nents under the conditions employed in our experiments were 34, 59, 62, 77 and 95 seconds. The component with the shortest retention time is ketobicyclo[2.2.1]heptane, and the other two major products with retention times of 59 and 62 seconds are believed to be the 1-nitro- and 7-nitrobicyclo-[2.2.1]heptanes. The vapor chromatogram showed that these latter two components were present in almost equal concentrations. The retention time for the alkali-soluble 2-nitrobicyclo[2.2.1]heptane under conditions identical to those employed above was 58 seconds. The minor components of the alkali-insoluble product were eluted at retention times of 77 and 95 seconds. In addition to the carbonyl and nitro bands found in the infrared spectrum of this sample a weak doublet at 2.83 and 2.87μ indicated the presence of some hydroxy compound.

Nitration of Decahydronaphthalene.—A 207-g. (1.5 moles) sample of decahydronaphthalene (n^{25}D 1.4694) was charged to a 1-liter stainless steel autoclave, pressured to 300 p.s.i.g. and heated to 120°. At this point 34.5 g. (0.75 mole) of nitrogen dioxide dissolved in 100 ml. of carbon tetrachloride (0–5°) was fed into the reaction zone by means of a Milton Roy feed pump. After a total reaction period of 1 hour (50 minutes feed and 10 minutes cook), the autoclave was cooled to room temperature. The reaction mixture was washed first with 150 ml. of water and then extracted with a 5% sodium hydroxide solution for 18 hours. The alkali-insoluble portion was washed with water and dried over anhydrous magnesium sulfate. Distillation of the dried solution at reduced pressure yielded 122.4 g. (59% recovery) of decahydronaphthalene, b.p. 70° (14 mm.), 32.1 g. of higher-boiling material (n^{25}D 1.4929–1.5010), and a pot residue weighing 16.7 g. The 32.1-g. portion of the distillate was extracted by 130 ml. of 10–15% sodium methoxide for 2.5 hours. The mixture then was diluted with 200 ml. of water, extracted by four 75-ml. portions of diethyl ether, and dried over anhydrous magnesium sulfate. Distillation of the alkali-insoluble material yielded 10 g. of 9-nitrodecahydronaphthalene, b.p. 60–65° (0.2 mm.). This amount of product represents a 9.0% yield based on the amount of decahydronaphthalene consumed. The infrared spectrum of the product coincided with that of 9-nitrodecahydronaphthalene which was reported previously,[14] Also, the refractive index of the product (n^{25}D 1.4925) was in excellent agreement with that reported in the literature.[14–16]

Acknowledgments.—The author wishes to thank Mr. L. J. Lohr for the interpretation of the infrared spectra and the vapor phase chromatographic work, and Prof. J. D. Roberts for supplying infrared spectra of authentic samples of 2-nitronorbornane and norcamphor.

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GIBBSTOWN, N. J.

# α-Hydroxy Amides and Related Compounds

BY SEYMOUR L. SHAPIRO, IRA M. ROSE AND LOUIS FREEDMAN

A series of α-hydroxyamides and the corresponding alkyl carbonate esters of type I have been synthesized and examined for anticonvulsant activity. The best activity has been noted with the N-aralkyl glycolamides. The spectra of I, where R is phenyl and substituted phenyl, have been determined and compared with the analogous acetanilides.

While a wide variety of recent studies of carboxylic acid amides has shown pharmacological activity,[1] there has been relatively little systematic exploration[2] of the amides of α-hydroxy acids. Studies[3] of such amides, and derivatives of these compounds of the type I are herein described.

$$R_2C—C—NR$$

with R₁ above C, O above the double-bond, H above N, and OR₃ below C.
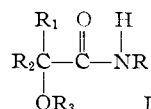
R = alkyl, aralkyl, aryl   R₃ = hydrogen   (H)
R₁, R₂ = H, CH₃, C₆H₅   –COOCH₃   (M)
                          –COOC₂H₅   (E)
                          –COOC₈H₇-n   (P)
                          –COO(CH₂)₂Cl   (CE)
                          –COO(CH₂)₃Cl   (CP)

Interest in the structures I (R₃ = H) was indicated from the noted therapeutic usefulness of the

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(2) (a) H. McIlwain, "Chemotherapy and the Central Nervous System," Little, Brown and Co., Boston, Mass., 1957, p. 67; (b) F. A. Grunwald, U. S. Patent 2,764,613 (Sept. 25, 1956).
(3) For related work see S. L. Shapiro, I. M. Rose and L. Freedman, THIS JOURNAL, **81**, 3083 (1959).

related acetanilides[4] and the potential for conversion of I to substituted oxazolidinediones.[5] In turn, the variant of I employing the carbonate esters (R₃, other than H), was introduced to afford more lipophilic structures of varying hydrolytic stability.[6] In addition, the carbonate esters were required as intermediates for conversion to carbamates.

The compounds prepared have been described in Table I. Some variants of I are detailed in the Experimental section.

Most of the amides (I, R₃=H) were prepared by ammonolysis of the ethyl esters of the α-hydroxy acids (method A).

$$R_1R_2C—C—OC_2H_5$$

with H and O on top, O⁻ adjacent, HNR below (labeled II).
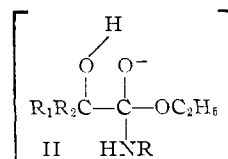
This is a relatively complex reaction, responsive to steric factors and the basicity of the amine, and is promoted by the α-hydroxy group in the acylating

(4) A. Burger, "Medicinal Chemistry," Interscience Publishers, Inc., New York, N. Y., 1951, pp. 196–199.
(5) S. L. Shapiro, I. M. Rose, F. C. Testa, E. Roskin and L. Freedman, THIS JOURNAL, **81**, Dec. 20, (1959).
(6) The order of decreasing hydrolytic stability would be estimated as R₁ = CE, M, E, P; see (a) K. H. Vogel and J. C. Warner, *ibid.*, **75**, 6072 (1953); (b) A. A. Colon, K. H. Vogel, R. B. Carlin and J. C. Warner, *ibid.*, **75**, 6075 (1953).

TABLE I

$$\text{α-HYDROXYAMIDES } R_1R_2\overset{\displaystyle O}{\underset{\displaystyle OR_3}{\overset{\|}{C}}}\overset{\displaystyle H}{\underset{}{\overset{|}{C}}}\text{—NR}$$

