[CONTRIBUTION FROM THE RESEARCH DIVISION, U. S. VITAMIN CORPORATION]

Aminoalkylamides and Oxazolidinediones[1]

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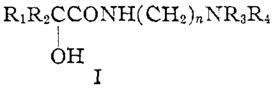
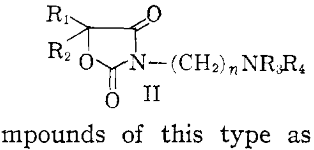
A series of α-hydroxyamides of the type I and the derived oxazolidinediones of the type II have been examined for central nervous system depressant effects. Many compounds showed significant activity. A new and convenient process for synthesis of oxazolidinediones of the type II in one step from the α-hydroxyester, the dialkylaminoalkylamine and diethyl carbonate is described.

In continuation of our studies in the search for central nervous system depressants,[3-5] this paper reports the synthesis and examination for pharmacological activity of aminoalkylamides (I), (Table I) and oxazolidinediones (II), (Table II). In these compounds R_1 and R_2 were retained as hydrogen and methyl, n was 3–4, while the secondary amino function, $-NR_3R_4$, was varied extensively.



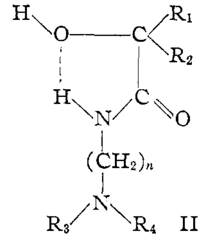
$R_1R_2\underset{\displaystyle OH}{C}CONH(CH_2)_nNR_3R_4$

I



II

The rationale for compounds of this type as central nervous system depressants was based on the assumption that a large measure of the selectivity of the central nervous system response was associated with a dialkylaminoalkyl function.[6] Variation of the alkyl chain of three carbon atoms ($n = 3$) was indicated by optimal effects noted with such structures in the phenothiazine-type tranquillizers,[3] and with four carbon atoms ($n = 4$) in newly reported simple analogs of reserpine.[7,8] The selection of the simple α-hydroxy acids indicated an element of rigidity for amides of the type I as a result of hydrogen bonded structures[9] as shown in III.



III

In turn, the known anticonvulsant effect of oxazolidinediones[4,10] suggested exploration of compounds of the type II.[11]

The noted retention of activity in a different series of bases[3] which showed depression of central nervous system activity upon quaternization indicated similar examination of such compounds in this series as $I \cdot R_5X$ and $II \cdot R_5X$.

The synthesis of the α-hydroxyamides of type I was effected readily by reflux with an excess of the α-hydroxyester.[9,12] In fifteen variants of $R_3R_4N(CH_2)_3$– the lactamides give the best average yields (87%), followed by the glycolamides (79%) and the α-hydroxyamides (76%).

The oxazolidinediones of the type II were prepared by treatment of the N-substituted α-hydroxyamides with ethyl carbonate using sodium alkoxide catalysis in an extension of the method of Wallingford.[13] In the course of the work, however, a far more useful development was exploited which permitted a one-step conversion of the amine, $R_3R_4N(CH_2)_nNH_2$ (IV), to the substituted oxazolidinedione II. This was achieved by reaction under sodium alkoxide catalysis of equivalent quantities of the amine IV and the α-hydroxyester V in diethyl carbonate (VI) as a solvent. The variety as well as sequence of reaction possibilities which may be involved are shown in Scheme I.

Further characterization of reaction mechanisms[14] is being studied in greater detail in a wide variety of systems.[15] Clearly, path A is a likely possibility since the diones II are prepared readily from the hydroxyamides I and diethyl carbonate. Path B involving reaction of the urethan VII with the α-hydroxyester is an alternate path for the preparation of diones II and has been demonstrated in other systems.[14] Path C has been shown to give a 61% yield of compound 111 (Table II).

While sodium ethoxide was used as the catalyst in most instances, sodium methoxide and benzyltrimethylammonium methoxide were also serviceable. In turn, aluminum isopropoxide and benzyltrimethylammonium hydroxide proved to be ineffective.

In the cyclization step to the diones II using the amides I, the average yield for 14 variants of $-N(CH_2)_3NR_3R_4$ for conversion to the diones where $R_1 = CH_3$, $R_2 = H$, was 80% as compared to an average of 68% for equivalent structures wherein $R_1 = R_2 = H$. The yield was greater for each

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[1] Presented in part at the Medicinal Chemistry Division, American Chemical Society, Boston, Mass., April, 1959.

[2] Nopco Chemical Co., Harrison, N. J.

[3] S. L. Shapiro, H. Soloway and L. Freedman, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 333 (1957).

[4] S. L. Shapiro, I. M. Rose, E. Roskin and L. Freedman, THIS JOURNAL, **80**, 1648 (1958).

[5] S. L. Shapiro, K. Weinberg, T. Bazga and L. Freedman, *ibid.*, **80**, 3734 (1958).

[6] Recent work has shown tranquillizing effects with dimethylaminoethanol; C. C. Pfeiffer, *et al.*, *Science*, **126**, 610 (1957).

[7] G. Di Paco and C. S. Tauro, *Farmaco (Pavia)*, **13**, 64, 429 (1958).

[8] B. V. Rama Sastry and A. Lasslo, *J. Org. Chem.*, **23**, 1577 (1958).

[9] S. L. Shapiro, I. M. Rose and L. Freedman, THIS JOURNAL, **80**, 6065 (1958).

[10] J. W. Clark-Lewis, *Chem. Revs.*, **58**, 63 (1958).

