These findings show that the absence of a depression of the pK' of the pyridine N does not establish the absence of bonding to the 3-phenolic group. The results do not mean, however, that the earlier conclusion as to the nature of M(pyridoxylidenevaline)$_2$, where M is Mn(II), Ni(II), Fe(II) or Zn(II), must be modified. The first 3, being hexacovalent, could form a link of predominantly ionic character to the phenolic oxygen without the presence of the link being betrayed by a low pK for the pyridine N. Such a linkage is unlikely, however, because these metals are already rendered neutral by the electrons received from the carboxylic oxygen. For zinc such bonding is particularly unlikely.

One of the strongest implications of a metal in a B_6-enzyme action has been found for a decarboxylation, namely of histidine.[7] If metals do participate and if we cannot anticipate that the phenolic oxygen will compete successfully with the α-carboxyl group for chelation to the metal, we must look to other groups to do so, since decarboxylation can hardly be expected for a carboxyl group involved in a 5-membered chelate ring. In this connection, apparently only amino acids having a third functional group are decarboxylated by B_6 enzymes. In histidine and aspartate, effective competition for chelation by the β-functional group with the α-carboxyl group may be anticipated. In the enzymatic reaction the hydrogen ion as a "chelator" might largely avoid this problem. Conceivably groups on the protein molecule could also help to release the α-carboxyl group from a chelate ring.

(7) B. M. Guirard and E. E. Snell, THIS JOURNAL, **76**, 4745 (1954).

The Cu chelate of the Schiff-base formed between pyridoxamine and pyruvate titrates with NaOH at about pH 6.3 in crude determinations eventually complicated by precipitation. Apparently the double bond does not need to lie inside the fused ring system to obtain a large downward shift of the pK (although understandably this chelate is much less stable, and also suffers spectral changes[8] that we find are due to extensive transamination, Cu-catalyzed autoöxidation of pyridoxamine to pyridoxal[9] and other reactions). Instead, the acidity of the imine N appears to determine how the Cu ion influences the acidity of the pyridine N. That is, an appropriate metal atom transfers the quality of acidity from the imine N to the pyridine N. Metals that show little of this effect are nevertheless catalytically quite effective in non-enzymatic transaminations.

Cell Permeability to Pyridoxylvaline, Pyridoxylglycine and 5-Phosphopyridoxylglycine.—These reduction products might be expected to have molecular shapes rather like those of the Schiff bases. Accordingly, Mr. Gene Sellers in this Laboratory, determined whether they enter Ehrlich ascites tumor cells readily, measuring their concentration in metaphosphoric acid extracts of cells by the absorbancy at 295 mμ. A positive finding might have important biological implications. As anticipated, however, these highly charged substances failed to enter the water of the cells to any significant extent during one hour at 37°.

(8) G. L. Eichhorn and J. W. Dawes, *ibid.*, **76**, 5663 (1954).
(9) D. E. Metzler and E. E. Snell, *ibid.*, **74**, 979 (1952).

[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES, U. S. VITAMIN & PHARMACEUTICAL CORP.]

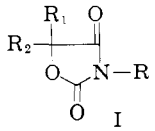
N-Substituted Oxazolidinediones

BY SEYMOUR L. SHAPIRO, IRA M. ROSE, FRANK C. TESTA, ERIC ROSKIN AND LOUIS FREEDMAN

RECEIVED MAY 21, 1959

A series of oxazolidine diones has been synthesized and examined for anticonvulsant activity, ultraviolet absorption characteristics and behavior upon alkaline hydrolysis.

Our investigations of oxazolidinediones with pharmacological activity[1] are herein extended to compounds of the type I. Such compounds and



R_1, R_2 = H, methyl, phenyl
R = alkyl, cycloalkyl, aralkyl, aryl

I

closely related systems have been inspected by others[2-7] and their synthesis has been reviewed.[8-10]

(1) (a) S. L. Shapiro, I. M. Rose, E. Roskin and L. Freedman, THIS JOURNAL, **80**, 1648 (1958); (b) **81**, 386 (1959); (c) S. L. Shapiro, I. M. Rose and L. Freedman, **81**, 3083 (1959); (d) S. L. Shapiro, I. M. Rose, F. C. Testa and L. Freedman, *ibid.*, **81**, 5646 (1959).
(2) M. A. Spielman, *ibid.*, **66**, 1244 (1944).
(3) M. A. Spielman and G. M. Everett, *ibid.*, **70**, 1021 (1948).
(4) F. Testa and R. Ettore, *Arch. Pharm.*, **290** [62], 532 (1957).
(5) C. A. Miller and L. M. Long, THIS JOURNAL, **73**, 4895 (1951), (succinimides).
(6) S. R. Safir and R. J. Lopresti, *ibid.*, **80**, 4921 (1958), (1,2,4-oxadiazolidinones).
(7) C. Chu and P. C. Teague, *J. Org. Chem.*, **23**, 1578 (1958), (hydantoins).

An extensive series of compounds of the type I was needed for consideration of the effect of structural variation on anticonvulsant activity, ultraviolet absorption spectra, and the pattern of alkaline hydrolysis of I to carbamoyloxyacids and α-hydroxyamides.

The compounds prepared have been described in Table I.

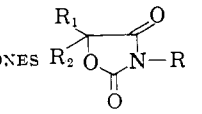
Synthesis.—To achieve the desired synthetic scope, the more familiar procedures involving reaction of I, R = H, with halides[9] or utilization of RNCO[8] as an initial reactant were not attractive, and a variety of other methods was evaluated.

The pyrolysis of carbonate esters of α-hydroxyamides[11] (method 1) proved to be a straightforward and effective procedure for obtaining I.

(8) R. F. Rekker, Thesis, University of Amsterdam, 1950.
(9) J. W. Clark-Lewis, *Chem. Revs.*, **58**, 63 (1958).
(10) R. C. Elderfield, "Heterocyclic Compounds," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 411.
(11) S. L. Shapiro, I. M. Rose and L. Freedman, THIS JOURNAL, **81**, 6322 (1959).