$R_3 = H$
M $(COOCH_3)$
E $(COOC_2H_5)$
P $(COOC_3H_7\text{-}n)$
CE $(COOCH_2CH_2Cl)$
CP $(COOCH_2CH_2CH_2Cl)$

No.[a]	R	R₃	M.p.[b] or b.p., °C. (mm.)	RS[c]	Yield,[d] %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
						$R_1 = H, R_2 = H$						
1	C_3H_5-[f]	H	90-110 (0.04)		80	$C_5H_9NO_2$	52.2	52.0	7.9	7.7		
2	C_3H_5-[f]	E	50-51	A	20	$C_8H_{13}NO_4$	51.3	51.4	7.0	6.8		
3[a1]	$C_6H_5CH_2$-	H	103-104	A	89							
4	$C_6H_5CH_2$-	M	101	A	56	$C_{11}H_{13}NO_4$	59.2	59.1	5.9	5.6		
5	$C_6H_5CH_2$-	E	81-82	A	70	$C_{12}H_{15}NO_4$	60.8	70.0	6.4	6.5		
6	$C_6H_5CH_2$-	P	64-66	A	70	$C_{13}H_{17}NO_4$	62.1	62.3	6.8	6.7		
7	$C_6H_5CH_2$-	CE	65-66	A	70	$C_{12}H_{14}ClNO_4$	53.0	53.4	5.2	5.5		
8	$C_6H_5CH_2$-	CP	66-67	A	80	$C_{13}H_{16}ClNO_4$					4.9	5.1
9	$2\text{-}ClC_6H_4CH_2$-	H	133-134	B	89	$C_9H_{10}ClNO_2$	54.2	54.2	5.1	5.0	7.0	6.7
10	$4\text{-}ClC_6H_4CH_2$-	H	140-142	B	79	$C_9H_{10}ClNO_2$	54.2	54.0	5.1	5.1	7.0	7.1
11	$4\text{-}ClC_6H_4CH_2$-	E	105-106	A	92	$C_{12}H_{14}ClNO_4$	53.0	53.1	5.2	5.3	5.2	4.9
12	C_5H_6O-[g]	H	55-56	A	88	$C_7H_9NO_3$	54.2	54.3	5.9	5.8	9.0	8.8
13	C_5H_6O-[g]	E	56-57	A	40	$C_{10}H_{13}NO_5$	52.9	53.7	5.8	5.9		
14	$C_6H_5CHCH_3$-	H	99-101	A	80	$C_{10}H_{13}NO_2$	67.0	67.2	7.3	7.4		
15	$C_6H_5CHCH_3$-	E	76-77	A	61	$C_{13}H_{17}NO_4$	62.1	62.3	6.8	6.8		
16	$C_6H_5CH_2CH_2$-	H	74-75	A	83	$C_{10}H_{13}NO_2$	67.0	67.3	7.3	7.3		
17	$C_6H_5CH_2CH_2$-	M	62-63	A	60	$C_{12}H_{15}NO_4$	60.8	60.9	6.4	6.4		
18	$C_6H_5CH_2CH_2$-	E	67-68	A	63	$C_{13}H_{17}NO_4$	62.1	62.1	6.8	6.8		
19	$C_6H_5CH_2CH_2$-	P	56-57	A	55	$C_{14}H_{19}NO_4$	63.4	63.2	7.2	7.2		
20	$C_6H_5CH_2CH_2$-	CP	66-68	A	71	$C_{13}H_{16}ClNO_4$	54.6	54.5	5.7	5.6		
21	$C_{10}H_{13}O_2$-[h]	H	75-76	A	76	$C_{12}H_{17}NO_4$	60.2	60.5	7.2	7.4		
22	$C_{10}H_{13}O_2$-[h]	E	79-80	A	62	$C_{15}H_{21}NO_6$	57.9	58.3	6.8	7.0		
23	$(C_6H_5)_2CH$-	H	95-98	A	90	$C_{15}H_{15}NO_2$					5.8	5.8
24	$(C_6H_5)_2CH$-	M	146-150	A	63	$C_{17}H_{17}NO_4$	68.2	68.5	5.7	5.8	4.7	4.8
25	$(C_6H_5)_2CH$-	E	122-123	A	75	$C_{18}H_{19}NO_4$	69.0	69.4	6.1	6.2		
26[a2]	C_6H_5-	H	91-92	C	89							
27	C_6H_5-	E	76-77	A	37	$C_{11}H_{13}NO_4$	59.2	59.2	5.9	5.9		
28[a3]	$2\text{-}CH_3C_6H_4$-	H	63-65	D	57							
29	$2\text{-}CH_3C_6H_4$-	E	93	A	79	$C_{12}H_{15}NO_4$	60.8	61.1	6.4	6.2		
30[a4]	$4\text{-}CH_3C_6H_4$-	H	143-145	B	71							
31	$4\text{-}CH_3C_6H_4$-	E	105-106	A	76	$C_{12}H_{15}NO_4$	60.8	61.2	6.4	6.6		
32[a5]	$2,6\text{-}diCH_3C_6H_3$-	H	92-94	A	62	$C_{10}H_{13}NO_2$	67.0	66.9	7.3	7.6	7.8	7.9
33	$2,6\text{-}diCH_3C_6H_3$-	E	129-130	A	88	$C_{13}H_{17}NO_4$	62.1	62.5	6.8	6.9		
34	$4\text{-}FC_6H_4$-	H	92-95	D	38	$C_8H_8FNO_2$					8.3	8.2
35	$4\text{-}FC_6H_4$-	E	99-101	A	76	$C_{11}H_{12}FNO_4$	54.8	54.7	5.0	5.3		
36	$2\text{-}ClC_6H_4$-	H	86-87	A	14	$C_8H_8ClNO_2$	51.8	51.9	4.3	4.5	7.6	7.6
37	$2\text{-}ClC_6H_4$-	E	93-94	A	75	$C_{11}H_{12}ClNO_4$	51.3	51.1	4.7	4.8		
38	$4\text{-}ClC_6H_4$-	H	169-170	B	68	$C_8H_8ClNO_2$	51.8	52.3	4.3	4.4		
39	$4\text{-}ClC_6H_4$-	M	100-101	A	54	$C_{10}H_{10}ClNO_4$	49.3	49.7	4.1	4.0		
40	$4\text{-}ClC_6H_4$-	E	100-101	A	78	$C_{11}H_{12}ClNO_4$	51.3	51.4	4.7	4.8		
41	$4\text{-}ClC_6H_4$-	P	105-106	A	80	$C_{12}H_{14}ClNO_4$	53.0	53.5	5.2	5.1		
42	$4\text{-}ClC_6H_4$-	CE	138	A	82	$C_{11}H_{11}Cl_2NO_4$	45.2	45.6	3.5	3.6		
43	$4\text{-}ClC_6H_4$-	CP	95-96	A	81	$C_{12}H_{13}Cl_2NO_4$	47.1	47.4	4.3	4.4	4.6	4.7
44	$2\text{-}CH_3\text{-}4ClC_6H_3$-	H	88-89	A	44	$C_9H_{10}ClNO_2$	54.2	54.4	5.1	5.0	7.0	7.3
45	$2\text{-}CH_3\text{-}4ClC_6H_3$-	E	130-131	A	93	$C_{12}H_{14}ClNO_4$	53.0	53.0	5.4	5.2		
46[a6]	$4\text{-}BrC_6H_4$-	H	177-178	E	94							
47	$4\text{-}BrC_6H_4$-	E	95-96	A	63	$C_{11}H_{12}BrNO_4$	43.7	43.6	4.0	4.0		
48	$4\text{-}BrC_6H_4$-	CE	110	A	75	$C_{11}H_{11}BrNO_4$	39.3	39.4	3.3	3.1		
49	$4\text{-}BrC_6H_4$-	[i]	166-168	A	34	$C_{13}H_{15}BrN_2O_3$	47.7	47.5	4.6	4.8	8.6	8.8
50	$2\text{-}CH_3OC_6H_4$-	H	107-108	C	51	$C_9H_{11}NO_3$	59.7	60.1	6.1	6.3	7.7	7.8
51	$2\text{-}CH_3OC_6H_4$-	E	59-60	A	96	$C_{12}H_{15}NO_5$	56.9	57.3	6.0	6.3		
52[a7]	$4\text{-}CH_3OC_6H_4$-	H	95-99	C	56							
53	$4\text{-}CH_3OC_6H_4$-	E	83-84	A	76	$C_{12}H_{15}NO_5$	56.9	57.0	6.0	6.0		
54	$2\text{-}C_2H_5OC_6H_4$-	H	80-81	A	35	$C_{10}H_{13}NO_3$	61.5	61.8	6.7	6.8		
55	$2\text{-}C_2H_5OC_6H_4$-	E	65-67	A	81	$C_{13}H_{17}NO_5$					5.2	5.1
56	$3\text{-}C_2H_5OC_6H_4$-	H	84-85	C	41	$C_{10}H_{13}NO_3$	61.5	61.1	6.7	6.7	7.2	7.0
57[a8]	$4\text{-}C_2H_5OC_6H_4$-	H	149-150	B	73							