[11] It is of interest that a simple congener of II with $n = 2$,3-(diethylaminoethyl)-5,5-dimethyl-1,3-oxazolidine-2,4-dione, has been reported by M. A. Spielman and G. M. Everett, THIS JOURNAL, **70**, 1021 (1948), and confirmed in our laboratories to be without significant pharmacological activity.

[12] (a) W. P. Ratchford, *J. Org. Chem.*, **15**, 326 (1950); (b) W. P. Ratchford and C. H. Fisher, *ibid.*, **15**, 317 (1950).

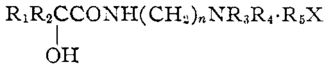
[13] V. H. Wallingford, M. A. Thorpe and R. W. Stoughton, THIS JOURNAL, **67**, 522 (1945).

[14] S. L. Shapiro, I. M. Rose and L. Freedman, in preparation.

[15] For a somewhat related study, see N. A. Leister and D. S. Tarkell, *J. Org. Chem.*, **23**, 1152 (1958).

TABLE I

AMINOALKYL-α-HYDROXYAMIDES



$R_1R_2\underset{\text{OH}}{\underset{|}{C}}CONH(CH_2)_nNR_3R_4\cdot R_5X$

No.	R_3	R_4	R_5X	B.p. (mm.)[a] or m.p.,[a,d] °C.	Yield,[b] %	Formula	Analyses[c]					
							Carbon, %		Hydrogen, %		Nitrogen, %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
$R_1 = H, R_2 = H, n = 3$												
1	CH_3–	CH_3–		128 (0.05)	72	$C_7H_{16}N_2O_2$	52.5	52.9	10.1	10.3		
2	CH_3–	CH_3–	CH_3I	124–125[da]	78	$C_8H_{19}IN_2O_2$	31.8	31.9	6.3	6.3		
3	C_2H_5–	C_2H_5–		140 (0.1)	82	$C_9H_{20}N_2O_2$	57.4	57.4	10.7	10.5		
4	$(CH_3)_2CH$–	CH_3–		134–180 (0.07)	76	$C_9H_{20}N_2O_2$	57.4	57.3	10.7	10.5	14.9	14.7
5	n-C_4H_9–	n-C_4H_9–		155 (0.03)	75	$C_{13}H_{28}N_2O_2$					11.5	10.9
6	–$(CH_2)_4$–			151 (.03)	56	$C_9H_{18}N_2O_2$	58.0	57.9	9.7	9.8	15.0	15.3
7	–$(CH_2)_4$–		CH_3I	143–144	80	$C_{10}H_{21}IN_2O_2$	36.6	36.6	6.5	5.9	8.5	9.0
8	–$(CH_2)_2O(CH_2)_2$–			170–178 (0.1)	77	$C_9H_{18}N_2O_3$	53.4	53.3	9.0	8.8	13.9	13.9
9	–$C_6H_{12}O$–[e]			170–172 (.08)	90	$C_{11}H_{22}N_2O_3$	57.4	57.2	9.6	9.6	12.2	12.1
10	C_6H_{11}–[f]	CH_3–		170–180 (.07)	85	$C_{12}H_{24}N_2O_2$	63.1	62.9	10.6	10.5	12.3	12.1
11	C_6H_{11}–[f]	C_2H_5–		172–180 (.05)	80	$C_{13}H_{26}N_2O_2$	64.4	64.8	10.8	10.8	11.6	11.7
12	C_6H_5–	CH_3–		198–200 (.1)	78	$C_{12}H_{18}N_2O_2$	64.8	64.5	8.2	8.5	12.6	12.6
13	C_6H_5–	C_2H_5–		195–198 (.07)	83	$C_{13}H_{20}N_2O_2$	66.1	66.2	8.5	8.5	11.9	11.9
14	$C_6H_5CH_2$–	CH_3–		192 (.08)	83	$C_{13}H_{20}N_2O_2$					11.9	12.3
15	$C_6H_5CH_2$–	$(CH_3)_2$–CH–		186–189 (.05)	83	$C_{15}H_{24}N_2O_2$	68.2	68.3	9.2	9.3	10.6	10.8
16	C_9H_{11}–[g]	CH_3–		203–205 (.1)	76	$C_{15}H_{24}N_2O_2$					10.6	10.8
17	–C_8H_8–[h]			224–228 (.2)	81	$C_{13}H_{18}N_2O_2$	66.6	66.6	7.7	7.8	12.0	11.9
$R_1 = H, R_2 = H, n = 4$												
18	CH_3–	CH_3–		142–149 (0.09)	70	$C_8H_{18}N_2O_2$					16.1	15.8
19	CH_3–	CH_3–	CH_3I	107–108	90	$C_9H_{21}IN_2O_2$	34.2	34.0	6.7	6.9	8.9	8.7
20	CH_3–	CH_3–	$C_4H_6Br_2$[i]	174–176	94	$C_{20}H_{42}Br_2N_4O_4$					10.0	10.0
21	C_2H_5–	C_2H_5–		148–154 (0.05)	83	$C_{10}H_{22}N_2O_2$	59.4	59.5	11.0	11.3		
