dimethylaminoethanol and 1000 ml. of dry toluene for 12 hours. The mixture on working up as usual (*via* the base) gave a 7% yield of 2-dimethylaminoethyl 2-hydroxy-4-nitrobenzoate hydrochloride.

**D.**—A mixture of 20.0 g. of 2-bromoethyl 2-hydroxy-4-nitrobenzoate (or an equivalent amount of the 2-chloroethyl ester), 25.0 g. of redistilled diethylamine and 250 ml. of dry toluene was stirred and refluxed for ten hours. From the resulting mixture, after acidification with ethereal hydrogen chloride and fractional recrystallization, there was isolated a 33% yield of 2-diethylaminoethyl 2-hydroxy-4-nitrobenzoate hydrochloride.

The dialkylaminoalkyl 2-hydroxy-4-nitrobenzoate hydrochlorides, prepared by the above methods, are listed in Table I.

A concentrated solution of 2-diethylaminoethyl 2-hydroxy-4-nitrobenzoate hydrochloride in water, when treated with an excess of saturated sodium bicarbonate solution, liberated the base in the form of a heavy orange oil. The base could be extracted into ethyl acetate, but on thorough drying the solution deposited the base as deep yellow needles, m.p. 219–221°. The base could not be obtained analytically pure; it was readily soluble in water and alcohol, insoluble in ethyl acetate, ether or benzene. Similar bases could be prepared from the homologs.

**Dialkylaminoalkyl 2-Acetoxy-4-nitrobenzoate Hydrochlorides.**—A mixture of 22.5 g. (0.10 mole) of 2-acetoxy-4-nitrobenzoic acid,<sup>10</sup> 15.0 g. (0.11 mole) of redistilled 2-diethylaminoethyl chloride and 200 ml. of isopropyl alcohol was stirred and refluxed for six hours. After cooling, the crystalline precipitate was filtered off and washed with isopropyl alcohol (this precipitate was shown to be a mixture of 1,1,4,4-tetraethylpiperazinium dichloride and 2-diethylaminoethyl 2-hydroxy-4-nitrobenzoate hydrochloride). The combined isopropyl alcohol filtrates were evaporated *in vacuo* and the residue was dissolved in hot acetone. The solution was filtered to remove a small amount of 2-diethylaminoethyl 2-hydroxy-4-nitrobenzoate hydrochloride and the filtrate was diluted, while hot, to turbidity with ethyl acetate. The product crystallized in white needles on cooling; recrystallization from acetone–ethyl acetate gave 8.4 g. of 2-diethylaminoethyl 2-acetoxy-4-nitrobenzoate hydrochloride, m.p. 132.8–133.6°.

*Anal.* Calcd. for C<sub>12</sub>H<sub>21</sub>ClN<sub>2</sub>O<sub>6</sub>: N, 7.77; Cl, 9.83. Found: N, 7.69; Cl, 9.87.

The mixed melting point of this material with a sample prepared by the treatment of 2-diethylaminoethyl 2-hydroxy-4-nitrobenzoate hydrochloride with excess boiling acetic anhydride showed no depression.

In a similar manner there were prepared from 2-acetoxy-4-nitrobenzoic acid:

**2-(4-Morpholinyl)-ethyl 2-acetoxy-4-nitrobenzoate hydrochloride**, rosettes of pale yellow prisms, m.p. 154.6–156.0°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>19</sub>ClN<sub>2</sub>O<sub>7</sub>: N, 7.48; Cl, 9.46. Found: N, 7.63; Cl, 9.51.

**3-(2-Methyl-1-piperidyl)-propyl 2-acetoxy-4-nitrobenzoate hydrochloride**, white prisms, m.p. 143.2–145.8°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>6</sub>: N, 6.99; Cl, 8.84. Found: N, 6.94; Cl, 8.92.

The yields in both cases were quite poor.

**Ethyl 2-Benzoyloxy-4-nitrobenzoate.**—A mixture of 84.4 g. (0.40 mole) of pure ethyl 2-hydroxy-4-nitrobenzoate, 55.6 g. (0.44 mole) of redistilled benzyl chloride, 29.6 g. (0.28

(7) All melting points are corrected. They were determined in a modified Hershberg apparatus using total-immersion N.B.S.-calibrated thermometers. The sample was immersed 15° below the melting point, 3.0° rise per minute. The analyses were done by Mr. Morris E. Auerbach and staff.