TABLE I (Continued)

No.[a]	R	R_3	M.p.[b] or b.p., °C. (mm.)	RS[c]	Yield,[d] %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
58	$4\text{-}C_2H_5OC_6H_4\text{-}$	E	105–106	A	90	$C_{13}H_{17}NO_5$	58.4	58.4	6.4	6.5		
59	$4\text{-}HOOCC_6H_4\text{-}$	H	240–241	E	70	$C_9H_9NO_4$	55.4	55.4	4.7	4.5	7.2	7.0
60	$4\text{-}HOOCC_6H_4\text{-}$	M	229–230	B	70	$C_{11}H_{11}NO_6$	52.2	52.1	4.4	4.6	5.5	5.3
61	$4\text{-}HOOCC_6H_4\text{-}$	E	207–209	F	31	$C_{12}H_{13}NO_6$	53.9	54.0	4.9	4.8	5.2	4.9
62	$4\text{-}HOOCC_6H_4\text{-}$	CE	200–203	B	84	$C_{12}H_{12}ClNO_6$	47.8	48.1	4.0	4.3	4.6	4.7
63[a9]	$C_{10}H_7\text{-}^i$	H	126–128	A	44							
64	$C_{10}H_7\text{-}^i$	E	134–135	A	82	$C_{15}H_{15}NO_4$	65.9	66.0	5.5	5.3		
65	^{k}	H	112–118 (0.07)		74	$C_{10}H_{13}NO_2$	67.0	66.7	7.3	7.0	7.8	7.7
66	^{l}	H	184–188	G	45	$C_{17}H_{15}N_2O_4$	65.0	64.8	5.8	5.8	8.9	9.1
67	^{m}	E	182–183	B	96	$C_{23}H_{26}N_2O_8$	60.3	60.1	5.7	5.6	6.1	6.4
68	$(C_2H_5)_2N(CH_2)_2\text{-}$	H	130–134 (0.1)		72	$C_8H_{18}N_2O_2$	55.1	55.1	10.4	10.1	16.1	15.8
69	^{n}	H	89–92 (0.08)		63	$C_7H_{14}N_2O_2$	53.1	53.4	8.9	9.1		
70	^{o}	H	92–93	H	55	$C_8H_{17}N_3O_2$					22.4	21.8
71	2-Pyridyl-	H	133–134	F	17	$C_7H_8N_2O_2$	55.3	55.2	5.3	5.3		

$R_1 = CH_3, R_2 = H$

No.[a]	R	R_3	M.p.[b] or b.p., °C. (mm.)	RS[c]	Yield,[d] %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
72[a10]	$C_3H_5\text{-}^f$	H	98 (0.04)		87							
73	$C_3H_5\text{-}^f$	E	45	D	75	$C_9H_{15}NO_4$	53.7	53.9	7.5	7.5	7.0	6.9
74[a11]	$i\text{-}C_4H_9\text{-}$	H	43–44	D	91							
75	$i\text{-}C_4H_9\text{-}$	E	81	I	43	$C_{10}H_{19}NO_4$	55.3	55.6	8.8	8.6	6.5	6.3
76	$C_8H_{17}\text{-}^p$	H	135 (0.04)		91	$C_{11}H_{23}NO_2$	65.6	65.8	11.5	11.7	7.0	6.9
77	$C_8H_{17}\text{-}^p$	E	110 (0.03)		73	$C_{14}H_{27}NO_4$	61.5	62.1	10.0	9.8	5.1	5.1
78[a12]	$C_6H_{11}\text{-}^q$	H	60	D	50							
79	$C_6H_{11}\text{-}^q$	E	97–98	I	45	$C_{12}H_{21}NO_4$	59.2	59.5	8.7	8.7		
80[a13]	$C_6H_5CH_2\text{-}$	H	47–48	D	61							
81	$C_6H_5CH_2\text{-}$	r	101–103	A	43	$C_{17}H_{18}N_2O_3$	68.4	68.3	6.1	5.9		
82	$C_6H_5CH_2\text{-}$	M	92–93	A	47	$C_{12}H_{15}NO_4$	60.8	60.8	6.4	6.2		
83	$C_6H_5CH_2\text{-}$	E	83–84	A	68	$C_{13}H_{17}NO_4$	62.1	62.0	6.8	6.8		
84	$C_6H_5CH_2\text{-}$	P	66–67	A	53	$C_{14}H_{19}NO_4$	63.4	63.3	7.2	7.2		
85	$C_6H_5CH_2\text{-}$	CE	93–94	A	76	$C_{13}H_{16}ClNO_4$	54.6	54.9	5.7	6.0		
86	$C_6H_5CH_2\text{-}$	CP	78–79	A	78	$C_{14}H_{18}ClNO_4$	56.1	56.3	6.1	6.5		
87	$2\text{-}ClC_6H_4CH_2\text{-}$	H	56–60	A	60	$C_{10}H_{12}ClNO_2$	56.2	56.7	5.7	5.9	6.6	7.0
88	$4\text{-}ClC_6H_4CH_2\text{-}$	H	90–92	A	62	$C_{10}H_{12}ClNO_2$	56.2	55.8	5.7	5.5	6.6	6.9
89	$4\text{-}ClC_6H_4CH_2\text{-}$	E	86–87	A	84	$C_{13}H_{16}ClNO_4$	54.6	54.8	5.7	5.5	4.9	4.8
90[a14]	$C_6H_5CHCH_3\text{-}$	H	94–95	A	65							
92	$C_6H_5CHCH_3\text{-}$	r	135–140	A	57	$C_{18}H_{20}N_2O_3$	69.2	69.5	6.5	6.6	9.0	9.1
93	$C_6H_5CHCH_3\text{-}$	E	97	A	58	$C_{14}H_{19}NO_4$	63.4	63.5	7.2	7.3	5.3	5.1
94[a15]	$C_6H_5CH_2CH_2\text{-}$	H	88–89	A	89							
95	$C_6H_5CH_2CH_2\text{-}$	r	123–124	A	61	$C_{15}H_{20}N_2O_3$	69.2	69.3	6.5	6.5	9.0	9.2
96	$C_6H_5CH_2CH_2\text{-}$	M	100–101	A	75	$C_{13}H_{17}NO_4$	62.1	62.3	6.8	6.7		
97	$C_6H_5CH_2CH_2\text{-}$	E	53	A	43	$C_{14}H_{19}NO_4$	63.4	63.5	7.2	7.3	5.3	5.1
98	$C_6H_5CH_2CH_2\text{-}$	CP	63–64	A	62	$C_{15}H_{20}ClNO_4$	57.4	57.8	6.4	6.7		
99	$C_{10}H_{13}O_2\text{-}^h$	H	69–72	A	80	$C_{15}H_{19}NO_4$	61.6	61.8	7.6	7.7	5.5	5.8
100	$C_{10}H_{13}O_2\text{-}^h$	E	71–72	A	58	$C_{16}H_{23}NO_6$	59.1	59.4	7.1	7.4		
101	$(C_6H_5)_2CH\text{-}$	H	85–86	D	81	$C_{16}H_{17}NO_2$	75.3	75.1	6.7	6.4	5.5	5.8
102	$(C_6H_5)_2CH\text{-}$	E	105–106	A	86	$C_{19}H_{21}NO_4$	69.7	69.9	6.5	6.5		
103[a16]	$C_6H_5\text{-}$	H	56–57	D	54							
104	$C_6H_5\text{-}$	M	100	A	54	$C_{11}H_{13}NO_4$	59.2	59.4	5.9	5.7		
105	$C_6H_5\text{-}$	E	83–84	I	78	$C_{12}H_{15}NO_4$	60.8	61.0	6.4	6.3	5.9	5.9
106[a17]	$2\text{-}CH_3C_6H_4\text{-}$	H	69–72	D	63							
107	$2\text{-}CH_3C_6H_4\text{-}$	E	116–117	A	58	$C_{13}H_{17}NO_4$	62.1	62.1	6.8	7.0		
108	$3\text{-}CH_3C_6H_4\text{-}$	H	130 (0.02)		78	$C_{10}H_{13}NO_2$	67.0	66.6	7.3	7.3	7.8	7.7
109[a18]	$4\text{-}CH_3C_6H_4\text{-}$	H	98–103	A	54							
110	$4\text{-}CH_3C_6H_4\text{-}$	E	110–111	A	77	$C_{13}H_{17}NO_4$	62.1	62.5	6.8	6.8		
111	$2,4\text{-}diCH_3C_6H_3\text{-}$	H	146 (0.05)		90	$C_{11}H_{15}NO_2$	68.4	67.9	7.8	8.1	7.3	7.2
112	$2,4\text{-}diCH_3C_6H_3\text{-}$	E	119–120	A	89	$C_{14}H_{19}NO_4$	63.4	63.2	7.2	7.0		
113	$2,5\text{-}diCH_3C_6H_3\text{-}$	H	150 (0.03)		89	$C_{11}H_{15}NO_2$					7.3	6.9
114	$2,6\text{-}diCH_3C_6H_3\text{-}$	H	139–140	B	62	$C_{11}H_{15}NO_2$	68.4	68.7	7.8	8.0	7.3	7.0
115	$2,6\text{-}diCH_3C_6H_3\text{-}$	E	122–123	A	76	$C_{14}H_{19}NO_4$	63.4	63.9	7.2	7.4		
116	$4\text{-}FC_6H_4\text{-}$	H	85–88	J	24	$C_9H_{10}FNO_2$	59.0	59.0	5.5	5.7	7.7	7.5
117	$4\text{-}FC_6H_4\text{-}$	E	83–84	A	72	$C_{12}H_{14}FNO_4$	56.5	56.4	5.5	5.7		
118	$2\text{-}ClC_6H_4\text{-}$	H	118–134 (0.02)		48	$C_9H_{10}ClNO_2$	54.2	54.2	5.1	5.2	7.0	7.1
119	$2\text{-}ClC_6H_4\text{-}$	E	89–90	I	72	$C_{12}H_{14}ClNO_4$	53.0	53.2	5.2	5.1		