TABLE I

OXAZOLIDINEDIONES



No.[a]	R	Method[b]	M.p.,[c] or b.p., °C. (mm.)	RS[d]	Yield,[e] %	Formula	Analyses,[f] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					R_1, R_2 = H							
1	C_3H_5–[g]	2	120–124 (8)	A	30	$C_6H_7NO_3$	51.1	51.2	5.0	4.8	9.9	10.1
2[a1]	$C_6H_5CH_2$–	2	54–55	B	40	$C_{10}H_9NO_3$	62.8	63.2	4.7	4.9	7.3	6.9
3	4-$ClC_6H_4CH_2$–	1	81–82	A	77	$C_{10}H_8ClNO_3$	53.2	53.2	3.6	3.7		
4	C_5H_6O–[h]	2	61–62	A	29	$C_8H_7NO_4$	53.0	53.3	3.9	3.8	7.7	7.4
5	$C_6H_5CHCH_3$–	2	115–120 (0.02)		58	$C_{11}H_{11}NO_3$	64.4	64.2	5.4	5.5	6.8	6.7
6	$C_6H_5CH_2CH_2$–	2	114	A	59	$C_{11}H_{11}NO_3$	64.4	64.8	5.4	5.4		
7	$C_{10}H_{13}O_2$–[i]	7	98–99	A	52	$C_{13}H_{15}NO_5$	58.9	59.3	5.7	6.0	5.3	5.3
8	$(C_6H_5)_2CH$–	3	128–129	A	43	$C_{16}H_{13}NO_3$	71.9	72.1	4.9	5.2	5.2	5.1
9[a2]	C_6H_5–	2	120–121	A	5	$C_9H_7NO_3$	61.0	61.1	4.0	3.7	7.9	8.1
10	2-$CH_3C_6H_4$–	1	99–101	A	54	$C_{10}H_9NO_3$	62.8	62.9	4.8	4.9	7.3	7.3
11	4-$CH_3C_6H_4$–	1	133–134	A	71	$C_{11}H_{11}NO_3$	64.4	64.3	5.4	5.3		
12	4-FC_6H_4–	1	142–143	A	62	$C_9H_6FNO_3$	55.4	55.6	3.1	3.3		
13	2-ClC_6H_4–	1	98–99	A	42	$C_9H_6ClNO_3$	51.1	50.9	2.9	2.8	6.6	6.5
14	4-ClC_6H_4–	1	138	A	67	$C_9H_6ClNO_3$	51.1	51.4	2.9	2.7	6.6	6.6
15	2-CH_3-4-ClC_6H_3–	1	145–146	A	53	$C_{10}H_8ClNO_3$					6.2	6.4
16	2-$CH_3OC_6H_4$–	1	134–137	A	11	$C_{10}H_9NO_4$	58.0	57.5	4.4	4.6		
17	4-$CH_3OC_6H_4$–	1	153–154	A	78	$C_{10}H_9NO_4$	58.0	58.1	4.4	4.3		
18	2-$C_2H_5OC_6H_4$–	1	126–127	A	43	$C_{11}H_{11}NO_4$	59.7	59.4	5.0	5.4	6.3	6.4
19	4-$HOOCC_6H_4$–	[j]	260–262	C		$C_{10}H_7NO_5$	54.3	54.0	3.2	3.2	6.3	6.2
20	$C_6H_4CH_2C_6H_4$–	1[j]	184–185	A	20	$C_{21}H_{20}N_2O_7$	61.2	60.8	4.9	4.3	6.8	6.9
					R_1 = CH_3, R_2 = H							
21[a3]	C_3H_5–[g]	3	125 (15)		50	$C_7H_9NO_3$	54.2	54.1	5.9	6.4	9.0	9.1
22	*i*-C_4H_9–	2	140 (33)		79	$C_8H_{13}NO_3$	56.1	55.8	7.7	7.7	8.2	8.3
23	C_8H_{17}–[k]	2	139–164 (0.03)		57	$C_{12}H_{21}NO_3$	63.4	63.4	9.3	9.7		
24	C_6H_{11}–[l]	1	60–61	D	46	$C_{10}H_{15}NO_3$	60.9	61.5	7.7	7.7	7.1	6.9
25[a4]	$C_6H_5CH_2$–	1	73–75	A	25	$C_{11}H_{11}NO_3$	64.4	64.4	5.4	5.2		
26	4-$ClC_6H_4CH_2$–	1	69–70	A	53	$C_{11}H_{10}ClNO_3$	55.1	55.2	4.2	4.0	5.9	5.8
27	$C_6H_5CHCH_3$–	7	94–98 (0.08)		76	$C_{12}H_{13}NO_3$	65.7	65.8	6.0	6.5	6.4	6.7
28	$C_6H_5CH_2CH_2$–	7	100–106 (0.08)		82	$C_{12}H_{13}NO_3$	65.7	66.2	6.0	6.0	6.4	6.0
29	$C_{10}H_{13}O_2$–[i]	7	111–113	A	62	$C_{14}H_{17}NO_5$	60.2	60.8	6.1	6.1		
30	$(C_6H_5)_2CH$–	1	86–87	E	5	$C_{17}H_{15}NO_3$	72.6	72.5	5.4	5.6	5.0	5.1
31[a5]	C_6H_5–	1	144–145	A	70	$C_{10}H_9NO_3$	62.8	63.0	4.7	5.0	7.3	7.0
32	2-$CH_3C_6H_4$–	1	103–104	A	71	$C_{11}H_{11}NO_3$	64.4	64.3	5.4	5.3	6.8	6.5
33	4-$CH_3C_6H_4$–	1	160–162	A	50	$C_{11}H_{11}NO_3$	64.4	64.5	5.4	5.5		
34	2,4-di$CH_3C_6H_3$–	1	100–110 (0.05)		86	$C_{12}H_{13}NO_3$					6.4	6.2
35	4-FC_6H_4–	1	137	A	60	$C_{10}H_8FNO_3$	57.4	57.3	3.9	3.8	6.7	7.1
36	2-ClC_6H_4–	1	85–87	A	51	$C_{10}H_8ClNO_3$	53.2	52.8	3.6	3.5	6.2	6.5
37	4-ClC_6H_4–	1	177–178	A	81	$C_{10}H_8ClNO_3$	53.2	52.8	3.6	3.5	6.2	6.3
38	4-BrC_6H_4–	1	182–183	A	54	$C_{10}H_8BrNO_3$	44.5	44.4	3.0	3.1		
39	2-$CH_3OC_6H_4$–	1	84–86	E	48	$C_{11}H_{11}NO_4$	59.7	60.1	5.0	5.6	6.3	6.2
40	4-$CH_3OC_6H_4$–	1	139	C	74	$C_{11}H_{11}NO_4$	59.7	59.8	5.0	5.2		
41	2-$C_2H_5OC_6H_4$–	1	99–100	A	63	$C_{12}H_{13}NO_4$	61.3	61.3	5.6	5.2	6.0	6.0
42	3-$C_2H_5OC_6H_4$–	1	93–100	A	60	$C_{12}H_{13}NO_4$	61.3	61.1	5.6	5.8		
43	4-$C_2H_5OC_6H_4$–	1	109–110	A	60	$C_{12}H_{13}NO_4$	61.3	61.1	5.6	5.8		
44	4-$NO_2C_6H_4$–	1	151–152	A	55	$C_{10}H_8N_2O_5$	50.9	50.8	3.4	3.2	11.9	12.2
					R_1, R_2 = CH_3							
45	C_6H_{11}–[l]	5	76–77	D	60	$C_{11}H_{17}NO_3$	62.5	62.9	8.1	8.0		
46	$C_6H_5CH_2$–	2	58–59	E	69	$C_{12}H_{13}NO_3$	65.7	65.5	6.0	5.9		
47	4-$ClC_6H_4CH_2$–	2	79–80	E	63	$C_{12}H_{12}ClNO_3$	56.8	57.0	4.8	4.8	5.5	5.9
48	$C_6H_5CHCH_3$–	2	34–35	E	64	$C_{13}H_{15}NO_3$	66.9	67.2	6.5	6.3	6.0	6.0
49	$C_6H_5CH_2CH_2$–	2	49–50	E	68	$C_{13}H_{15}NO_3$	66.9	67.2	6.5	6.5		
50	$C_{10}H_{13}O_2$–[i]	2	99–100	A	75	$C_{15}H_{19}NO_5$	61.4	61.8	6.5	6.4	4.8	4.8
51[a6]	C_6H_5–	4	108–109	A	61	$C_{11}H_{11}NO_3$	64.4	64.1	5.4	5.4	6.8	7.2
52	2-$CH_3C_6H_4$–	2	92–93	A	44	$C_{12}H_{13}NO_3$	65.7	65.7	6.0	5.8	6.4	6.2
53	4-$CH_3C_6H_4$–	2	97–106	A	30	$C_{12}H_{13}NO_3$	65.7	66.0	6.0	6.1		
54	4-ClC_6H_4–	6	124	A	67	$C_{10}H_{10}ClNO_3$	55.1	54.7	4.2	4.5	5.8	6.1