22	$(CH_3)_2CH$–	$(CH_3)_2CH$–		154 (.05)	61	$C_{12}H_{26}N_2O_2$	62.6	62.0	11.4	11.1		
23	n-C_4H_9–	n-C_4H_9–		175 (.07)	78	$C_{14}H_{30}N_2O_2$					10.8	10.9
$R_1 = CH_3, R_2 = H, n = 3$												
24	CH_3–	CH_3–		122 (0.07)	93	$C_8H_{18}N_2O_2$	55.1	54.7	10.4	10.3		
27	CH_3–	CH_3–	CH_3I	124–125[da]	85	$C_9H_{21}IN_2O_2$	34.2	34.3	6.7	6.6		
28	CH_3–	CH_3–	$C_4H_7BrO_2$[j]	152	94	$C_{12}H_{25}BrN_2O_4$	42.2	42.4	7.4	7.1	8.2	8.3
29	CH_3–	CH_3–	$C_6H_5CH_2Br$	157	91	$C_{15}H_{25}BrN_2O_2$	52.2	52.1	7.3	7.6	8.1	7.8
30	CH_3–	CH_3–	$C_4H_6Br_2$[i]	158–159	83	$C_{20}H_{42}Br_2N_4O_4$	42.7	42.9	7.5	7.7		
31	C_2H_5–	C_2H_5–		110 (0.02)	84	$C_{10}H_{22}N_2O_2$	59.4	59.5	11.0	10.8	13.9	14.2
32	$(CH_3)_2CH$–	CH_3–		112–115 (.05)	79	$C_{10}H_{22}N_2O_2$	59.4	58.9	11.0	11.0	13.9	13.9
33	n-C_4H_9–	n-C_4H_9–		140–145 (.03)	83	$C_{14}H_{30}N_2O_2$	65.1	65.1	11.7	11.7	10.8	11.0
34	–$(CH_2)_4$–			134–144 (.03)	88	$C_{10}H_{20}N_2O_2$					14.0	13.6
35	–$(CH_2)_2O(CH_2)_2$–			142 (.04)	84	$C_{10}H_{20}N_2O_3$					13.0	12.7
36	–$(CH_2)_2O(CH_2)_2$–		CH_3I	145–146[da]	86	$C_{11}H_{23}IN_2O_3$	36.9	37.2	6.5	6.4	7.8	7.9
37	–$C_6H_{12}O$–[e]			170–172 (0.08)	90	$C_{11}H_{22}N_2O_3$	57.4	57.2	9.6	9.6	12.2	12.1
38	C_6H_{11}–[f]	CH_3–		164–170 (.03)	91	$C_{13}H_{26}N_2O_2$	64.4	64.2	10.8	10.7	11.6	12.0
39	C_6H_{11}–[f]	C_2H_5–		170 (.04)	87	$C_{14}H_{28}N_2O_2$	65.6	65.5	11.0	10.7	10.9	10.7
40	C_6H_5–	CH_3–		176 (.04)	93	$C_{13}H_{20}N_2O_2$	66.1	65.9	8.5	8.3	11.9	11.8
41	C_6H_5–	C_2H_5–		182–184 (.04)	85	$C_{14}H_{22}N_2O_2$					11.2	11.2
42	$C_6H_5CH_2$–	CH_3–		174–178 (.1)	88	$C_{14}H_{22}N_2O_2$	67.2	66.9	8.9	9.0	11.2	10.9
43	$C_6H_5CH_2$–	$(CH_3)_2CH$–		168–171 (.03)	88	$C_{16}H_{26}N_2O_2$	69.0	69.3	9.4	9.3	10.1	10.0
44	C_9H_{11}–[g]	CH_3–		182 (.02)	91	$C_{16}H_{26}N_2O_2$	69.0	69.1	9.4	9.6	10.1	9.7
45	–C_8H_8–[h]			208–210 (.08)	85	$C_{14}H_{20}N_2O_2$	67.7	67.3	8.1	8.1	11.3	11.3
$R_1 = CH_3, R_2 = H, n = 4$												
46	CH_3–	CH_3–		124–131 (0.03)	74	$C_9H_{20}N_2O_2$	57.4	57.0	10.7	10.6	14.9	14.7
47	C_2H –	C_2H_5–		132–136 (.03)	87	$C_{11}H_{24}N_2O_2$					13.0	12.7
48	$(CH_3)_2CH$–	$(CH_3)_2CH$–		138–142 (.06)	86	$C_{13}H_{28}N_2O_2$	63.9	64.1	11.6	11.4		
49	$(CH_3)_2CH$–	$(CH_3)_2CH$–	CH_3I	115–116	70	$C_{14}H_{13}IN_2O_2$	43.5	43.8	8.1	8.5	7.3	7.2
50	n-C_4H_9–	n-C_4H_9–		156–160 (.08)	76	$C_{15}H_{32}N_2O_2$	66.1	65.7	11.8	11.7	10.3	9.9
$R_1 = CH_3, R_2 = CH_3, n = 3$												
51	CH_3–	CH_3–		115(0.06)	86	$C_9H_{20}N_2O_2$					14.9	13.1
52	CH_3–	CH_3–	CH_3I	170–171[da]	77	$C_{10}H_{23}IN_2O_2$	36.4	36.2	7.0	6.9		
53	CH_3–	CH_3–	$C_6H_5CH_2Cl$	202–203	80	$C_{16}H_{27}ClN_2O_2$	61.0	61.3	8.7	8.6	8.8	8.7
54	C_2H_5–	C_2H_5–		128 (0.1)	80	$C_{11}H_{24}N_2O_2$	61.1	60.9	11.2	11.1	13.0	12.7
55	$(CH_3)_2CH$–	CH_3–		114–118 (.05)	73	$C_{11}H_{24}N_2O_2$	61.1	60.9	11.2	11.5	13.0	12.7

TABLE I (*Continued*)