(8) Clinton and Laskowski, *THIS JOURNAL*, **70**, 3135 (1948).

(9) A certain amount of the alcohol-insoluble 1,1,4,4-tetraethylpiperazinium dichloride was always isolated at this point.

(10) This compound has been disclosed by Goodacre, Mitchell and Seymour, *Quart. J. Pharm. Pharmacol.*, **21**, 301 (1948), but no properties were recorded. The acyloxy acid, prepared in the usual manner, formed cottony white needles from an ethyl acetate–Skellysolve C mixture, m.p. 155.2–156.6°. *Anal.* Calcd. for C<sub>8</sub>H<sub>7</sub>NO<sub>6</sub>: C, 48.01; H, 3.13; N, 6.22. Found: C, 48.18; H, 3.33; N, 6.17.

mole, 0.56 equiv.) of anhydrous sodium carbonate, 6 g. of sodium iodide and 400 ml. of alcohol was stirred and refluxed for eight hours. The mixture was filtered while hot and the insoluble material was washed well with hot alcohol. The combined filtrates were mixed with an equal volume of ethyl acetate (for dehydration) and evaporated to dryness *in vacuo*. The residual oil on crystallization from Skellysolve B formed long, slender, rectangular rods, m.p. 57.0–58.5°. The yield was 105.1 g. (87.3%).

*Anal.* Calcd. for  $C_{18}H_{15}NO_3$ : N, 4.65; C, 63.78; H, 5.02. Found: N, 4.47; C, 64.10; H, 4.77.

**2-Benzoyloxy-4-nitrobenzoic Acid.**—The benzylation of 0.40 mole of ethyl 2-hydroxy-4-nitrobenzoate was carried out as described above. At the conclusion of the eight hour reflux period there was added 82.4 g. of anhydrous sodium carbonate and 400 ml. of water, and stirring and refluxing were continued for an additional eight hours. The insoluble precipitate of sodium bicarbonate was filtered off and washed with absolute alcohol. The alcohol was removed from the combined filtrates *in vacuo*, and the residual aqueous solution was cooled and acidified to congo red with concentrated hydrochloric acid. The precipitate was filtered off, washed thoroughly with water, pressed dry, and recrystallized twice from isopropyl alcohol. There was thus obtained 95.0 g. of product, m.p. 171–173° (87% over-all yield). On further recrystallization from isopropyl alcohol the product was obtained in large, pale yellow needles, m.p. 172.0–173.0°.

*Anal.* Calcd. for  $C_{18}H_{13}NO_5$ : C, 61.54; H, 4.06; N, 5.13. Found: C, 61.73; H, 4.29; N, 5.16.

When the benzylation procedure was carried out using 2-hydroxy-4-nitrobenzoic acid as starting material, and doubling the equivalents of the other components, there was obtained a 60% over-all yield of 2-benzoyloxy-4-nitrobenzoic acid, *via* the intermediate **benzyl 2-benzoyloxy-4-nitrobenzoate**, rosettes of large white needles (pale yellow in bulk) from Skellysolve C, m.p. 88.5–89.5°.

*Anal.* Calcd. for  $C_{21}H_{17}NO_6$ : C, 69.41; H, 4.72; N, 3.86. Found: C, 69.06; H, 4.85; N, 4.13.

Potassium hydroxide saponification of the alkyl 2-benzoyloxy-4-nitrobenzoates gave chiefly polymeric products and a low yield of the acid.

**Ethyl 4-Amino-2-benzoyloxybenzoate.**—A generalized procedure was used for the reduction of the 2-benzoyloxy-4-nitrobenzoates to the 4-amino-2-benzoyloxybenzoates.

To a stirred, boiling mixture of 56.7 g. of powdered iron, 400 ml. of alcohol, 100 ml. of water and 1 ml. of concentrated hydrochloric acid was added 51.0 g. of ethyl 2-benzoyloxy-4-nitrobenzoate in small portions. When the (mildly exothermic) addition was complete (ten minutes) the stirring and gentle boiling were continued for a further 20 minutes. There was then cautiously added 18 g. of powdered sodium bicarbonate, the black mixture was further stirred and heated for ten minutes, and then filtered while hot. The insoluble filter cake was thoroughly washed with hot alcohol and the alcohol was removed from the combined filtrates *in vacuo*. The residual crystalline paste was filtered and the precipitate was recrystallized several times from benzene. The product formed white prisms, m.p. 128.6–129.2°; the yield was 69%.