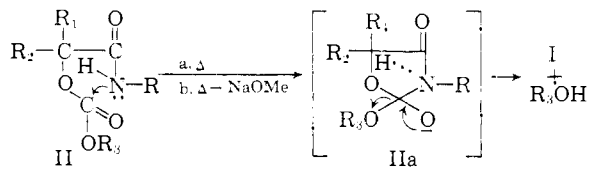
TABLE I (*Continued*)

No.[a]	R	Method[b]	M.p.,[c] or b.p., °C. (mm.)	RS[d]	Yield,[e] %	Formula	Analyses,[f] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
55	2-$CH_3OC_6H_4$–	2	110–111	A	28	$C_{12}H_{13}NO_4$	61.3	61.3	5.6	5.8	6.0	6.2
56	4-$CH_3OC_6H_4$–	2	103–104	A	64	$C_{12}H_{13}NO_4$	61.3	61.2	5.6	5.8		
57	2,5-di$CH_3OC_6H_3$–	2	129–130	A	25	$C_{13}H_{15}NO_5$	58.9	58.9	5.7	5.4		
58	2-$C_2H_5OC_6H_4$–	2	107–109	A	38	$C_{13}H_{15}NO_4$	62.6	62.8	6.1	6.1	5.6	5.9
59	3-$C_2H_5OC_6H_4$–	2	91–92	E	25	$C_{13}H_{15}NO_4$					5.6	5.8
60	4-$HOOCC_6H_4$–	7	237–238	F	5	$C_{12}H_{11}NO_5$	57.8	57.8	4.5	4.1	5.6	5.2
				R_1 = C_6H_5, R_2 = H								
61[a7]	*i*-C_3H_7–	7	86–92	E	73							
62	*i*-C_4H_9–	2	71–72	E	60	$C_{13}H_{15}NO_3$	66.9	66.7	6.5	6.5	6.0	6.0
63	$C_6H_5CH_2$–	3	85–86	A	60	$C_{16}H_{13}NO_2$	71.9	72.2	4.9	5.3		
64	4-$ClC_6H_4CH_2$–	7	132–133	A	50	$C_{12}H_{12}ClNO_3$	63.7	64.2	4.0	3.7	4.6	4.9
65	$C_6H_5CH_2CH_2$–	3	115–118	A	39	$C_{17}H_{15}NO_3$					5.0	5.3
66[a8]	C_6H_5–	7	121–125	D	68							
67	4-ClC_6H_4–	1	154–155	A	60	$C_{15}H_{10}ClNO_3$	62.6	62.5	3.5	3.7		

[a] Compounds previously reported; [a1] J. S. H. Davies, M. E. H. Fitzgerald and W. H. Hook, *J. Chem. Soc.*, 34 (1950), m.p. 44–45°; [a2] R. F. Rekker, A. C. Faser, D. H. E. Tom, H. Verleur and W. T. Naute, *Rec. trav. chim.*, **70**, 113 (1951), m.p. 121°; [a3] M. A. Spielman and G. M. Everett, THIS JOURNAL, **70**, 1021 (1948), b.p. 137–140° (35 mm.); [a4] *ibid.*, m.p. 74–76°; [a5] ref. a_2, m.p. 141–142°; [a6] *ibid.*, m.p. 119–120.5°. Also prepared by method 2 (85%), m.p. 109–110°; [a7] ref. 8, m.p. 85–86°; [a8] *ibid.*, reports m.p. 123°. [b] The various methods are discussed in the text and described in the Experimental section. [c] Melting points are uncorrected and were established on a Fisher–Johns melting point block. [d] RS = recrystallizing solvent: A = ethyl acetate–hexane; B = purified by sublimation; C = ethyl acetate; D = ethanol–water; E = hexane; F = water. [e] Yields are reported on the basis of recrystallized or distilled product. [f] Analyses are by Weiler and Strauss, Oxford, England. [g] C_3H_5– is allyl. [h] C_5H_6O– is furfuryl. [i] $C_{10}H_{13}O_2$– is 3,4-dimethoxyphenethyl. [j] See Experimental. [k] C_8H_{17}– is 2-ethylhexyl. [l] C_6H_{11}– is cyclohexyl.

The pyrolysis proceeds as shown in Scheme I.