No.	R_3	R_4	R_5X	B.p. (mm.)[a] or m.p.,[a,d] °C.	Yield,[b] %	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
56	n-C_4H_9	n-C_4H_9	$(CH_3)_2SO_4$	132–140 (.04)	51	$C_{15}H_{32}N_2O_2$	66.1	66.0	11.8	12.0	10.3	10.0
57	$-(CH_2)_4-$			114–124 (.03)	78	$C_{11}H_{22}N_2O_2$	61.7	61.7	10.4	9.9		
58	$-(CH_2)_4-$		$C_4H_7BrO_2$[j]	156–157		$C_{15}H_{29}BrN_2O_4$	47.3	47.1	7.7	8.0		
59	$-(CH_2)_2O(CH_2)_2-$			145 (0.04)	91	$C_{11}H_{22}N_2O_3$					12.2	12.2
60	$-(CH_2)_2O(CH_2)_2-$		MT[k]	77–81[db]	27	$C_{19}H_{32}N_2O_6S$	54.8	54.8	7.7	7.9	6.7	7.0
61	$-C_6H_{12}O-$[e]			81–83[dd]	79	$C_{13}H_{26}N_2O_3$	60.4	60.4	10.1	9.9	10.8	10.7
62	$C_6H_{11}-$[f]	CH_3-		56–58	82	$C_{14}H_{28}N_2O_2$	65.6	65.4	11.0	10.7	10.9	10.7
63	$C_6H_{11}-$[f]	C_2H_5-		144–154 (0.03)	72	$C_{15}H_{30}N_2O_2$	66.6	66.5	11.2	10.8		
64	C_6H_5-	CH_3-		164–169 (.05)	72	$C_{14}H_{22}N_2O_2$	67.2	67.5	8.9	9.0		
65	C_6H_5-	C_2H_5-		164–170 (.03)	79	$C_{15}H_{24}N_2O_2$	68.2	68.0	9.2	8.9		
66	$C_6H_5CH_2-$	CH_3-		160 (.2)	80	$C_{15}H_{24}N_2O_2$	68.2	68.6	9.2	9.1		
68	$C_9H_{11}-$[g]	CH_3-		174 (.03)	78	$C_{17}H_{28}N_2O_2$	69.8	69.3	9.6	9.5	9.6	9.7
69	$-C_8H_8-$[h]			99–100[db]	52	$C_{15}H_{22}N_2O_2$	68.7	68.9	8.5	8.6	10.7	10.8
				$R_1 = CH_3$, $R_2 = CH_3$, $n = 4$								
70	CH_3-	CH_3-		120 (0.03)	75	$C_{10}H_{22}N_2O_2$	59.4	59.3	11.0	10.6	13.8	14.0
71	CH_3-	CH_3-	CH_3I	134–136	75	$C_{11}H_{25}IN_2O_2$	38.4	38.4	7.3	6.8	8.2	8.1
72	C_2H_5-	C_2H_5-		122–126 (0.06)	74	$C_{12}H_{26}N_2O_2$	62.6	62.6	11.4	11.3	12.2	11.8
73	$(CH_3)_2CH-$	$(CH_3)_2CH-$		58[dc]	51	$C_{14}H_{30}N_2O_2$	65.1	65.0	11.7	11.8	10.8	10.9
74	$(CH_3)_2CH-$	$(CH_3)_2CH-$	CH_3I	135–137	77	$C_{15}H_{33}IN_2O_2$	45.0	45.3	8.3	8.1	7.0	7.1
75	n-C_4H_9-	n-C_4H_9-		144–148 (0.08)	73	$C_{16}H_{34}N_2O_2$	67.1	66.6	12.0	11.8	9.8	9.9

[a] Boiling points are not corrected; melting points are not corrected and have been taken on a Fisher–Johns melting point block. [b] Yields are based on distilled product or recrystallized product. [c] Analyses by Weiler and Strauss, Oxford, Eng. [d] Solids were recrystallized from ethanol-ethyl acetate unless otherwise shown; [da] acetonitrile, [db] ethyl acetate, [dc] hexane, [dd] hexane–ethyl acetate. [e] R_3 and R_4 with attached N represent 4-(2,6-dimethylmorpholino). [f] $C_6H_{11}-$ = cyclohexyl. [g] $C_9H_{11}-$ = the "d"-form of $C_6H_5CH_2CHCH_3-$. [h] C_8H_8- with the attached N represents the 1-indolino derivative. [i] $C_4H_6Br_2 = BrCH_2CH{=}CHCH_2Br$ and the compound described in the bis-quaternary salt with this dihalide. [j] $C_4H_7BrO_2 = BrCH_2COOC_2H_5$. [k] MT = methyl tosylate.

variant of $-N(CH_2)_3NR_3R_4$ in the $R_1 = CH_3$, $R_2 = H$ category (except compounds 84 and 111 which were the same). The diones II wherein R_1, $R_2 = CH_3$ were obtained in an average yield of 85%, with a noted greater yield over each individual variant in the $R_1 = CH_3$, $R_2 = H$ category (except compounds 135, 139, 140, 145).

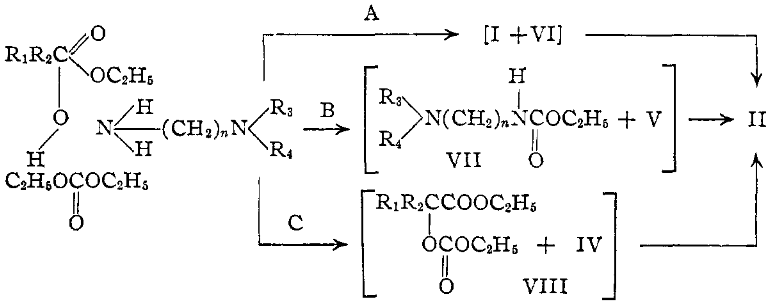
These findings are of interest in that the best yields are obtained from the α-hydroxy-isobutyramides which have a tertiary hydroxyl group which must react for cyclization to occur. In this regard it has been demonstrated that transesterification of diethyl carbonate by ethyl α-hydroxyisobutyrate occurs under sodium ethoxide catalysis to give a 23% yield of the carbonate VIII, R_1, $R_2 = CH_3$. With the glycolamides the noted poorer yields might be ascribed to the presence of α-hydrogen atoms which could induce complicating side reactions. In this analysis of the yields there did not appear to be any criticality associated with the variation of $-NR_3R_4$.