TABLE I (Continued)

No.[a]	R	R₃	M.p.[b] or b.p., °C. (mm.)	RS[c]	Yield,[d] %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
120	4-ClC₆H₄–	H	100–101	A	40	$C_9H_{10}ClNO_2$	54.2	54.1	5.1	5.1	7.0	7.1
121	4-ClC₆H₄–	M	132	A	76	$C_{11}H_{12}ClNO_4$	51.3	51.7	4.7	4.7	5.4	5.3
122	4-ClC₆H₄–	E	101	A	81	$C_{12}H_{14}ClNO_4$	53.0	53.1	5.2	5.4	5.2	5.1
123	4-ClC₆H₄–	P	95–97	A	64	$C_{13}H_{16}ClNO_4$	54.6	54.8	5.7	5.6		
124	4-ClC₆H₄–	CE	93–95	A	74	$C_{12}H_{13}Cl_2NO_4$[e1]	47.1	48.4	4.3	3.6		
125	4-ClC₆H₄–	CP	118–119	A	73	$C_{13}H_{15}Cl_2NO_4$	48.8	48.7	4.7	4.5		
126	4-BrC₆H₄–	H	104–110	E	76	$C_9H_{10}BrNO_2$	44.3	44.6	4.1	4.3	5.7	5.9
127	4-BrC₆H₄–	E	97–100	A	75	$C_{12}H_{14}BrNO_4$	45.6	45.9	4.5	4.1	4.4	4.4
128	2-CH₃OC₆H₄–	H	71–72	J	55	$C_{10}H_{13}NO_3$	61.5	61.9	6.7	6.4		
129	2-CH₃OC₆H₄–	E	65–66	A	70	$C_{13}H_{17}NO_5$	58.4	58.3	6.4	6.1		
130	2,5-diCH₃OC₆H₃–	H	73–77	A	2	$C_{11}H_{15}NO_4$	58.7	58.6	6.7	6.7	6.2	6.5
131[a,19]	4-CH₃OC₆H₄–	H	105–106	A	73							
132	4-CH₃OC₆H₄–	E	102–103	A	81	$C_{13}H_{17}NO_5$	58.4	58.5	6.4	6.2		
133	2-C₂H₅OC₆H₄–	H	64–87	K	65	$C_{11}H_{15}NO_3$	63.1	63.5	7.2	7.1	6.7	6.7
134	2-C₂H₅OC₆H₄–	E	52–53	L	81	$C_{14}H_{19}NO_5$	59.8	59.9	6.8	6.8	5.0	5.3
135	3-C₂H₅OC₆H₄–	H	94–96	K	60	$C_{11}H_{15}NO_3$	63.1	63.1	7.2	7.1	6.7	7.0
136	3-C₂H₅OC₆H₄–	E	98–99	K	80	$C_{14}H_{19}NO_5$	59.8	59.8	6.8	6.8		
137[a,20]	4-C₂H₅OC₆H₄–	H	117–118	A	65							
138	4-C₂H₅OC₆H₄–	E	125–126	K	89	$C_{14}H_{19}NO_5$	59.8	60.0	6.8	6.7		
139	4-HOOCC₆H₄–	H	221–222	E	30	$C_{10}H_{11}NO_4$	57.4	57.2	5.3	5.1		
140	4-NO₂C₆H₄–	H	138–139	E	10	$C_9H_{10}N_2O_4$	51.4	51.6	4.8	4.6	13.3	13.4
141	4-NO₂C₆H₄–	E	73–75	A	90	$C_{12}H_{14}N_2O_6$	51.1	50.6	5.0	4.7	9.9	9.5
142[a,21]	C₁₀H₇–	H	107–108	L	30							
143	[k]	H	112 (0.06)		84	$C_{11}H_{15}NO_2$					7.3	6.8
144	(C₂H₅)₂N(CH₂)₂–	H	118–120 (0.05)		82	$C_9H_{20}N_2O_2$					14.9	14.8
145	[n]	H	94–100 (0.06)		47	$C_8H_{16}N_2O_3$	55.8	55.9	9.4	9.4		
146	[s]	H	204–205	H	77	$C_9H_{19}IN_2O_2$	34.4	34.5	6.1	5.9	8.9	9.0
147	[o]	H	113–115	C	57	$C_9H_{19}N_3O_2$					20.9	21.0
			R₁, R₂ = CH₃									
148	C₆H₁₁–	H	82–83	D	65	$C_{10}H_{19}NO_2$	64.8	65.3	10.3	10.4		
149	C₆H₅CH₂–	H	60–61	D	71	$C_{11}H_{15}NO_2$	68.4	68.3	7.8	8.1		
150	4-ClC₆H₄CH₂–	H	102–103	A	48	$C_{11}H_{14}ClNO_2$	58.0	57.8	6.2	6.3		
151	C₆H₅CHCH₇–	H	67–69	D	40	$C_{12}H_{17}NO_2$	69.5	69.3	8.3	8.2	6.8	6.8
152	C₆H₅CH₂CH₂–	H	102–103	A	63	$C_{12}H_{17}NO_2$	69.5	69.4	8.3	8.1		
153	$C_{10}H_{13}O_2$–[h]	H	80–81	A	50	$C_{14}H_{21}NO_4$	62.9	62.5	7.9	7.8		
154	(C₆H₅)₂CH–	H	137–138	A	29	$C_{17}H_{19}NO_2$	75.8	75.8	7.1	6.7	5.2	5.0
155[a,22]	C₆H₅–	H	132–133	M	30							
156	C₆H₅–	[r]	167–177	A	55	$C_{17}H_{18}N_2O_3$	68.4	68.7	6.1	6.0	9.4	9.3
157[a,23]	2-CH₃C₆H₄–	H	84–85	A	27							
158	3-CH₃C₆H₄–	H	112–113	C	56	$C_{11}H_{15}NO_2$	68.4	68.4	7.8	7.8		
159[a,24]	4-CH₃C₆H₄–	H	132–134	D	54							
160	4-ClC₆H₄–	H	140	E		$C_{10}H_{12}ClNO_2$					6.6	6.4
161	2-CH₃OC₆H₄–	H	91–93	J	44	$C_{11}H_{15}NO_3$	63.1	63.2	7.2	7.0		
162	4-CH₃OC₆H₄–	H	138–140	K	53	$C_{11}H_{15}NO_3$	63.1	63.0	7.2	7.3		
163	2,5-diCH₃OC₆H₃–	H	101–102	N	41	$C_{12}H_{17}NO_4$	60.2	60.5	7.2	7.1	5.9	5.7
164	2-C₂H₅OC₆H₄–	H	118–120	A	36	$C_{12}H_{17}NO_3$	64.6	64.9	7.7	7.8		
165	3-C₂H₅OC₆H₄–	H	103–104	A	35	$C_{12}H_{17}NO_3$	64.6	64.8	7.7	7.8		
166[a,25]	4-C₂H₅OC₆H₄–	H	151–152	A	31							
167	$C_{10}H_7$–[i]	H	162–163	K	8	$C_{13}H_{15}NO_2$	73.3	73.0	6.5	6.5	6.1	6.0
168	(C₂H₅)₂N(CH₂)₂–	H	106–110 (0.25)		81	$C_{10}H_{22}N_2O_2$	59.4	59.2	11.0	10.9	13.9	13.9
169	[o]	H	126–128	H	30	$C_{10}H_{21}N_3O_2$	55.8	56.3	9.8	9.8	19.5	19.9
			R₁ = C₆H₅, R₂ = H									
170	i-C₄H₉–	H	64–65	D	75	$C_{12}H_{17}NO_2$					6.8	6.6
171	C_8H_{17}–[p]	H	163 (0.04)		80	$C_{16}H_{25}NO_2$	73.0	73.2	9.6	9.9	5.3	5.1
172	C_8H_{17}–[p]	E	82–83	I	30	$C_{19}H_{29}NO_4$	68.0	68.3	8.7	8.8	4.1	3.8
173	C₆H₅CH₂–	H	96–98	A	89	$C_{15}H_{15}NO_2$	74.7	75.0	6.3	6.6		
174	C₆H₅CH₂–	E	97–98	A	78	$C_{18}H_{19}NO_4$	69.0	68.7	6.1	6.2		
175	C₆H₅CH₂CH₂–	H	98–99	A	80	$C_{16}H_{17}NO_2$	75.3	75.2	6.7	6.8		
176	C₆H₅CH₂CH₂–	E	87–91	A	94	$C_{19}H_{21}NO_4$	69.7	69.7	6.5	6.4		
177	4-ClC₆H₄–	H	161–164	B	56	$C_{14}H_{12}ClNO_2$	64.2	64.3	4.6	4.7		
178	4-ClC₆H₄–	E	134–135	A	93	$C_{17}H_{16}ClNO_4$	61.2	61.2	4.8	5.2		