SCHEME I: PYROLYSIS OF CARBONATES



In most instances the pyrolysis proceeded readily and quantitatively at temperatures ranging from 150–230°. While basic catalysis is not required, the use of trace amounts of powdered sodium methoxide lowered the reaction temperature and made it independent of structural variants of R.

A definite influence of R and R_3 in the non-catalyzed pyrolysis was demonstrated. For II, R = *p*-ClC_6H_4–, R_1 = H, R_2 = CH_3–, variation of R_3 as CH_3–, C_2H_5–, *n*-C_3H_7–, $ClCH_2CH_2$–, $ClCH_2CH_2CH_2$– was associated with the following temperatures, respectively, at which reaction proceeded: 150–152°, 180°, 188–190°, 205° and 205–210°. In turn, with R_1 = CH_3–, R_2 = H, R_3 = C_2H_5– and variation of R as phenyl and substituted phenyl, the reaction proceeded most readily with R = C_6H_5– at 150–160°, followed by *p*-substituted phenyls (CH_3O–, C_2H_5O–, CH_3–, F) in the range of 179–185°, then *m*-substituted phenyl (C_2H_5O–) at about 187–193°, and finally *o*-substituted phenyl (Cl, CH_3–, CH_3O–, 2,4-di-CH_3–) at 212–240°. The initial reaction temperature with the *o*-substituted phenyl compounds paralleled the steric hindrance[11] (from ultraviolet absorption studies) associated with each group; Cl (240°), CH_3– (226°) and CH_3O– (212°). The pyrolysis for these compounds under sodium methoxide catalysis occurred at about 170°, and was the most serviceable method for obtaining I, where R = substituted *o*-phenyl.

Certain carbonates, particularly the ethyl carbonates of N-benzhydrylglycolamide and lactamide, were recovered unchanged when heated at 215°.

The data for the uncatalyzed reaction are consistent with a mechanism of intramolecular aminolysis of the carbonate ester[12] involving the electron pair on the amido nitrogen, with probable *trans* elimination of ethanol from the transition state intermediate IIa. Alternatively, in the catalyzed reaction the noted absence of steric factors on reactivity would indicate that the reaction proceeds by stripping of the amido hydrogen by the base, and subsequent nucleophilic attack by the amido nitrogen.

The utility of the pyrolytic procedure[13–18] is associated with the stability of the product I at elevated temperatures. The over-all serviceability of the method suffers in the difficulty of obtaining the necessary reactant II, when R_1, R_2 = methyl.[11,19]

When the N,N'-(*p*,*p*'-methylene-dianilino)-bis-(carbethoxyoxyglycolamide) was pyrolyzed by this method only one mole of ethanol was eliminated to give III.

The base-catalyzed reaction of the N-substituted-α-hydroxyamide[11] with an excess of diethyl carbonate[1c] is shown in Scheme II (method 2).

(12) C. J. M. Stirling, *J. Chem. Soc.*, 4531 (1958).

(13) J. L. R. Williams, D. D. Reynolds, K. R. Dunham and J. F. Tinker, *J. Org. Chem.*, **24**, 64 (1959).

(14) D. Davidson and M. Karten, THIS JOURNAL, **78**, 1066 (1956).

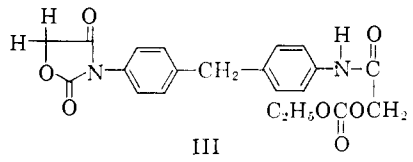
(15) W. J. Bailey and C. N. Bird, *J. Org. Chem.*, **23**, 996 (1958).

(16) H. E. Baumgarten, F. A. Bower, R. A. Setterquist and R. E. Allen, THIS JOURNAL, **80**, 4588 (1958).

(17) J. L. R. Williams, K. R. Dunham and T. M. Laakso, *J. Org. Chem.*, **23**, 676 (1958).

(18) D. Davidson and H. Skovronek, THIS JOURNAL, **80**, 376 (1958).

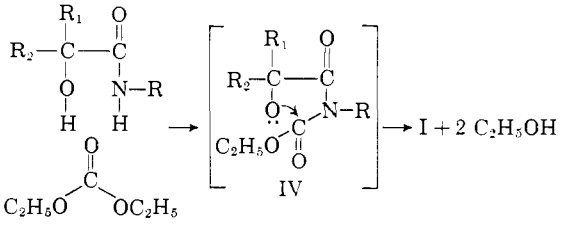
(19) Rekker (ref. 8, p. 29) has shown that heating ethyl methylcarbamoyl-α-hydroxyisobutyrate at 220° gives a 93% yield of 3,5,5-trimethyloxazolidinedione.



III

The over-all mechanism requires further clarification. It is of interest that use of α-hydroxyamides in which the hydroxy group is tertiary is not associated with any difficulty of ring closure as shown in IV. Evidence that IV may be the transition state intermediate in this method was obtained by the separation of the side-product, *p*-chlorophenylurethan, in the isolation of I (compound 37, Table I).

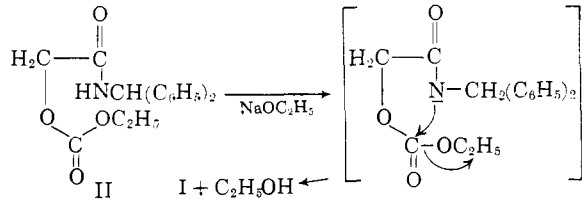
SCHEME II: CYCLIZATION OF AMIDES IN DIETHYL CARBONATE



IV

An alternative procedure (method 3) was the sodium alkoxide-catalyzed cyclization of the ethyl carbonate ester of N-benzhydrylglycolamide (Scheme III).[20] This synthesis failed using method 1.

SCHEME III: CYCLIZATION OF CARBONATE ESTER



II

When the phenylurethan of N-cyclohexyl-α-hydroxyisobutyramide[11] (V) was treated in acetic acid with trifluoroacetic acid (method 4), a 78% yield of 5,5-dimethyl-3-phenyloxazolidinedione, along with aniline which had been converted to acetanilide (isolated as β-bromoacetanilide) was obtained. The isolation of the bromoacetanilide is suggestive that some I, R = C_6H_{11}– also had been formed.