Pharmacology.—A number of the compounds showed a depressant effect on the central nervous system (Table III). Although clearcut relationships between structure and activity are not evident, inspection of the active structures reported in Table III shows several interesting relationships.

The variant $R_1R_2 = H$ showed the greatest number of active structures while R_3R_4 = methyl gave the fewest. Considering the number of compounds examined, approximately equal effects were obtained with n as 3 or 4.

Although eight of the active structures shown are quaternaries, there is no instance where the free base and its quaternary both show high order of activity. In the $-NR_3R_4$ variable the most consistent in yielding central nervous system depressant effects were the dibutylamino (compounds 5, 33, 101, 108), diethylamino (compounds 47, 79, 97, 105), dimethylamino (compounds 20, 27, 102, 149) and the morpholino (compounds 8, 85, 137) groups. Within this group of active structures, ten are hydroxyamides and twelve are oxazolidinediones. Compounds 33 and 108 were the only pair in which the amide I and the oxazolidinedione II are interrelated in terms of all variables.

SCHEME I
ONE-STEP SYNTHESIS OF OXAZOLIDINEDIONES

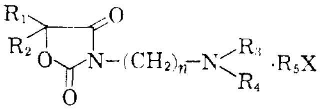


The only noted regularity is within the group II wherein the congeners (compounds 102, 105, 108) show effect.

Further investigation is required to select the key structures in this series and at present the methiodide of N-dimethylaminopropyl lactamide (compound 27) is undergoing clinical trial.