a Compounds previously reported: [a1] O. C. Dermer and J. King, *J. Org. Chem.*, **8**, 168 (1943), m.p. 103–104°; [a2] H. K. Iwamoto and deC. Farson, *J. Am. Pharm. Assoc., Sci. Ed.*, **35**, 50 (1946), m.p. 92°; [a3] C. A. Bischoff and P. Walden, *Ann.*, **279**, 45 (1894), m.p. 67°; [a4] *ibid.*, m.p. 143°; [a5] N. Löfgren and I. Fischer, *Svensk Kem. Tidskr.*, **58**, 206 (1946), m.p. 90–91°; [a6] "Beilstein," Vol. XII, p. 648, m.p. 180°; [a7] "Beilstein," Vol. VIII, p. 172, m.p. 101°; [a8] "Beilstein," Vol. XIII, p. 173, m.p. 153°; [a9] "Beilstein," Vol. XII, p. 1246, m.p. 128°; [a10] W. P. Ratchford and C. H. Fisher, *J. Org. Chem.*, **15**, 317 (1950), b.p. 86–87° (0.2 mm.); [a11] *ibid.*, b.p. 104–106° (0.1 mm.), m.p. 42–48°; [a12] *ibid.*, m.p. 60–60.5°; [a13] *ibid.*, m.p. 47.5–48.5°; [a14] M. L. Fein and E. M. Filachione, This Journal, **75**, 2097 (1953), m.p. 92–94°; [a15] *ibid.*, m.p. 86–87°; [a16] ref. a10, m.p. 57–58°; [a17] "Beilstein," Vol. XII, p. 819, m.p. 72°; [a18] "Beilstein," Vol. XII, p. 963, m.p. 102–103°, m.p. 109°; [a19] "Beilstein," Vol. XIII, p. 491, m.p. 106.5°; [a20] "Beilstein," Vol. XIII, p. 491, m.p. 117.5–118°; [a21] "Beilstein," Vol. XII, p. 1246, m.p. 108°; [a22] R. F. Rekker and W. T. Nauta, *Rec. trav. chim.*, **70**, 24 (1951), m.p. 135°; [a23] "Beilstein," Vol. XII, p. 820, m.p. 88°; [a24] "Beilstein," Vol. XII, p. 965, m.p. 132–133°; [a25] "Beilstein," Vol. XIII, p. 493, m.p. 151–152°   *b* Melting points were determined on a Fisher-Johns melting point block and are not corrected.   *c* RS = recrystallizing solvent; A = ethylacetate–hexane; B = ethylacetate; C = ethylacetate–ether; D = ether; E = water; F = ethyl acetate–benzene; G = ethanol; H = acetonitrile; I = hexane; J = ether–hexane; K = ethanol–hexane; L = ethanol–water; M = ethanol–ether; N = benzene–hexane.   *d* Yields are expressed as percentage of recrystallized or distilled product.   *e* Analyses are by Weiler and Strauss, Oxford, England; [e1] not obtained analytically pure.   *f* C_3H_5– is allyl.   *g* C_5H_6O– is furfuryl.   *h* $C_{10}H_{13}O_2$– is 3,4-dimethoxyphenethyl.   *i* R_3 is N,N-tetramethyleneamido-.   *j* $C_{10}H_7$– is α-naphthyl.   *k* –NHR group is replaced by N-methylbenzyl.   *l* Product is the bisamide from methylenedianiline.   *m* Bis-derivative, R_3 = $OCOC_2H_5$, of compound immediately above.   *n* –NHR group is replaced by N-methylpiperazyl.   *o* The amine reacted is β-N-piperazylethylamine. It is likely that the product reflects amidation by the primary amine group.   *p* C_8H_{17}– is 2-ethylhexyl.   *q* C_6H_{11}– is cyclohexyl.   *r* Phenylurethan of compound immediately above.   *s* Methiodide of compound immediately above.

reactant as a result of stabilization of the proposed transition state II by hydrogen bonding.[7] While the formed ethanol catalyzes the reaction,[8] it also lowers the boiling point of the reactant mixture, and it proved desirable to remove it as the reaction proceeded. This permitted higher reaction temperatures and was a convenient index of completion of the reaction.