*Anal.* Calcd. for  $C_{18}H_{17}NO_3$ : C, 70.83; H, 6.31; N, 5.16. Found: C, 71.05; H, 6.42; N, 5.15.

**2-Benzoyloxy-4-butylaminobenzoic Acid.**—To a stirred, refluxing mixture of 14.5 g. of zinc dust, 13.7 g. of glacial acetic acid, 15.0 g. of ethyl 4-amino-2-benzoyloxybenzoate and 100 ml. of benzene was added dropwise during 20 minutes a solution of 4.9 g. of redistilled *n*-butyraldehyde in 20 ml. of benzene. When the addition was complete, the mixture was stirred and refluxed for a further one-hour period, filtered while hot, and the insoluble filter cake was washed thoroughly with dilute acetic acid and with benzene. The combined filtrates were made strongly basic with concentrated ammonium hydroxide, mixed well, and the benzene layer was separated. After drying, the benzene extract was evaporated *in vacuo*. The residual **ethyl 2-benzoyloxy-4-butylaminobenzoate** crystallized from Skellysolve B in large, white, blunt needles, m.p. 51.6–52.6°. The yield of pure material was 74%.

*Anal.* Calcd. for  $C_{20}H_{23}NO_3$ : C, 73.36; H, 7.70; N, 4.28. Found: C, 73.50; H, 7.49; N, 4.33.

(11) Nitro nitrogen, by titration with titanous chloride.

Hydrolysis by means of an aqueous alcoholic potassium hydroxide solution (two-hour reflux) gave a quantitative yield of the acid, brilliant white leaflets from dilute alcohol, m.p. 108.0–108.8°.

*Anal.* Calcd. for  $C_{18}H_{15}NO_3$ : C, 72.21; H, 7.07; N, 4.68. Found: C, 72.36; H, 6.83; N, 4.74.

**2-(3'-Methylbenzyloxy)-4-nitrobenzoic Acid.**—The condensation of *m*-xylyl bromide with ethyl 2-hydroxy-4-nitrobenzoate was carried out under the conditions described for simple benzylation above, using proportionate amounts of the components. The yield of the intermediate **ethyl 2-(3'-methylbenzyloxy)-4-nitrobenzoate** was ca. 40%; pale yellow needles from absolute alcohol, m.p. 73.0–74.1°.

*Anal.* Calcd. for  $C_{17}H_{17}NO_5$ : C, 64.75; H, 5.44; N, 4.44. Found: C, 64.65; H, 5.34; N, 4.28.

Hydrolysis of the ethyl ester by means of an aqueous alcoholic sodium carbonate solution gave an 80% yield of the acid, pale yellow needles, m.p. 185.3–186.3°.

*Anal.* Calcd. for  $C_{18}H_{19}NO_3$ : C, 62.70; H, 4.56; N, 4.87. Found: C, 62.92; H, 4.33; N, 4.69.

Using the modified iron-hydrochloric acid reduction procedure described above, the nitro-ester gave a high yield of **ethyl 4-amino-2-(3'-methylbenzyloxy)-benzoate**, white prisms from benzene, m.p. 102.4–103.0°.

*Anal.* Calcd. for  $C_{17}H_{19}NO_3$ : C, 71.56; H, 6.71; N, 4.91. Found: C, 71.49; H, 6.68; N, 4.89.

**4-Nitro-2-(4'-nitrobenzyloxy)-benzoic Acid.**—The reaction between ethyl 2-hydroxy-4-nitrobenzoate and 4-nitrobenzyl chloride, carried out as above, gave a 91% yield of **ethyl 4-nitro-2-(4'-nitrobenzyloxy)-benzoate**, rosettes of large blunt needles, pale yellow in bulk, m.p. 148.6–149.8°.

*Anal.* Calcd. for  $C_{18}H_{14}N_2O_7$ : N, 8.09. Found: N, 8.21.

Hydrolysis with an aqueous alcoholic sodium carbonate solution gave the acid, pale yellow needles from isopropyl alcohol, m.p. 225.0–225.9°.

*Anal.* Calcd. for  $C_{14}H_{10}N_2O_7$ : N, 8.80. Found: N, 8.99.