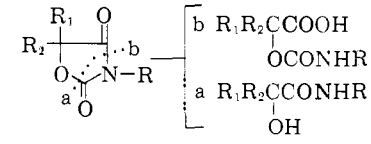
By contrast (method 5), when V is treated under basic catalysis, I, R = C_6H_{11}–, was obtained in 60% yield along with smaller quantities of I, R = C_6H_5–.[21]

Treatment of the urethan $RNHCO_2C_2H_5$ with the α-hydroxy ester under sodium alkoxide catalysis in diethyl carbonate as a solvent (method 6) gave the dione I, and was preferred to method 2 for preparation of I, R = *p*-chlorophenyl. Using this procedure 3,5,5-trimethyloxazolidinedione was prepared in 79% yield from methylurethan and ethyl lactate.

The most convenient synthetic method was the one-step conversion to the dione I of a mixture of the amine RNH_2, the ester $R_1R_2C(OH)COOC_2H_5$ and excess diethyl carbonate under sodium alkoxide catalysis (method 7). This method has been more fully described elsewhere[1c] using dialkylaminoalkylamines and the present work has extended its application to the variety of amines, RNH_2.

The availability of the oxazolidinediones indicated examination of their response to mild alkaline hydrolysis, particularly as a means for obtaining the corresponding carbamoyl-oxy acids (Table II) as shown in Scheme IV.

SCHEME IV: ALKALINE HYDROLYSIS OF I



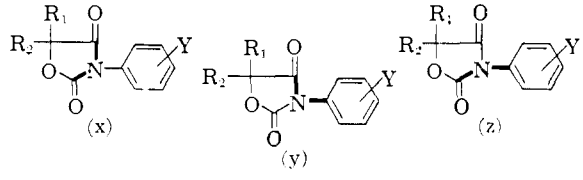
In many of the reactions the relative ratios of products obtained through path a *vs.* path b (Scheme IV) have been established and as a general rule it appears that the ratio of isolated carbamoyloxy acid to hydroxyamide is largely in favor of hydrolysis *via* path b to give the acid.

Of particular interest was the reversal of this trend with compounds 17 and 18 (see compounds 4, 5 and 10, 11) of Table II where the hydrolysis proceeded largely by path a. The compound R_1,R_2 = C_6H_5–, R = *d*-$C_6H_5CH_2CH(CH_3)$–[1d] showed the same effects.

All of these compounds have 5,5-substituents on the ring while the 3-substituent has a β-phenethyl chain, and the preference for path a may reflect steric inhibition of path b *via* Newman's "Rule of Six."[25]

Ultraviolet Absorption Spectra.—The spectra of the 3-aryloxazolidinediones (Table III) were established to characterize group conformation in these diones.

SCHEME V



(x) (y) (z)

The alternative conformations are shown in Scheme V. If the aryl group is out of plane, shown for (x), no characteristic aniline spectra will be obtained, and the noted spectral effects will be dependent on the Y substituent. If the electron pair on the nitrogen, the aryl group and the N–C bond are coplanar as shown for (y), spectral characteristics similar to those of the α-hydroxyamides[26] should be obtained. In turn, if the electron pair on the nitrogen, the aryl group and the N–C bond are coplanar as shown for (z), spectral characteristics similar to the substituted phenylurethans would

(20) E. Fischer and H. O. L. Fischer, *Ber.*, **47**, 768 (1914), treated compounds of the type II with aqueous base and obtained the carbamoyl-α-oxy acids and proposed diones of the type I as intermediates in the rearrangement.

(21) The provocative structural problem of this work was not investigated in any greater detail; for related work see ref. 12, 22, 23, 24.

(22) N. A. Leister and D. S. Tarbell, *J. Org. Chem.*, **23**, 1152 (1958).

(23) S. Sarel and A. Greenberger, *ibid.*, **23**, 330 (1958).

(24) H. W. Heine and Z. Proctor, *ibid.*, **23**, 1554 (1958).

(25) M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 204 *et seq.*

(26) These spectra are reported in ref. 11.

TABLE II

CARBAMOYLOXY ACIDS $RNHCOOC(R_1)(R_2)COOH$

No.	R	M.p., °C.[a,b]	Yield, %[c]	Formula	Analyses,[d] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
				$R_1, R_2 = H$						
1	$C_6H_5CH_2-$	135	39	$C_{10}H_{11}NO_4$	57.4	57.7	5.3	5.1	6.7	6.3
2	$4\text{-}ClC_6H_4CH_2-$	153–155	72/18	$C_{10}H_{10}ClNO_4$	49.3	49.7	4.1	4.5	5.8	6.3
3	$C_6H_5CHCH_3-$	111	60	$C_{11}H_{13}NO_4$	59.2	59.1	5.9	5.8	6.3	6.0
4	$C_6H_5CH_2CH_2-$	129–131	74	$C_{11}H_{13}NO_4$	59.2	59.1	5.9	5.8	6.3	6.5
5	$3,4\text{-}diCH_3OC_6H_3CH_2CH_2-$	134–136	75/21	$C_{13}H_{17}NO_6$	55.1	55.3	6.1	6.2	5.0	5.5
6	$4\text{-}ClC_6H_5-$	153–154	39/14	$C_9H_8ClNO_4$	47.1	46.8	3.6	3.7	6.1	6.1
				$R_1 = CH_3, R_2 = H$						
		101–102[e]								
7	$C_6H_5CH_2-$	113–114	27/12	$C_{11}H_{13}NO_4$	59.2	59.7	5.9	5.4	6.3	5.9
8	$p\text{-}ClC_6H_4CH_2-$	130–131	84/10	$C_{11}H_{12}ClNO_4$	51.3	51.7	4.7	5.0	5.4	5.4
9	$C_6H_5CHCH_3-$	119–122	64/25	$C_{12}H_{15}NO_4$	60.8	60.8	6.4	6.9	5.9	5.9
10	$C_6H_5CH_2CH_2-$	112–113	71/23	$C_{12}H_{15}NO_4$	60.8	60.7	6.4	6.5	5.9	5.6
11	$3,4\text{-}diCH_3OC_6H_3CH_2-$	103–104[b1]	57/23	$C_{14}H_{19}NO_6$	56.6	56.6	6.4	6.5	4.7	5.1
12	ClC_6H_4-	154–157	67	$C_{10}H_{10}ClNO_4$	49.3	49.2	4.1	4.1	5.8	5.9
				$R_1, R_2 = CH_3$						
13	CH_3-	110–116[f1]	21							
14	$C_6H_5CH_2-$	134–135	48	$C_{12}H_{15}NO_4$	60.8	61.1	6.4	5.9	5.9	5.6
15	$4\text{-}ClC_6H_4CH_2-$	126–129	63/29	$C_{12}H_{14}ClNO_4$	53.1	53.2	5.2	4.9	5.2	4.9
16	$C_6H_5CHCH_3-$	157–158	63/32	$C_{13}H_{17}NO_4$	62.1	61.9	6.8	6.6	5.6	6.0
17	$C_6H_5CH_2CH_2-$	125–127	1/89	$C_{13}H_{17}NO_4$	62.1	62.3	6.8	6.2	5.6	5.6
18	$3,4\text{-}diCH_3OC_6H_3CH_2CH_2-$	151–153	13/75	$C_{15}H_{21}NO_6$	57.9	57.8	6.8	6.8	4.5	4.5
19	C_6H_5-	134–135[f2]	55							
20	$4\text{-}ClC_6H_4-$	138–140	65/21	$C_{11}H_{12}ClNO_4$	51.3	51.2	4.7	4.7	5.4	5.1
				$R_1 = C_6H_5, R_2 = H$						
21	$i\text{-}C_3H_7-$	121–123[f3]	63							
22	$4\text{-}ClC_6H_4CH_2-$	145–146	79/12	$C_{16}H_{14}ClNO_4$	60.1	60.4	4.4	4.7		
23	C_6H_5-	142–145[f4]	65							