With the amine *p*-aminobenzoic acid, good results were noted when its basicity was increased[9] by using the sodium salt as the reactant.[10] Some of the amides were obtained through dehydration of the corresponding amine salts by reflux with benzene or xylene (method B),[11,12] or reaction of the amine with lactide or polyglycolide (method C).

The carbonate esters I (R_3, other than H) were prepared by treating the α-hydroxyamide with the alkyl chlorocarbonate in pyridine–acetonitrile. Acetonitrile was a particularly convenient solvent since it solubilized the formed pyridine hydrochloride.

While the carbonate esters were obtained readily for all variants of R_3, the comparable compounds

(7) See S. L. Shapiro, I. M. Rose and L. Freedman, This Journal, **80**, 6065 (1958), for discussion of the amidation reaction.

(8) G. R. Wolf, J. G. Miller and A. R. Day, *ibid.*, **78**, 4372 (1956).

(9) P. H. Bell and R. O. Roblin, Jr., *ibid.*, **64**, 2905 (1942).

(10) C. van der Stelt, A. J. Zwart. Voorspuij and W. T. Nauta, *Arzneimittel-Forsch.*, **4**, 544 (1954).

(11) The mechanism of this type of amidation has not been convincingly rationalized. It is of interest that it is not as dependent on base strength or steric factors in the amine, as the aminolysis of esters.

(12) L. F. Fieser and J. E. Jones, *Org. Syntheses*, **12**, 66 (1950).

from the α-hydroxy isobutyramides did not form, presumably because of the relative inactivity of the *t*-hydroxyl group to the acylation reaction[13] in pyridine.

The carbonate esters were generally solids, and it is of interest that although these compounds were readily responsive to pyrolysis to the oxazolidinediones,[5] a liquid carbonate (Table I, compound 77) could be distilled unchanged.

The ultraviolet absorption spectra of some 70 of the compounds in this series have been compared with those noted for the corresponding acetanilides[14] in Table II.

The spectra permit an assessment of the replacement of hydrogens on the methyl group of acetanilide by a hydroxy group, a hydroxy group and one methyl group, and a hydroxy and two methyl groups, respectively, in the classes of compounds evaluated. Ungnade[14] has shown that replacement of the three hydrogens by three methyl groups (pivalanilide) results in hypo- and hypsochromic effects. ω-Trifluoroacetanilide shows batho- and hypochromic effects. In turn, replacement with one methyl group (propionanilide) yields essentially the same spectrum as acetanilide.

The availability of many of the ethyl carbonate esters of the α-hydroxyamides permitted an assessment of the role of hydroxyl hydrogen, as well as the hydroxy group in the noted spectra.

In general, spectra reported in this series follow trends noted with the acetanilides,[14] but some of the interesting distinctions will be described in more detail.

The structural feature which was of principal interest was the characterization of the hydrogen bonding effects with the α-hydroxyamide.

The structure of acetanilide[15] is planar, and other studies[16,17] have shown that the amide hydrogen in simple amides is *trans* to the carbonyl carbon. These factors suggest the structural model for the α-hydroxy amides as III, R_3 = H.
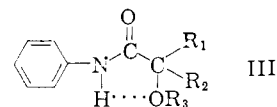
The hydrogen bonding as shown between the amide hydrogen atom and the OR_3 group would require the proper conformation of the groups attached to the acetanilide methyl group.

Ungnade had noted that with selected *o*-substituted acetanilides the acetamino group is twisted out of the plane of the ring with resultant decrease in absorption intensity and hypochromic shifts.

In Table II the carbonate esters of the *o*-substituted anilides of the α-hydroxy acids show virtually the same spectra as the acetanilides (see 2-CH_3–, 2-Cl–, 2-CH_3O–), while the α-hydroxy-

(13) (a) J. A. Campbell, *J. Org. Chem.*, **22**, 1259 (1957); (b) K. B. Wiberg and T. M. Shryne, This Journal, **77**, 2774 (1955); (c) S. Nakanishi, T. C. Myers and E. V. Jensen, *ibid.*, **77**, 5033 (1955); (d) J. L. Hales, J. I. Jones and W. Kynaston, *J. Chem. Soc.*, 618 (1957); (e) H. K. Hall, Jr., This Journal, **79**, 5439 (1957); (f) W. Gerrard and F. Schild, *Chemistry & Industry*, 1232 (1954).

(14) H. E. Ungnade, This Journal, **76**, 5133 (1954).

(15) C. J. Brown and D. E. C. Corbridge, *Acta Cryst.*, **7**, 711 (1954).

(16) J. E. Worsham, Jr., and M. E. Hobbs, This Journal, **76**, 206 (1954).

(17) A. Kotera, S. Shibata and K. Sone, *ibid.*, **77**, 6183 (1955).
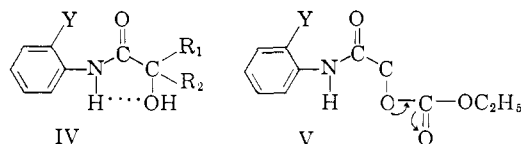
TABLE II

ULTRAVIOLET ABSORPTION SPECTRA[a]

$$R_1\underset{OR_3}{\overset{R_2}{C}}-\overset{O}{C}-\overset{H}{N}-\!\!\!\!\bigcirc\!\!\!-Y$$

R₃[b]	Y	R₁, R₂ = H λmax, mμ	ε × 10⁻³	R₁ = CH₃, R₂ = H λmax, mμ	ε × 10⁻³	R₁, R₂ = CH₃ λmax, mμ	ε × 10⁻³	λmax,[c] mμ	ε × 10⁻³
H	H	241	13.2	241	12.9	241	13.4	242	14.4
E	H	240	13.9	242	13.7				
H	2-CH₃-	235	7.4	237	7.8			230	6.3
E	2-CH₃-	229	6.3	227	6.5				
H	3-CH₃-			243	13.0	245	13.7	245	14.0
H	4-CH₃-	244	14.1	243	14.4	243	15.0	245	14.85
E	4-CH₃-	241	14.5	245	14.9				
H	2,4-di-CH₃-			238	7.5				
E	2,4-di-CH₃-			225[d]	7.3				
H	2,5-di-CH₃-			241	8.1				
H	2,6-di-CH₃-	[e]		[e]					
H	4-F	238	12.4	237	13.0			240	13.1
E	4-F	238	12.4	239	12.7				
H	2-Cl	243	12.6	244	12.7			240	10.4
E	2-Cl	240	10.6	238	8.8				
H	4-Cl	247	18.2	247	17.8			249	17.8
M	4-Cl	247	17.8						
E	4-Cl	247	18.5						
P	4-Cl	247	18.5						
CE	4-Cl	247	19.7						
CP	4-Cl	247	19.0						
H	4-Br	250	19.0	250	20.6			252	18.7
E	4-Br	251	20.8	250	18.8				
H	2-CH₃O-	245	13.0	245	13.2	245	14.4	244	10.4
		282	5.1	282	5.5	282	5.7	280	4.55
E	2-CH₃O-			244	11.5				
				282	5.5				
H	4-CH₃O-	248	14.8	249	14.6	249	13.9	249	14.9
E	4-CH₃O-	244	13.0	249	14.9				
H	2-C₂H₅O-	243	14.4	245	13.9	244	15.0		
		282	5.4	282	4.7	283	5.9		
E	2-C₂H₅O-	244	11.9	244	11.7				
		282	5.1	283	5.1				
H	3-C₂H₅O-	244	11.7	245	11.0	244	11.9	245	11.7[f]
		280	3.3	281	3.0	281	3.6	280	3.1[f]
E	3-C₂H₅O-			245	11.1				
				281	3.2				
H	4-C₂H₅O-	249	13.7	249	16.0	249	14.3		
E	4-C₂H₅O-	250	15.1	251	15.4				
H	4-HOOC-	265	21.2	267	21.9			270	21.2
H	4-NO₂			310	13.4			316	11.4