**Dialkylaminoalkyl 2-Benzoyloxy-4-nitrobenzoates.** A.—A mixture of 54.4 g. (0.20 mole) of 2-benzoyloxy-4-nitrobenzoic acid, 38.8 g. (0.24 mole) of 3-(1-piperidyl)propyl chloride, and 600 ml. of isopropyl alcohol was refluxed for 20 hours. The solution was evaporated *in vacuo* and the residual paste was dissolved in water. An excess of solid potassium carbonate was added to the clear solution and the liberated base was extracted with ethyl acetate. After drying, the ethyl acetate extracts were evaporated *in vacuo*. The residual oil crystallized on cooling and scratching. One recrystallization from dilute alcohol gave a 96.5% yield of 3-(1-piperidyl)propyl 2-benzoyloxy-4-nitrobenzoate as short, thick, pale yellow needles, m.p. 76–78°.

When 2-dialkylaminoethyl chlorides were used in the above procedure, the reflux period was shortened to five hours. The yields were very high except with 2-dimethylaminoethyl chloride, in which case cyclization of the halide to 1,1,4,4-tetramethylpiperazinium dichloride was the predominant reaction. For this type of compound Method B, below, proved more suitable.

B.—To a stirred mixture of 104.0 g. (0.38 mole) of 2-benzoyloxy-4-nitrobenzoic acid, 32.4 g. (0.41 mole) of pure, dry pyridine and 750 ml. of dry benzene was added dropwise 47.6 g. (0.40 mole) of pure thionyl chloride during a period of ten minutes (exothermic reaction). The heterogeneous mixture (heavy layer of pyridine hydrochloride) was stirred and refluxed for ten minutes, cooled to 50°, and there was added slowly with stirring 39.1 g. (0.38 mole) of 3-dimethylamino-2-propanol. After stirring for ten minutes at 40–50° the mixture was cooled, diluted to two liters with Skellysolve A, and filtered. The insoluble precipitate, after washing with Skellysolve A, was dissolved in water, the solution was made basic with solid potassium carbonate, and the liberated base was extracted into ethyl acetate. After drying, the extract was evaporated *in vacuo*, 200 ml. of xylene was added to the residual oil and the solution was again evaporated *in vacuo* to remove traces of pyridine. The residual pale yellow oil did not crystallize; the yield of 3-dimethylamino-2-propyl 2-benzoyloxy-4-nitrobenzoate was 88%.

Comparable yields were obtained with other dialkylaminoalkanol. The dialkylaminoalkyl 2-benzoyloxy-4-nitroben-

zoate bases were very photosensitive, developing a pronounced yellow to yellow-orange color on standing in the light. The compounds and characterizing derivatives are listed in Table II.

By means of the Hörenstein-Pählicke method, as described above, there were also prepared:

**2-Diethylaminoethyl 2-(3'-methylbenzyloxy)-4-nitrobenzoate hydrochloride**, long, white needles from isopropyl alcohol, m.p. 161.3–162.0°.

*Anal.* Calcd. for  $C_{21}H_{27}ClN_2O_5$ : Cl, 8.38. Found: Cl, 8.35.

The picrate had m.p. 172.0–172.9°.

*Anal.* Calcd. for  $C_{27}H_{31}N_3O_{12}$ : N, <sup>12</sup> 2.28; N, <sup>11</sup> 9.12. Found: N, <sup>12</sup> 2.28; N, <sup>11</sup> 9.12.

**3-(1-Piperidyl)-propyl 2-(3'-methylbenzyloxy)-4-nitrobenzoate hydrochloride**, white prisms from isopropyl alcohol, m.p. 176.1–177.8°.

*Anal.* Calcd. for  $C_{23}H_{29}ClN_2O_5$ : Cl, 7.90. Found: Cl, 7.90.

The picrate melted at 157.3–158.2°.

*Anal.* Calcd. for  $C_{29}H_{31}N_3O_{12}$ : N, <sup>12</sup> 2.18; N, <sup>11</sup> 8.72. Found: N, <sup>12</sup> 2.18; N, <sup>11</sup> 8.68.

**2-Diethylaminoethyl 4-nitro-2-(4'-nitrobenzyloxy)-benzoate**, brilliant, long needles (pale yellow in bulk) from alcohol, m.p. 79.5–80.8°. The base was extremely photosensitive.

*Anal.* Calcd. for  $C_{20}H_{23}N_3O_7$ : N, <sup>12</sup> 3.36; N, <sup>11</sup> 6.72. Found: N, <sup>12</sup> 3.24; N, <sup>11</sup> 6.75.