[a] Melting points are not corrected and were taken on a Fisher–Johns melting point block. [b] The compounds were isolated by neutralization from their alkaline solutions; [b1] recrystallized from ethyl acetate–hexane. [c] Yields are expressed as % acid/% α-hydroxyamide; where ratio is not shown the yield is for the acid of this table. [d] Analyses by Weiler and Strauss, Oxford, England. [e] Compound resolidifies after melting, and remelts at the higher melting point. [f] Ref. 8 reports m.p.: [f1] 112–114°; [f2] 133–134°; [f3] 118.5–119.5°; [f4] 147–148°.

be expected. Selected spectra of substituted phenylurethans have been established and are reported in Table IV.

The observed spectra have little regularity and indeed are notable for the low extinctions obtained with the multiplicity of accessible chromophoric possibilities (Table III, compounds 9, 31, 51, 66, 10, 32, 52, 15, 39, 55, 58, 18, 41, 42, 59).

Certain of the compounds show a fairly strong band in the area λ_{max} 217–231 mμ (Table III, compounds 33, 53, 12, 13, 37, 67, 54, 38, 17, 56). This band may represent the spectral character of the oxazolidinediones (Scheme V (x)), as shown by compounds 50 and *f*, although the absence of the band throughout many compounds of the series would not be too persuasive for this assignment. Another explanation for the band is steric inhibition with resultant hypo- and hypsochromic effects of the forms (y) and (z) of Scheme V of anilide[11] or urethan (Table IV) spectra, and steric inhibition of amide resonance.[27]

The four spectra determined in 0.1 *N* sodium hydroxide (compounds 31, 51, 37, 38) indicate hydrolysis to the carbamoyloxy acid with the resultant spectra reflecting these compounds (see Table III, 12[g], 19[g], 20[g]).

The observed bands of many of the compounds indicate only the ultraviolet absorption characteristic of monosubstituted benzene derivatives[28] which varied with Y, and particularly the bands for the alkoxy derivatives at λ_{max} 270–280 mμ and the bands for compounds 44 and 60.

Of ancillary interest, the spectra of the urethans of Table IV have hyper- and hypsochromic relationship to the corresponding acetanilides[29] and anilides of the α-hydroxy acids,[11] and are closely related to the spectra of the compounds of Table II.

Pharmacology.—The compounds of Table I were examined for anticonvulsant activity and certain of the compounds were inspected for additional pharmacological effects (Table V).

The best compound of the series was compound 15, 3-(4-chloro-2-methylphenyl)-oxazolidinedione, which in addition to having good anticonvulsant

(27) R. W. Holley, *Science*, **117**, 23 (1953).

(28) L. Doub and J. M. Vandenbelt, THIS JOURNAL, **69**, 2714 (1947).

(29) H. E. Ungnade, *ibid.*, **76**, 5133 (1954).

TABLE III

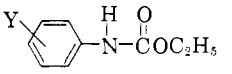
SPECTRA OF 3-ARYL-OXAZOLIDINEDIONES[a,b]

No.[c]	$\lambda_{max.}$ mμ	ε × 10^{-3}	No.[c]	$\lambda_{max.}$ mμ	ε × 10^{-3}	No.[c]	$\lambda_{max.}$ mμ	ε × 10^{-3}
9	280[d]	0.11	36	270	3.1	42	276	2.4
31	262	2.6	37	228	11.2	59	275	2.5
31[b1]	234	16.6	37[b1]	241	21.4		280[d]	2.3
31[b2]	229	8.0	37[b2]	239	15.0	43	228	12.7
51	262	2.0	54	224	12.9	60	235	14.0
51[b1]	235	16.4	67	235	14.9	44	270	10.4
			38	234	14.1	50	226	7.7
66	[e]		38[b1]	243	22.0		275	2.5
10	261	0.48	38[b2]	240	16.1	[f]	226	0.13
	267	0.39	15	266	0.44	12[g]	239	21.7
							278	0.85
32	260	0.41	39	271	2.8	19[g]	236	16.9
	267	.34	55	272	3.2		271	0.78
52	260	.46		277[d]	2.9	20[g]	240	21.3
	268	.37	17	231	12.0		279	0.8
				272	1.4			
33	218	9.0		277	1.2			
53	219	8.8	56	227	12.4			
12	217[d]	6.2		272	1.4			
	261	0.46	18	272	2.7			
	266	0.47	41	271	2.6			
13	222	10.2	58	216[d]	8.5			
				273	2.8			

[a] The spectra were determined in a model DK Beckman recording spectrophotometer. [b] The solvent was methanol unless otherwise stated; [b1] 0.1 *N* sodium hydroxide in 50% methanol; [b2] 0.1 *N* hydrochloric acid in 50% methanol. [c] The number corresponds to the compound number in Table I. [d] Shoulder. The extinction coefficient is reported at the locus of the center of the shoulder. [e] Non-specific absorption. [f] 3,5,5-Trimethyl-oxazolidinedione. [g] Compound number in Table II.