TABLE II

3-(AMINOALKYL)-OXAZOLIDINEDIONES



No.	R_3	R_4	R_5X	B.p. (mm.)[a] or m.p.,[a,d] °C.	Yield,[b] %	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$R_1 = H, R_2 = H, n = 3$												
76	CH_3–	CH_3–		80–83 (0.05)	66	$C_8H_{14}N_2O_3$	51.6	51.6	7.6	7.3	15.1	15.0
77	CH_3–	CH_3–	CH_3I	218–219	71	$C_9H_{17}IN_2O_3$	32.9	33.2	5.2	4.9	8.5	8.9
78	C_2H_5–	C_2H_5–		95 (0.05)	70	$C_{10}H_{18}N_2O_3$	56.1	56.2	8.5	8.8	13.1	13.0
79	C_2H_5–	C_2H_5–	CH_3I	150–151	92	$C_{10}H_{18}IN_2O_3$	37.1	37.4	5.9	6.0	7.9	7.9
80	$(CH_3)_2CH$–	CH_3–		100–102 (0.05)	70	$C_{10}H_{18}N_2O_3$	56.1	56.1	8.5	8.6	13.1	12.9
81	n-C_4H_9–	n-C_4H_9–		136–138 (.3)	64	$C_{14}H_{26}N_2O_3$	62.2	62.3	9.7	9.9		
82	–$(CH_2)_4$–			110 (.03)	66	$C_{10}H_{16}N_2O_3$	56.6	57.2	7.6	8.0		
83	–$(CH_2)_4$–		CH_3I	203–204	63	$C_{11}H_{19}IN_2O_3$	37.3	37.5	5.4	5.2	7.9	8.0
84	–$(CH_2)_2O(CH_2)_2$–			63–64[dd]	61	$C_{10}H_{16}N_2O_4$	52.6	53.1	7.1	7.3	12.3	12.3
85	–$(CH_2)_2O(CH_2)_2$–		CH_3I	230–231	72	$C_{11}H_{19}IN_2O_4$	35.7	35.9	5.2	5.0		
86	–$C_6H_{12}O$–[e]			130–133 (0.2)	68	$C_{12}H_{20}N_2O_4$	56.2	56.4	7.9	8.1		
87	C_6H_{11}–[f]	CH_3–		146–150 (.5)	56	$C_{13}H_{22}N_2O_3$	61.4	61.3	8.7	8.9	11.0	10.9
88	C_6H_{11}–[f]	C_2H_5–		138–140 (.1)	76	$C_{14}H_{24}N_2O_3$	62.7	63.1	9.0	9.4	10.4	10.2
89	C_6H_5–	CH_3–		172–178 (.1)	73	$C_{13}H_{16}N_2O_3$	62.9	63.0	6.5	6.9	11.3	11.2
90	C_6H_5–	C_2H_5–		188–190 (.7)	66	$C_{14}H_{18}N_2O_3$	64.1	63.9	6.9	7.5	10.7	10.7
91	$C_6H_5CH_2$–	CH_3–		170–179 (.7)	65	$C_{14}H_{18}N_2O_3$	64.1	64.1	6.9	6.8	10.7	11.0
92	$C_6H_5CH_2$–	$(CH_3)_2CH$–		170–174 (.2)	83	$C_{16}H_{22}N_2O_3$	66.2	66.3	7.6	7.9	9.7	9.7
94	–C_6H_8–[h]			182–184 (.4)	69	$C_{14}H_{16}N_2O_3$	64.6	64.6	6.2	6.3	10.8	10.6
$R_1 = H, R_2 = H, n = 4$												
95	CH_3–	CH_3–		104 (0.08)	71	$C_9H_{16}N_2O_3$	54.0	54.2	8.1	8.0	14.0	13.9
96	CH_3–	CH_3–	CH_3I	188–189	99	$C_{10}H_{19}IN_2O_3$	35.1	35.2	5.6	6.0	10.9	10.7
97	C_2H_5–	C_2H_5–		114 (0.1)	81	$C_{11}H_{20}N_2O_3$	57.8	58.2	8.8	8.8	12.3	12.0
98	C_2H_5–	C_2H_5–	CH_3I	87–89	60	$C_{12}H_{23}IN_2O_3$	38.9	38.8	6.3	6.4	7.6	7.8
99	$(CH_3)_2CH$–	$(CH_3)_2CH$–		130 (0.2)	76	$C_{13}H_{24}N_2O_3$	60.9	61.1	9.4	9.3		
100	$(CH_3)_2CH$–	$(CH_3)_2CH$–	CH_3I	136–138	95	$C_{14}H_{27}IN_2O_3$	42.2	42.3	6.8	7.1		
101	n-C_4H_9–	n-C_4H_9–		138 (0.06)	74	$C_{15}H_{28}N_2O_3$	63.4	63.4	9.9	9.9	9.9	10.2
$R_1 = CH_3, R_2 = H, n = 3$												
102	CH_3–	CH_3–		76 (0.03)	86	$C_9H_{16}N_2O_3$	54.0	53.9	8.1	8.3	14.0	13.9
103	CH_3–	CH_3–	CH_3I	171–172	95	$C_{10}H_{19}IN_2O_3$	35.1	35.3	5.6	6.1	8.2	8.0
104	CH_3–	CH_3–	C_3H_5Br[l]	190–195	86	$C_{12}H_{21}BrN_2O_3$	44.9	44.8	6.6	6.7	8.7	8.8
105	C_2H_5–	C_2H_5–		87–100 (0.04)	78	$C_{11}H_{20}N_2O_3$	57.9	57.9	8.8	8.8	12.3	12.3
106	C_2H_5–	C_2H_5–	CH_3I	129–130	62	$C_{12}H_{23}IN_2O_3$	38.9	39.0	6.3	6.2	7.6	7.7
107	$(CH_3)_2CH$–	CH_3–		90–92 (0.08)	81	$C_{11}H_{20}N_2O_3$	57.9	58.0	8.8	8.9		
108	n-C_4H_9–	n-C_4H_9–		128 (0.2)	82	$C_{15}H_{28}N_2O_3$	63.4	63.1	9.9	9.8	9.9	9.8
109	–$(CH_2)_4$–			102 (.02)	79	$C_{11}H_{18}N_2O_3$	58.4	58.3	8.0	7.8		
110	–$(CH_2)_4$–		CH_3I	181–182	89	$C_{12}H_{21}IN_2O_3$	39.2	39.2	5.8	5.5		
111	–$(CH_2)_2O(CH_2)_2$–			115–120 (.08)	57	$C_{11}H_{18}N_2O_4$	54.5	53.8	7.5	7.5	11.6	11.5
111A	–$(CH_2)_2O(CH_2)_2$–		HCl	218–219	61	$C_{11}H_{19}ClN_2O_4$	47.4	47.2	6.9	7.1	10.1	9.7
112	–$(CH_2)_2O(CH_2)_2$–		CH_3I	224–227	54	$C_{12}H_{21}IN_2O_4$	37.5	37.9	5.5	5.7	7.3	7.4
113	–$C_6H_{12}O$–[e]			120 (.03)	84	$C_{13}H_{22}N_2O_4$	57.8	58.4	8.2	8.5	10.4	10.1
114	C_6H_{11}–[f]	CH_3–		134–138 (.1)	71	$C_{14}H_{24}N_2O_3$	62.7	62.9	9.0	9.0		
115	C_6H_{11}–[f]	C_2H_5–		130–136 (.05)	78	$C_{15}H_{26}N_2O_3$	63.8	63.8	9.3	9.5	9.9	9.8
116	C_6H_5–	CH_3–		158–164 (.1)	82	$C_{14}H_{18}N_2O_3$	64.1	64.2	6.9	7.1	10.7	10.8
117	C_6H_5–	C_2H_5–		154–170 (.05)	80	$C_{15}H_{20}N_2O_3$	65.2	65.1	7.3	7.3	10.1	10.3
118	$C_6H_5CH_2$–	CH_3–		145–146 (.08)	84	$C_{15}H_{20}N_2O_3$	65.2	65.5	7.3	7.5	10.1	10.2
119	$C_6H_5CH_2$–	$(CH_3)_2CH$–		156–158 (.1)	90	$C_{17}H_{24}N_2O_3$					9.2	9.1
120	C_9H_{11}–[g]	CH_3–		160–164 (.03)	91	$C_{17}H_{24}N_2O_3$	67.1	66.8	8.0	8.2		
121	–C_8H_8–[h]			168 (.06)	77	$C_{15}H_{18}N_2O_3$	65.7	66.1	6.6	6.9	10.2	10.2
$R_1 = CH_3, R = H, n = 4$												
122	CH_3–	CH_3–		93 (0.05)	69	$C_{10}H_{18}N_2O_3$	56.1	56.4	8.5	8.5	13.1	12.7
123	CH_3–	CH_3–	CH_3I	235–236	95	$C_{11}H_{21}IN_2O_3$	37.1	37.4	5.9	6.1	7.9	7.8
124	C_2H_5–	C_2H_5–		100 (.04)	91	$C_{12}H_{22}N_2O_3$	59.5	59.1	9.2	9.1	11.6	12.0
125	$(CH_3)_2CH$–	$(CH_3)_2CH$–		110–111 (.04)	89	$C_{14}H_{26}N_2O_3$	62.2	62.3	9.7	9.5		
126	n-C_4H_9–	n-C_4H_9–		135–137 (.05)	76	$C_{16}H_{30}N_2O_3$	64.4	64.0	10.1	9.8	9.4	9.1