The hydrochloride formed silky, pale yellow needles from alcohol, m.p. 170.6–171.8°.

*Anal.* Calcd. for  $C_{20}H_{23}ClN_3O_7$ : N, <sup>11</sup> 6.17; Cl, 7.81. Found: N, <sup>11</sup> 6.05; Cl, 7.73.

The picrate crystallized from a glacial acetic acid-absolute alcohol mixture in cottony, canary-yellow needles, m.p. 164.0–164.9°.

*Anal.* Calcd. for  $C_{28}H_{28}N_6O_{14}$ : N, <sup>12</sup> 2.17; N, <sup>11</sup> 10.85. Found: N, <sup>12</sup> 2.17; N, <sup>11</sup> 10.94.

**3-(1-Piperidyl)-propyl 4-nitro-2-(4'-nitrobenzyloxy)-benzoate**, rosettes of long, pale yellow needles from absolute alcohol, m.p. 122.6–124.0°. The base was extremely photosensitive.

*Anal.* Calcd. for  $C_{22}H_{25}N_3O_7$ : N, <sup>12</sup> 3.16; N, <sup>11</sup> 6.32. Found: N, <sup>12</sup> 3.08; N, <sup>11</sup> 6.33.

The hydrochloride crystallized from absolute alcohol-ethyl acetate in pale yellow leaflets, m.p. 198.0–199.0°.

*Anal.* Calcd. for  $C_{22}H_{25}ClN_3O_7$ : N, <sup>11</sup> 5.84; Cl, 7.39. Found: N, <sup>11</sup> 5.73; Cl, 7.40.

The picrate melted at 145.8–147.0°.

*Anal.* Calcd. for  $C_{28}H_{28}N_6O_{14}$ : N, <sup>12</sup> 2.08; N, <sup>11</sup> 10.40. Found: N, <sup>12</sup> 2.05; N, <sup>11</sup> 10.21.

**Dialkylaminoalkyl 4-Amino-2-hydroxybenzoates.** A.—A suspension of 6.4 g. of 2-diethylaminoethyl 2-hydroxy-4-nitrobenzoate hydrochloride and 500 mg. of platinum oxide in 150 ml. of absolute alcohol was shaken with hydrogen on a modified<sup>12</sup> Parr-Burgess apparatus at 40° and 40 p.s.i. Reduction was complete within ten minutes. The mixture was filtered while hot and the filtrate was evaporated to a small volume *in vacuo*; 2-diethylaminoethyl 4-amino-2-hydroxybenzoate monohydrochloride crystallized on cooling. The compound formed slender white needles from isopropyl alcohol, m.p. 154.0–154.8°. The yield was ca. 90%.

B.—Eighty-three and two-tenths grams of 3-(2-methyl-1-piperidyl)-propyl 2-hydroxy-4-nitrobenzoate hydrochloride was reduced by the iron-hydrochloric acid procedure outlined above. The filtrate from the reduction (after the sodium bicarbonate treatment) was mixed with a solution of 5 g. of sodium sulfide nonahydrate in 20 ml. of water. The mixture was treated with Darco G60, filtered, and the alcohol was removed from the filtrate *in vacuo*. The precipitated heavy oil was extracted into benzene, the solution was dried and decolorized, and the benzene was removed *in vacuo*. The residual pale yellow, oily 3-(2-methyl-1-piperidyl)-propyl 4-amino-2-hydroxybenzoate weighed 61.2 g. (90.4% yield).

To a solution of 10.0 g. of the base in 100 ml. of hot absolute alcohol was added a solution of 3.8 g. of 85% phosphoric

acid in 100 ml. of hot absolute alcohol. The mixture was mixed well and heated to boiling; the thick gum crystallized on scratching. The mixture was diluted with an equal volume of ethyl acetate, cooled and filtered. The precipitate was recrystallized by solution in the minimum amount of hot water, filtration and slow dilution of the filtrate with warm absolute alcohol. 3-(2-Methyl-1-piperidyl)-propyl 4-amino-2-hydroxybenzoate phosphate crystallized in brilliant white prisms, m.p. 201.0–201.5°.