TABLE IV

SPECTRA OF PHENYLURETHANS[a,b,h,i,j]



No.	Y	$\lambda_{max.}$ mμ	ε × 10^{-3}	No.	Y	$\lambda_{max.}$ mμ	ε × 10^{-3}
1	H	233	16.1	7	4-Br	242	21.8
		270	0.64			280[d]	0.91
2	2-CH_3–	228	7.89	8	2-CH_3O–	234	13.3
		265	0.4			277	3.54
3	3-CH_4–	234	14.0	9	4-CH_3O–	238	17.4
		275	0.6			287	1.73
4	4-CH_3–	234	17.3	10	2-C_2H_5O–	235	13.2
		276	0.86			278	3.45
5	3-Cl	236	16.2	11	4-C_2H_5O–	238	18.1
		276	1.01			288	1.8
6	4-Cl	240	21.3				
		279	0.46				

[h] Footnotes *a* and *b* are the same as shown for Table III. [i] Reported compounds had physical properties in satisfactory agreement with those described in the literature; compound 10, b.p. 142–144° (5 mm.); compound 3, b.p. 148–149° (6 mm.); compound 8, b.p. 139–140° (6 mm.). [j] The spectra for compounds 1, 2 and 4 (ethanol) are reported by W. A. Schroeder, P. E. Wilcox, K. N. Trueblood and A. O. Dekker, *Anal. Chem.*, **23**, 1740 (1951).

activity, was desirably without effect on Evipal sleeping time and did not reduce motor activity in the test animals.[1a]

Structure–activity relationships indicate that best activities are noted when the 3-substituent is aralkyl (compounds 2, 4, 6, 27, 48, 49, 46) or *o*-substituted phenyl (compounds 15, 52, 58, 59) with the α-phenethyl groups (compounds 5, 27, 48) being particularly effective. With the R_1R_2 variable, R_1R_2 = H had five active compounds; R_1 = CH_3, R_2 = H had two and R_1, R_2 = CH_3 had six.

TABLE V

PHARMACOLOGICAL FINDINGS OF COMPOUNDS OF TABLE I

Anticonvulsant 4+[a]	2/450, 4/200, 5/450, 15/1000, 48/450, 49/450, 59/1000
Anticonvulsant 3+[a]	6/125, 22/250, 27/1000, 46/1000, 52/200, 58/700
Antihistamine[b]	3, 22, 26
Evipal sleeping time[c]	14, 21, 27

[a] For method of testing see S. L. Shapiro, V. A. Parrino and L. Freedman, THIS JOURNAL, **81**, 3996 (1959). The data show the compound number of Table I and (LD_{min} in mg./kg., s.c.). [b] For method of testing, see S. L. Shapiro, H. Soloway and L. Freedman, *J. Am. Pharm. Assoc.*, (*Sci. Ed.*), **46**, 333 (1957). [c] For method of testing, see ref. 1a. The compounds noted potentiated Evipal sleeping time 50–150% when evaluated at one-third of their LD_{min}.

The carbamoyloxy acids of Table II were only examined briefly for pharmacological effects. It was of interest that the acids (compounds 3 and 16, Table II) corresponding to the active diones (compounds 5 and 48, Table I) were without anticonvulsant activity.

Experimental[30]

3-*p*-Chlorophenyl-5-phenyl-2,4-oxazolidinedione (Table I, Compound 67. Method 1).—Two grams (0.006 mole) of the ethyl carbonate ester of *p*-chloromandelamide was heated in an oil-bath. The liberation of the formed ethanol (bubbling) started at 197°, was brisk at 204°, and ceased after 1 hour at 222°. Heating at 222° was continued for 0.5 hour. When cool, the residue of product solidified.

Effect of Structural Variation (Method 1).—When the series of alkyl carbonate esters of the structure $CH_2CH(OCOR_3)CONHC_6H_4$-*p*-Cl was pyrolyzed in a slowly heated oil-bath (stirring), the following bath temperatures were associated with vigorous evolution of ethanol as R_3 was varied, respectively: CH_3–, 150–152°; C_2H_5–, 180°; *n*-C_3H_7–, 188–195°; $ClCH_2CH_2$–, 205°; $Cl(CH_2)_3$–, 205–210°. These procedures afforded compound 37 (Table I).

When a series of ethyl carbonate esters of substituted lactanilides of the structure $CH_3CH(OCOOC_2H_5)CONHC_6H_4$–X was treated as above, vigorous evolution of ethanol was associated with the following bath temperatures as X was varied: 2-Cl, 263–270°; 4-CH_3O–, 182–183°; 2-CH_3–, 238–256°; 3-C_2H_5O–, 191–193°; 4-C_2H_5O–, 184–186°; 4-CH_3–, 181–185°; H, 160–165°; 4-F, 179–181°; 2-CH_3O–, 241–264°; 2,4-diCH_3–, 195°. Upon completion of the reaction as described above, the corresponding diones were isolated.

The point at which significant evolution of ethanol is noted is quite specific and readily characterized. If 20 mg. of sodium methoxide is added to 0.01 mole of the respective reactants, brisk evolution of ethanol is noted in the range of 160–170° with essentially quantitative yields of the product after heating for 0.5 hour.

3-(*p*-[α-(*p*'-[Carbethoxyoxyglycolamido]-tolyl)]-phenyl)-2,4-oxazolidinedione (Compound III).—When 2.0 g. (0.00435 mole) of N,N'-(*p*,*p*'-methylene-dianilino)-bis-(carbethoxyoxyglycolamide) was pyrolyzed as above, brisk evolution of ethanol was noted at 195°; after 0.5 hour at 195–200° the evolution of ethanol had practically ceased. The residue was dried and on recrystallization (ethanol–ethyl acetate) gave 0.34 g., m.p. 184–185°, with melting point depression on admixture with reactant amide (m.p. 182–183°), mixed m.p. 159–167°. The analyses indicated cyclization of but one of the two accessible groups.

Anal. Calcd. for $C_{21}H_{20}N_2O_7$: C, 61.2; H, 4.9; N, 6.8. Found: C, 60.8; H, 4.3; N, 6.9.

When the ethyl carbonate ester of N-benzhydrylglycolamide was heated to 215° as described above, no evolution

(30) Descriptive data shown in the tables are not herein reproduced. Initial reactants were commercially available and the α-hydroxy amides and their corresponding carbonate esters used have been described in ref. 11. Typical procedures are given to illustrate the general methods.

of ethanol was noted and the cooled residue afforded essentially quantitative recovery of the reactant amide.