[a] The spectra were determined in methanol and were established using a Beckman recording spectrophotometer, model DK. The following spectra were established for comparison compounds (name, λmax, mμ (methanol), ε × 10⁻³, respectively); formanilide, 242, 13.3; o-chloroformanilide, 243, 12.2; propionanilide, 243, 14.1. [b] The abbreviations for R₃ have been detailed in Table I. [c] The spectra (ethanol) for the corresponding acetanilides have been drawn from ref. 14 and are shown in the Table to permit more ready comparison. [d] Shoulder. [e] Non-specific absorption only. [f] The data shown for comparison are for m-methoxyacetanilide from ref. 14.

acetanilides each reflect a spectral pattern which is bathochromic, and hyperchromic relative to the acetanilide, with the order of this effect being CH₃– > Cl– > CH₃O–. In turn, with the 2,6-dimethyl-aniline derivative, only non-specific absorption is obtained.

These observations suggest that in the absence of a stabilizing influence the spectra reflect some measure of free rotation[16] about the nitrogen with accompanying interaction between the amido hydrogen and the o-substituent. This is the case with the acetanilides and the carbonate esters in this series. Alternatively, with the α-hydroxy anilides, conformational stabilization through hydrogen bonding on the side opposite to that of the o-substituent as shown (IV) would account for the noted effects. The alternate possibility for a hy-

drogen-bonded form involving juncture of the hydroxyl hydrogen to the electron pair of the nitrogen would be reflected by spectra which would show

considerably less benzenoid character, and is unlikely.

When the hydroxyl group is derivatized to form the carbonate esters, the electron density on the hydroxy oxygen is decreased through forms such as V and hydrogen bonding as shown for IV apparently does not make significant contributions in V.[18]

Forbes and Sheratte[19] have questioned Ungnade's[14] contention that the o-methoxy substituent contributes no steric effect in the spectra of the acetanilides. Our data with o-methoxy and o-ethoxy substituents are in agreement with Forbes' position in that steric effects are noted with compounds of the type V, although not with those of the preferred orientation of type IV.

However, the fact that order of stabilization $(\Delta\lambda_{max}[\alpha$-hydroxyacetanilide $-$ acetanilide]) is $CH_3 > Cl > -OCH_3$ would suggest some measure of contribution from forms for V similar to those proposed by Ungnade, which are shown as VI.
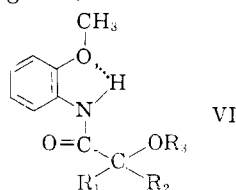
These data with the o-substituents tend to emphasize the relative hypochromicity of the m-alkoxy substituents in this series and in spectra tabulated by others.[14,19] This is emphasized in that the secondary band (at about 282 mμ) for the m-alkoxy derivatives is also more hypochromic than the secondary band of the corresponding o-alkoxy compounds. Since m-alkoxy substituents have positive σ-values in contrast to the strongly negative σ-values of p-alkoxy derivatives,[20] the noted spectral effects with the m-alkoxy derivatives in this series may be a result of drainage of ring electron density by these groups through the inductive effect with consequent lesser population of resonance forms contributing to the extinction coefficient.

No clear-cut effects could be ascribed to variations of R_1 and R_2 as hydrogen and/or methyl[21] within the compounds of this series, and the compounds V (Y = H) paralleled the spectrum of trimethylacetanilide.[14]

Pharmacology.—Almost all of the compounds described in Table I were evaluated for their anticonvulsant action in mice and the results have been described in Table III.

With respect to the anticonvulsant effect, some interesting generalizations may be made relating structure to activity. Of the carbonate esters

(18) Evidence for this effect based on pharmacological data has been reported by S. L. Shapiro, I. M. Rose and L. Freedman, THIS JOURNAL, **80**, 6065 (1958).

(19) W. F. Forbes and M. B. Sheratte, Can. J. Chem., **33**, 1829 (1955).

(20) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 188.

(21) A. P. de Jonge and W. den Hertog, Rec. trav. chim., **75**, 85 (1956), in a study of ultraviolet absorption spectra of fatty acid anilides have indicated that the only branched-chain acid anilide studied, isovaleranilide, had little influence on the spectra relative to that observed with the straight-chain anilides.

TABLE III

PHARMACOLOGICAL ACTIVITY OF COMPOUNDS

4+ anticonvulsant activity[a,d]	3/500, 5/200, 9/250, 11/300, 16/750, 20/350, 39/225, 89/400, 152/750
3+ anticonvulsant activity[a]	25/100, 34/800, 72/250, 94/750, 111/850, 113/800, 127/150, 149/300, 162/225, 170/150
Potentiation of Evipal sleeping time[b]	3, 9, 16, 18
Reduction in motor activity[c]	70/>1000/18%/10; 94/750/26%/ 100; 120/450/23%/100

[a] For method of testing see S. L. Shapiro, I. M. Rose, E. Roskin and L. Freedman, THIS JOURNAL, **80**, 1648 (1958); also, S. L. Shapiro, V. A. Parrino and L. Freedman, ibid., **81**, 3996 (1959). The data record Table I compound number/LD_{min} in mg./kg. [b] The method of testing is described in footnote a. The compounds listed showed 50–100% potentiation of the Evipal sleeping time when evaluated at $^1/_3$ of the LD_{min}. [c] For method of testing see footnote a. The data record compound number/LD_{min} mg./kg./% reduction in motor activity/test dose (subcutaneous) in mg./kg. [d] The known anticonvulsants phenobarbital and trimethadione show 4+ activity in this test.

showing a good response (compounds 5, 20, 25, 127), 5 and 20 are relatable to active hydroxyamides 3 and 16, respectively. Among the hydroxyamides, all the 4+ compounds were derived from aralkylamides but one (compound 39). With the substituted anilides, the following substituents in the ring were associated with good to moderate activity: halogen (compounds 34, 39, 127), dimethyl (compounds 111, 113) and methoxy (compound 162). The R_1, R_2 variants showed the following number of active compounds: R_1, R_2 = H, 9; R_1 = CH_3, R_2 = H, 6; R_1, R_2 = CH_3, 3; R_1 = C_6H_5, R_2 = H, 1.

In this series it appears that the best results are to be found with N-aralkyl glycolamides.

Experimental[22]

Preparation of Amides (Method A).—A mixture of 0.1 mole of amine and 0.105 mole of the ethyl ester of the α-hydroxy acid was heated until the internal temperature of the refluxing mixture had dropped approximately 20–30°. The formed ethanol was removed and measured. If the quantity of ethanol collected did not approach theoretical, reflux and removal of formed ethanol was repeated. The residue was recrystallized or distilled to yield the product.