C.—A mixture of 34.4 g. (0.10 mole) of 2-dimethylaminoethyl 2-benzyloxy-4-nitrobenzoate or 31.4 g. (0.10 mole) of 2-dimethylaminoethyl 4-amino-2-benzyloxybenzoate (*vide infra*), 1.0 g. of 7% palladium chloride on Darco G60 catalyst, 16.8 ml. (0.20 mole) of concentrated hydrochloric acid, 20 ml. of water, and 110 ml. of alcohol was shaken with hydrogen at 45° and 50 p.s.i. The reduction was very rapid. The catalyst was filtered off on a pad of Filtercel and washed with dilute alcohol. The combined filtrates and washings were neutralized with an excess of solid sodium bicarbonate and the alcohol and toluene were removed *in vacuo*. The residual crystalline slurry was filtered and the precipitate of 2-dimethylaminoethyl 4-amino-2-hydroxybenzoate was recrystallized several times from benzene-Skellysolve B. The pure base crystallized in feathery white needles, m.p. 136.1–137.2°. The yield of product was 93%.

The dialkylaminoalkyl 4-amino-2-hydroxybenzoates and their characterizing derivatives are listed in Table III.

**Dialkylaminoalkyl 4-Amino-2-benzyloxybenzoates.**—The dialkylaminoalkyl 2-benzyloxy-4-nitrobenzoate bases were reduced by the general iron-hydrochloric acid procedure outlined above for ethyl 2-benzyloxy-4-nitrobenzoate. The 4-amino bases were obtained in 90–95% yields. The bases were characterized through the crystalline derivatives listed in Table IV. The picrates proved unsuitable as derivatives because of their indeterminate melting points.

With 2-(2-methyl-1-piperidyl)-ethyl 4-amino-2-benzyloxybenzoate, no crystalline derivative other than the flavianate could be obtained.

Utilizing the same procedure, there were also prepared:

**2-Diethylaminoethyl 4-amino-2-(3'-methylbenzyloxy)-benzoate monohydrochloride**, white prisms from isopropyl alcohol-ethyl acetate, m.p. 135.5–136.4°.

*Anal.* Calcd. for  $C_{21}H_{29}ClN_2O_3$ : N, 7.13; Cl, 9.02. Found: N, 7.20; Cl, 8.86.

The diflavianate crystallized from alcohol in yellow-orange needles, m.p. 193.0–194.0° (dec.).

*Anal.* Calcd. for  $C_{41}H_{46}N_6O_{19}S_2$ : S, 6.51. Found: S, 6.62.

**3-(1-Piperidyl)-propyl 4-amino-2-(3'-methylbenzyloxy)-benzoate monohydrochloride**, white prisms from absolute alcohol-ethyl acetate, m.p. 163.8–165.0°.

*Anal.* Calcd. for  $C_{23}H_{31}ClN_2O_3$ : N, 6.69; Cl, 8.46. Found: N, 6.70; Cl, 8.44.

The flavianate formed tiny orange prisms from alcohol, m.p. 175.2–176.6°.

*Anal.* Calcd. for  $C_{43}H_{56}N_6O_{11}S$ : S, 4.60; C, 56.88; H, 5.21. Found: S, 4.59; C, 57.01; H, 5.21.

**2-Dialkylaminoalkyl 4-Alkylamino-2-hydroxybenzoates.** A.—A mixture of 24.8 g. of 3-(2-methyl-1-piperidyl)-propyl 4-amino-2-hydroxybenzoate, 22.2 g. of zinc dust, 20.9 g. of glacial acetic acid and 200 ml. of benzene was treated with a solution of 8.9 g. of *n*-butyraldehyde in 20 ml. of benzene, under the conditions used with ethyl 4-amino-2-benzyloxybenzoate above. However, in order to prevent partial solution of the base, the acetic acid-benzene filtrate was carefully adjusted to litmus-basicity with sodium hydroxide solution. The golden-yellow viscous oil obtained (27.0 g.) was dissolved in dilute hydrochloric acid, the solution was washed with ether, decolorized with Darco G60, and made basic with solid potassium carbonate. The liberated base was extracted into ethyl acetate, the solution was dried and decolorized, and the ethyl acetate was removed *in vacuo*. The residue was dissolved in ether, again decolorized, and the ether was removed *in vacuo*, finally at 80° and 0.01 mm. for three hours. After filtration through a layer of dry Filtercel on a sintered glass funnel the analytically pure 3-(2-methyl-1-piperidyl)-propyl 4-butylamino-2-hydroxybenzoate was obtained as a nearly colorless, very viscous oil. The yield was 19.2 g.