TABLE II (*Continued*)

No.	R_3	R_4	R_5X	B.p. (mm.)[a] or m.p.,[a d] °C.	Yield,[b] %	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$R_1 = CH_3, R_2 = CH_3, n = 3$												
127	CH_3-	CH_3-		67–68 (0.03)	87	$C_{10}H_{18}N_2O_3$	56.1	56.2	8.5	8.7	13.0	12.8
128	CH_3-	CH_3-	CH_3I	233–234	93	$C_{11}H_{21}IN_2O_3$	37.1	37.4	5.9	6.2	7.9	7.9
129	CH_3-	CH_3-	C_2H_5I	154–155	82	$C_{12}H_{23}IN_2O_3$	38.9	38.8	6.3	5.9	7.6	7.6
130	C_2H_5-	C_2H_5-		82–86 (.03)	89	$C_{12}H_{22}N_2O_3$	59.5	59.9	9.2	9.4	11.6	11.9
131	C_2H_5-	C_2H_5-	CH_3I	121–122	91	$C_{13}H_{25}IN_2O_3$	40.6	40.9	6.6	6.8	7.3	7.2
132	$(CH_3)_2CH-$	CH_3-		88 (.05)	87	$C_{12}H_{22}N_2O_3$	59.5	59.6	9.2	9.1		
133	n-C_4H_9-	n-C_4H_9-		116 (.05)	95	$C_{16}H_{30}N_2O_3$	64.4	64.4	10.1	10.1		
134	n-C_4H_9-	n-C_4H_9-	CH_3I	101–102	75	$C_{17}H_{33}IN_2O_3$	46.4	46.4	7.6	7.4	6.4	6.4
135	$-(CH_2)_4-$			94 (.04)	74	$C_{12}H_{20}N_2O_3$	60.0	60.3	8.4	8.2	11.7	11.6
136	$-(CH_2)_4-$		CH_3I	123–125	83	$C_{13}H_{23}IN_2O_3$	40.9	41.0	6.1	6.3	7.3	6.9
137	$-(CH_2)_2O(CH_2)_2-$			127–128 (.2)	94	$C_{12}H_{20}N_2O_4$	56.2	56.2	7.9	8.0	10.9	10.7
138	$-(CH_2)_2O(CH_2)_2-$		CH_3I	200–201	76	$C_{13}H_{23}IN_2O_4$	39.2	39.5	5.8	5.9	7.0	7.0
139	$-C_6H_{12}O-$[e]			122–128 (.05)	83	$C_{14}H_{24}N_2O_4$	59.1	59.4	8.5	8.8	9.9	9.8
140	$C_6H_{11}-$[f]	CH_3		49–51[dc]	63	$C_{15}H_{26}N_2O_3$	63.8	64.1	9.3	9.3	9.9	9.8
141	$C_6H_{11}-$[f]	C_2H_5-		130–132 (.04)	86	$C_{16}H_{28}N_2O_3$	64.8	65.1	9.5	9.4	9.5	9.0
142	C_6H_5-	CH_3-		146–148 (.03)	92	$C_{15}H_{20}N_2O_3$	65.2	65.6	7.3	7.3	10.1	9.7
143	C_6H_5-	C_2H_5-		156–157 (.06)	89	$C_{16}H_{22}N_2O_3$	66.2	66.4	7.6	8.1	9.7	9.7
144	$C_6H_5CH_2-$	CH_3-		140 (.05)	84	$C_{16}H_{22}N_2O_3$	66.2	66.3	7.6	7.8	9.7	9.8
145	$C_6H_5CH_2-$	$(CH_3)_2CH-$		146–148 (.03)	81	$C_{18}H_{26}N_2O_3$	67.9	68.3	8.2	8.3	8.8	8.9
146	$C_9H_{11}-$[g]	CH_3-		156–158 (.01)	78	$C_{18}H_{26}N_2O_3$	67.9	67.9	8.2	8.5		
147	$-C_8H_8-$[h]			164 (.03)	91	$C_{16}H_{20}N_2O_3$	65.2	65.6	7.0	7.0	10.1	9.7
$R_1 = CH_3, R_2 = CH_3, n = 4$												
148	CH_3-	CH_3-		82 (0.03)	77	$C_{11}H_{20}N_2O_3$	57.9	58.1	8.8	8.9		
149	CH_3-	CH_3-	CH_3I	237–238	96	$C_{12}H_{34}IN_2O_3$	38.9	39.0	6.3	6.4	7.6	8.0
150	CH_3-	CH_3-	$C_7H_6Cl_2$[m]	176–181[db]	78	$C_{18}H_{26}Cl_2N_2O_3$					7.2	7.1
151	C_2H_5-	C_2H_5-		93–96 (0.03)	89	$C_{13}H_{24}N_2O_3$	60.9	61.1	9.4	9.3	10.9	10.9
152	$(CH_3)_2CH-$	$(CH_3)_2CH-$		106 (.03)	84	$C_{15}H_{28}N_2O_3$	63.4	63.5	9.9	10.1	9.9	9.7
153	$(CH_3)_2CH-$	$(CH_3)_2CH-$	CH_3I	156–158	92	$C_{16}H_{31}IN_2O_3$	45.1	45.2	7.3	7.6	7.6	7.0

Footnotes are the same as for Table I. [l] C_3H_5Br = allyl bromide. [m] $C_7H_6Cl_2$ = *p*-chlorobenzyl chloride.