Method B.—A mixture of 0.1 mole of 70% glycolic acid (or 85% lactic acid), 0.11 mole of amine and 50 ml. of benzene (or xylene) was vigorously stirred and heated under reflux in a Dean–Stark apparatus until the theoretical water of reaction had been obtained. The benzene solution was filtered (charcoal), the benzene removed and the residue dissolved in chloroform. Following a washing with dilute hydrochloric acid and water, the chloroform was removed and the product recrystallized or distilled.

The following compounds in Table I were prepared using this procedure: 21, 28, 30, 34, 36, 38, 44, 50, 52, 54, 56, 57, 63, 118 and 140.

Method C.—A mixture of 0.1 mole of lactide (or polyglycolide) and 0.15 mole of amine was maintained at 200–210° for 18 hours. When cool, the residue was processed as for method B to give the product.

These compounds were prepared by this method: 32, 111, 113, 114 and 116. Compound 16 was prepared using this procedure in 86% yield, m.p. 74–76°.

p-Carboxyglycolanilide (Compound 59).—A mixture of 80 g. (0.50 mole) of sodium p-aminobenzoate and 97 g. (excess) of ethyl glycolate was heated for 20 hours in an oil-bath maintained at 110°. When cool, after trituration with 500 ml. of acetone, there was obtained 92 g. (85%) of the sodium salt of the product. To obtain the free acid, 44 g. of the sodium salt was dissolved in 750 ml. of boiling water, 15 ml.

(22) Descriptive data shown in the table are not herein reproduced.

of concentrated hydrochloric acid was added, and the product crystallized; 31 g. (66%), m.p. 242–243°.

Compound 139 was obtained in a similar manner.

p-Bromoglycolanilide (Compound 46).—A solution of 10.0 g. (0.066 mole) of glycolanilide (compound 26) in 125 ml. of water was maintained at 70° while treated under vigorous stirring with bromine water until a slight excess of bromine remained. The excess bromine was removed with sodium bisulfite and the product separated: 14.3 g. (94%), m.p. 169–171°.

Compound 126 was prepared in a similar manner.

N-β-Phenethyl-*dl*-pantoamide was prepared by the method of Shive and Snell,[23] in 82% yield, m.p. 92–93° (ethyl acetate–hexane).

N-Benzyl-*dl*-pantoamide was prepared in the same manner in 74% yield, m.p. 79–81° (ethyl acetate–hexane).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.1. Found: C, 66.2; H, 7.9.

N-Isobutyl-γ-hydroxybutyramide.—A solution of 20 g. (0.232 mole) of γ-butyrolactone and 20 g. (0.273 mole) of isobutylamine was heated slowly to 95–100° and maintained at that temperature for 3 hours. Volatiles were removed at 100° (0.2 mm.). The yield of residue was 36.5 g. (100%) and the *p*H of an aqueous solution was about 5. There were indications that the material decomposes on distillation and the analysis was run on the residue.

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.4; H, 10.8; N, 8.8. Found: C, 60.2; H, 10.9; N, 8.7.

N-Isobutyl-γ-hydroxyvaleramide was prepared as above using γ-valerolactone.

(23) W. Shive and E. E. Snell, *J. Biol. Chem.*, **160**, 287 (1945); m.p. 90–91°.

Anal. Calcd. for $C_9H_{19}NO_2$: C, 62.4; H, 11.1; N, 8.1. Found: C, 62.7; H, 11.4; N, 7.9.

Carbonate Esters of α-Hydroxyamides (General Procedure).—To a solution of 0.1 mole of the α-hydroxyamide in 10 ml. of pyridine and 60 ml. of acetonitrile, 0.11 mole of the alkyl (or haloalkyl) chloroformate was added slowly with continued stirring, and cooling (below 15°). After storage at 20° for 2 hours, the reaction mixture was transferred to an open dish and the volatiles evaporated. The solid residue was triturated with dilute hydrochloric acid, then water, filtered, dried and recrystallized.

Under these reaction conditions the attempted preparation of carbonate esters of the α-hydroxy-isobutyramides failed and the reactant amide was recovered.

N,N-Tetramethylenecarbamate of *p*-Bromoglycolanilide (Compound 49).—To 1.0 g. (0.003 mole) of compound 48 in 10 ml. of acetone was added 1.0 ml. of pyrrolidine and the slowly darkening solution stored at 20° for 20 hours. The acetone was removed, the residue was dissolved in benzene and washed with dilute hydrochloric acid, then water. The benzene solution was filtered (charcoal), the benzene removed, and the residue, granulated under hexane, gave 0.75 g. of product which was recrystallized.

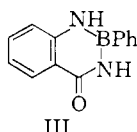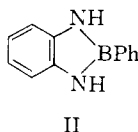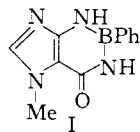
COMMUNICATIONS TO THE EDITOR

A BORON-CONTAINING PURINE ANALOG

Sir:

The preparation of boron compounds which might be of use in the treatment of cancer is of current interest.[1] An obvious class of such compounds would be purine analogs containing boron in the ring. We wish to report the first preparation of such a compound (I).

The possibility of preparing stable compounds of this type was indicated by recent syntheses of heterocyclic boron compounds, in particular (II), which seemed to show aromatic properties.[2] In an extension of this work we first prepared the quinazolone analog (III) from *o*-aminobenzamide, either with phenylboron dichloride in benzene (20% yield), or by heating with dibutyl phenylboronate and removing butanol (63% yield). (III) crystallized from benzene in small plates, m.p. 210–211°. *Anal.* Calcd. for $C_{13}H_{11}N_2OB$: C, 70.27; H, 4.95; N, 12.61; B, 5.0; mol. wt., 222. Found: C, 70.22; H, 4.86; N, 12.68; B, 5.1; mol. wt., 213. Solutions of (III) in ethanol showed an ultraviolet spectrum with peaks at 260 mμ (log ε, 3.84) and 314 mμ (log ε, 3.4). The infrared spectrum of the solid

(1) E. Nyilas and A. H. Soloway, THIS JOURNAL, **81**, 2681 (1959).

(2) M. J. S. Dewar, V. P. Kubba and R. Pettit, *J. Chem. Soc.*, 3076 (1958).

showed the presence of a CO group, but not OH, supporting the lactam formulation (III). The alcoholic solution of (III) was not stable; after a few hours the ultraviolet spectrum became identical with that of a mixture of *o*-aminobenzamide and phenylboronic anhydride.

Analogous condensation of 4-amino-1-methyl-5-imidazolecarboxamide[3] with dibutyl phenylboronate gave a solid (62% yield) which appeared to be the purine analog (I). It crystallized with difficulty from ethanol and sublimed without melting at *ca.* 300°. *Anal.* Calcd. for $C_{11}H_{11}N_4OB$: C, 58.41; H, 4.87; N, 24.78; B, 4.9. Found: C, 58.40; H, 4.78; N, 24.66; B, 4.9. Owing to the insolubility of the compound its molecular weight could not be determined. For the same reason the ultraviolet spectrum could be studied only in alcohol, where under all conditions it was identical with that of an equimolecular mixture of the imidazolecarboxamide and phenylboronic anhydride. The structure of (I) is established by its method of preparation, analogy with (III), analysis, and infrared spectrum (different from that of a mixture of the imidazolecarboxamide and phenylboronic anhydride, notably in the loss of the NH_2 and BO bands).

The solvolysis of (I) is reversible. On mixing concentrated alcoholic solutions of the imidazole carboxamide and phenylboronic anhydride (effectively diethyl phenylboronate), (I) crystallized in 97% yield. This novel synthesis was extended to (II) (35% yield) and (III) (82% yield).

(3) J. Sarasin and W. E. Wegmann, *Helv. Chim. Acta*, **7**, 713 (1924).