B.—A mixture of 14.2 g. of 2-diethylaminoethyl 2-hydroxy-4-nitrobenzoate hydrochloride, 200 mg. of platinum

(12) Basic amino nitrogen by titration with perchloric acid in glacial acetic acid solution.

(13) Buck and Jenkins, *This Journal*, **51**, 2163 (1929)



oxide and 140 ml. of 50% alcohol was shaken with hydrogen at 25° and 50 p.s.i. on a Parr-Burgess apparatus. When the uptake of hydrogen had ceased (18 minutes), the catalyst was removed by filtration and to the filtrate was added 3.9 g. of redistilled *n*-butyraldehyde and 300 mg. of platinum oxide. The mixture was shaken with hydrogen at 45° and 50 p.s.i. until hydrogen uptake ceased (90 minutes). The mixture was filtered and the filtrate was mixed with 5 ml. of concentrated hydrochloric acid and evaporated *in vacuo*. Recrystallization of the residual paste from absolute alcohol-acetone gave a 70% yield of 2-diethylaminoethyl 4-butylamino-2-hydroxybenzoate dihydrochloride as tiny white prisms, m.p. 162–166°.

C.—A mixture of 13.0 g. of pure 3-(1-piperidyl)-propyl 4-amylamino-2-benzyloxybenzoate (*vide infra*), 2.0 g. of 7% palladium chloride on Darco G60 catalyst, 20 ml. of water, 12 ml. of concentrated hydrochloric acid and 120 ml. of alcohol was shaken with hydrogen at 45° and 50 p.s.i. until hydrogen uptake ceased (30 minutes). The catalyst was filtered off and the filtrate was treated with an excess of powdered sodium bicarbonate. The alcohol was removed *in vacuo*, the precipitated oil was taken up in benzene, and the benzene solution, after drying, was evaporated *in vacuo*. The residual 3-(1-piperidyl)-propyl 4-amylamino-2-hydroxybenzoate was then purified as in A, above.

The dialkylaminoalkyl 4-alkylamino-2-hydroxybenzoates prepared by the above methods are listed with their derivatives in Table V.

**Dialkylaminoalkyl 4-Alkylamino-2-benzyloxybenzoates.**—The dialkylaminoalkyl 4-amino-2-benzyloxybenzoates were reductively alkylated with an aldehyde, zinc dust and glacial acetic acid as described for ethyl 4-amino-2-benzyloxybenzoate above. The bases were purified by the method described for the corresponding 2-hydroxy bases above (the crude bases could not be catalytically debenzylated due to catalyst poisoning) and characterized as the flavianates. These are listed in Table VI.

The reaction between 2-benzyloxy-4-butylaminobenzoyl chloride (prepared *in situ* from the acid, pyridine and thionyl chloride at 10°) and a dialkylaminoalkanol gave 30–40% crude yields of the desired products. The compounds when prepared in this manner proved very difficult to purify, and the method was not as desirable as that described above.

**3-Diethylaminopropyl 4-Aminobenzoate Phosphate.**—The 4-amino base was prepared as previously described<sup>14</sup> and converted into the phosphate in absolute alcoholic solution. The product crystallized from alcohol in white needles, m.p. 215.5–217.5°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>25</sub>N<sub>2</sub>O<sub>8</sub>P: N, 8.04; H<sub>3</sub>PO<sub>4</sub>, 28.14. Found: N, 7.88; H<sub>3</sub>PO<sub>4</sub>, 27.81.

(14) Kamm, *ibid.*, **42**, 1031 (1920); v. Braun, Braunsdorf and Rath, *Ber.*, **65**, 1672 (1922).

The picrate formed yellow prisms from alcohol, m.p. 147.0–148.4°.

*Anal.* Calcd. for C<sub>20</sub>H<sub>25</sub>N<sub>5</sub>O<sub>9</sub>: N, 12 5.84. Found: N, 12 5.87.

**3-(1-Piperidyl)-propyl 4-Butylaminobenzoate.**—The reduction of 3-(1-piperidyl)-propyl 4-nitrobenzoate hydrochloride, m.p. 212.0–212.6° (lit.<sup>15</sup> m.p. 206–208°) to the 4-amino base<sup>15</sup> was carried out by means of iron and hydrochloric acid. The phosphate crystallized from alcohol in white prisms, m.p. 191.2–192.3°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>23</sub>N<sub>2</sub>O<sub>8</sub>P: N, 7.77; H<sub>3</sub>PO<sub>4</sub>, 27.20. Found: N, 7.82; H<sub>3</sub>PO<sub>4</sub>, 27.20.