3-Benzyl-5,5-dimethyl-2,4-oxazolidinedione (Table I, Compound 46. Method 2).—To a solution of 1.5 g. (0.0078 mole) of N-benzyl-α-hydroxyisobutyramide in 5 ml. of diethyl carbonate, 0.4 ml. of a solution of 0.09 g. of sodium metal in 2 ml. of ethanol was added and the whole heated under reflux for 1 hour. When cool, the reaction product was dissolved in 50 ml. of benzene and 50 ml. of 1.2 *N* hydrochloric acid. The benzene layer was washed twice with water, filtered, and the benzene removed to yield the crystalline product, 1.5 g. (88%), m.p. 57–58°.

3-(*p*-Chlorophenyl)-5-methyl-2,4-oxazolidinedione (Table I, Compound 37. Method 2. **Isolation of *p*-Chlorophenylurethan**).—When a 0.03-mole run of the ethyl carbonate ester of *p*-chloroacetanilide was processed as above, there was obtained, after drying (clay plate), 4.2 g. of a mixture of products. Upon treatment with hexane, the hexane-insoluble portion proved to be compound 37, while evaporation of the hexane filtrate and recrystallization from cold hexane yielded 1.77 g. of a product, m.p. 63–68°, which did not depress the melting point of authentic *p*-chlorophenylurethan, m.p. 67°, mixed m.p. 65–67°.

3-Benzhydryl-2,4-oxazolidinedione (Table I, Compound 8. Method 3).—A solution of 3.05 g. (0.01 mole) of the ethyl carbonate ester of N-benzhydrylglycolamide in 15 ml. of diethyl carbonate was treated with 0.4 ml. of sodium ethoxide solution as described above and processed as in method 2. The residue (2.43 g.) was recrystallized.

Phenylurethan of N-Cyclohexyl-α-hydroxyisobutyramide.—A solution of 8.0 g. (0.0432 mole) of N-cyclohexyl-α-hydroxyisobutyramide and 4.8 g. (0.04 mole) of phenyl isocyanate in 40 ml. of pyridine was stored at 20° for 72 hours. Upon dilution with water the product crystallized and the whole was acidified (with cooling and stirring) with concentrated hydrochloric acid. The product was separated (9.2 g.) and recrystallized (ethyl acetate) to give 7.25 g. (55%), m.p. 163–165°.

Anal. Calcd. for $C_{17}H_{24}N_2O_3$: C, 67.1; H, 8.0; N, 9.2. Found: C, 67.3; H, 7.7; N, 9.0.

5,5-Dimethyl-3-phenyl-2,4-oxazolidinedione (Table I, Compound 51. Method 4).—A solution of the urethan above, 2.0 g. (0.066 mole) in 10 ml. of acetic acid plus 1 ml. of trifluoroacetic acid, was heated under reflux for 40 hours. The volatiles were removed, the residue granulated under 10 ml. of water and the product separated, there being obtained 1.05 g. (78%), m.p. 106–107°.

The aqueous filtrate on treatment with bromine water gave 0.28 g. (m.p. 138–154°) which on recrystallization (ethanol–water) melted at 162–166°, and was identified as *p*-bromoacetanilide.

When the same reaction was carried out, omitting the trifluoroacetic acid and refluxing for 65 hours, reactant urethan was still present.

3-Cyclohexyl-5,5-dimethyl-2,4-oxazolidinedione (Table I, Compound 45. Method 5).—A solution of the urethan above, 3.0 g. (0.01 mole) in 10 ml. of diethylcyclohexylamine was heated under reflux for 4 hours. When cool, 0.57 g. of crude diphenylurea, m.p. 224–225°, was obtained, recrystallized (ethyl acetate) m.p. 231–234°, not depressing the melting point of authentic diphenylurea (m.p. 242°), mixed m.p. 239–241°.

The filtrate was diluted with water and 6 *N* hydrochloric acid was added to *p*H 6.0. The oily product was separated, granulated with hexane and recrystallized to give 0.63 g. of compound 45, m.p. 76–78°. The acidic filtrate on standing deposited a small quantity of crystals which proved to be compound 51.

3-(*p*-Chlorophenyl)-5-methyl-2,4-oxazolidinedione (Table I, Compound 37. Method 6).—A solution of 9.95 g. (0.05 mole) of *p*-chlorophenylurethan in 6.5 g. (10% excess) of ethyl lactate in 25 ml. of diethyl carbonate, was treated with 0.10 g. (0.005 mole) of sodium in 2 ml. of ethanol and then heated under reflux for 1 hour. When cool, the formed ethanol was removed and the residue granulated with benzene. Trituration with dilute hydrochloric acid, washing with water and drying gave 4.12 g. (37%) of product, m.p. 178° alone, or when mixed with the compound prepared by method 1.

3-β-Phenethyl-5-methyl-2,4-oxazolidinedione (Table I, Compound 28. Method 7).—A mixture of 12.1 g. (0.1 mole) of β-phenethylamine and 13.0 g. (0.11 mole) of ethyl lactate in 37 ml. of diethyl carbonate was treated with a solution of 0.1 g. of sodium in 2 ml. of ethanol and heated under reflux for 0.5 hour. The formed ethanol was removed and addition of sodium ethoxide, reflux, and removal of formed ethanol twice repeated, when the theoretical amount of ethanol had been collected. When cool, the residue was filtered and the filtrate distilled. The product (17.9 g., 82%) was collected at b.p. 100–106° (0.08 mm.).

3-*p*-Carboxyphenyl-2,4-oxazolidinedione (Table I, Compound 19).—In the attempted preparation of the chloroethyl carbonate ester of *p*-carboxyglycolanilide[11] (0.14 mole run) the hydrochloric acid wash of the product precipitated 0.58 g. of product which proved to be the dione. The mechanism for this cyclization to the dione at 20° has not been clarified.

N-(2-[3,4-Dimethoxyphenyl]-ethyl)-carbamoylo-α-hydroxyisobutyric Acid (Table II, Compound 18).—A suspension of 5.0 g. (0.017 mole) of compound 50 (Table I) in 45 ml. of water and 12 ml. of 3 *N* sodium hydroxide was stored at 20°, with intermittent shaking, for 96 hours when complete solution was effected. The reaction mixture was extracted with three 50-ml. portions of chloroform. Upon acidification of the aqueous phase, the product (0.7 g., 13%) crystallized.

The chloroform extracts were combined, the chloroform removed, and the residue upon trituration with hexane afforded 3.65 g. (75%) of N-(3,4-dimethoxyphenethyl)-α-hydroxyisobutyramide, m.p. 79–82°, not depressing the melting point of authentic amide[11] (m.p. 80–81°), mixed m.p. 79–82°.

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