The picrate had m.p. 178.8–180.2°.

*Anal.* Calcd. for C<sub>21</sub>H<sub>26</sub>N<sub>5</sub>O<sub>9</sub>: N, 12 5.70. Found: N, 12 5.68.

Reductive alkylation with zinc dust, acetic acid and *n*-butyraldehyde (*vide supra*) gave the 4-butylamino base in high yield. The monohydrochloride crystallized from absolute alcohol in white prisms, m.p. 179.6–181.7°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>2</sub>: N, 7.87; Cl, 9.99. Found: N, 7.74; Cl, 9.95.

The flavianate crystallized from dilute alcohol in orange needles, m.p. 185.4–186.4°.

*Anal.* Calcd. for C<sub>29</sub>H<sub>36</sub>N<sub>4</sub>O<sub>10</sub>S: S, 5.07. Found: S, 5.01.

**2-Diethylaminoethyl 2-Benzyloxybenzoate.**—The Hörenstein-Pählicke reaction between 2-benzyloxybenzoic acid<sup>6</sup> and 2-diethylaminoethyl chloride in isopropyl alcohol gave a high yield of the hydrochloride, rosettes of white needles from isopropyl alcohol, m.p. 109.0–110.3°.

*Anal.* Calcd. for C<sub>20</sub>H<sub>23</sub>ClNO<sub>3</sub>: C, 66.01; H, 7.20; Cl, 9.74. Found: C, 66.24; H, 7.45; Cl, 9.81.

The picrate crystallized from absolute alcohol in rosettes of cottony yellow needles, m.p. 122.8–123.6°.

*Anal.* Calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>4</sub>O<sub>10</sub>: N, 12 2.52; N, 11 7.56. Found: N, 12 2.65; N, 11 7.70.

**3-Diethylaminopropyl 2-benzyloxybenzoate hydrochloride**, prepared as above, crystallized from isopropyl alcohol in hygroscopic white needles, m.p. 105.4–106.5°.

*Anal.* Calcd. for C<sub>21</sub>H<sub>23</sub>ClNO<sub>3</sub>: C, 66.74; H, 7.47; Cl, 9.38. Found: C, 66.75; H, 7.28; Cl, 9.23.

The picrate formed yellow needles from absolute alcohol, m.p. 102.6–103.6°.

*Anal.* Calcd. for C<sub>27</sub>H<sub>30</sub>N<sub>4</sub>O<sub>10</sub>: N, 12 2.46; N, 11 7.38. Found: N, 12 2.56; N, 11 7.52.

(15) Barnes and Adams, *THIS JOURNAL*, **49**, 1313 (1927); Brill, *ibid.*, **54**, 2484 (1932).

RENSSELAER, N. Y.

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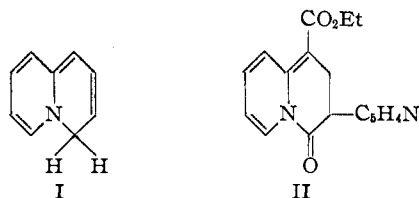
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

## A Study of Some Quinolizone Derivatives

BY V. BOEKELHEIDE AND J. P. LODGE, JR.<sup>1</sup>

The condensation of ethyl 2-pyridylacetate and diethyl ethoxymethylenemalonate has been found to be a convenient reaction for the preparation of quinolizone derivatives. By hydrolysis and decarboxylation, the initial condensation product, 1,3-dicarbethoxy-4-quinolizone, was converted to either 1-carbethoxy-4-quinolizone or 4-quinolizone itself. Incidental to the establishment of structure of 1-carbethoxy-4-quinolizone, a new synthesis of *d,l*-lupinine was accomplished.

As part of a general study of quinolizine (I) and related compounds, we have investigated the use of



(1) Sherman Clarke Fellow, 1949–1950.

ethyl 2-pyridylacetate as starting material for their synthesis. In view of previous successful utilizations of the condensation of ethyl 2-pyridylacetate and ethyl orthoformate for preparing II, an intermediate in the synthesis of *d,l*-sparteine,<sup>2,3,4,5</sup> it

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