TABLE III

CENTRAL NERVOUS SYSTEM DEPRESSANT EFFECT

No.[a]	LD_{min}[b]	DMA[c,d] %	No.[a]	LD_{min}[a]	DMA[c,d] %
5	1000	13*	83	150	41
7	200	30	85	>1000	24*
8	>1000	17*	86	400	38
15	>1000	26	94	500	24
17	500	60	97	>1000	27
20	>1000	21	101	750	51
27	>1000	27*	102	>1000	52*
33	400	56*	105	>1000	16*
47	>1000	40	108	250	15*
58	>1000	30	137	>1000	45*
79	500	39*	149	300	21

[a] The numbers correspond to the compound numbers in Tables I and II. [b] LD_{min} is the minimum dose lethal to mice, subcutaneous, in mg./kg. [c] DMA = the percentage depression of motor activity as established in rats and the method has been described in ref. 4. [d] The dosage level used for the test was 20 mg./kg. subcutaneous, except those compounds marked with an asterisk which were evaluated at 10 mg./kg.

Experimental[16]

Reactants.—Most of the dialkylaminoalkylamines were obtained from commercial sources. Some of these were prepared by cyanoethylation of the secondary amine R_3R_4NH, and reduction to the $R_3R_4N(CH_2)_3NH_2$. The compounds so prepared are described in Table IV.

General Procedure for α-Hydroxyamides of Table I.—A solution of 0.2 mole of the amine $R_3R_4(CH_2)_nNH_2$ in 30 ml. of the α-hydroxyester (ethyl glycolate, ethyl lactate or ethyl α-hydroxyisobutyrate) was heated under reflux over five hours while removing the formed ethanol during the course of the reaction. The excess ester was removed and the residue distilled to yield the product I.

General Procedure for Oxazolidinediones of Table II (from α-Hydroxyamides *via* Path A, Scheme I).—A solution of 0.1 mole of the α-hydroxyamide (Table I) in 50 ml. of diethyl carbonate was treated with a charge of catalyst (0.2 g. of sodium dissolved in 4 ml. of ethanol) and the reaction mixture heated under reflux for 1 hour. The formed alcohol (quantitative) was removed by distillation. The reaction mixture was filtered, the excess diethyl carbonate removed and the residue distilled to yield the product II.

General Procedure for Oxazolidinediones of Table II (from Amines Directly).—A solution of 0.05 mole of the amine $R_3R_4N(CH_2)_nNH_2$ and 0.05 mole of the α-hydroxyester in 25 ml. of diethyl carbonate was treated with a charge of catalyst (0.2 g. of sodium in 4 ml. of ethanol) and the reaction mixture heated under reflux for 1 hour. The formed ethanol was removed by distillation. The reaction mixture was filtered, the excess diethyl carbonate removed and the product distilled.

The yields of oxazolidinediones II obtained directly from the amine, compared to the over-all yield based on the amine when II is obtained from the α-hydroxyamide, are shown for a few typical cases.

Compound 137, 89% *vs.* 86% (from compound 59); compound 76, 63% *vs.* 48% (from compound 1); compound 108, 85% *vs.* 68% (from compound 33); compound 133, 83% *vs.* 48% (from compound 56).

Quaternary salts of Tables I and II were prepared using an excess of the halide in refluxing ethanol or acetonitrile.

Ethyl α-(Carbethoxyoxy)-isobutyrate (Compound VIII, $R_1R_2 = CH_3$).—A mixture of 13.2 g. (0.1 mole) of ethyl α-hydroxyisobutyrate and 25 ml. of diethyl carbonate under

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[16] Data shown in the tables are not reproduced in the Experimental section.

TABLE IV

NITRILES AND AMINES $R_3R_4NCH_2CH_2$–Z: Z = –CN = A; Z = –CH_2NH_2 = B

No.[n,o]	R_3	R_4	B.p.,[a] °C.	B.p.,[a] Mm.	Yield,[b] %	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1A[p]	$(CH_3)_2CH$–	CH_3–	86	8.0	81							
1B[q]	$(CH_3)_2CH$–	CH_3–	80	32.0	60							
2A[r]	C_6H_{11}–[f]	CH_3–	74	0.06	86							
2B[s]	C_6H_{11}–[f]	CH_3–	60–66	.06	68							
3A[t]	C_6H_{11}–[f]	C_2H_5–	64–68	.04	61	$C_{11}H_{20}N_2$	73.3	73.2	11.2	11.1	15.5	15.7
3B[u]	C_6H_{11}–[f]	C_2H_5–	72–80	.13	71							
4A[v]	C_6H_5–	CH_3–	110	.15	84	$C_{10}H_{12}N_2$	75.0	75.0	7.6	7.9	17.5	17.0
4B[w]	C_6H_5–	CH_3–	94	.05	85							
5A[x]	C_6H_5–	C_2H_5–	105–122	.15	73	$C_{11}H_{14}N_2$	75.8	75.6	8.1	8.1	16.1	15.7
5B	C_6H_5–	C_2H_5–	89	.1	66	$C_{11}H_{18}N_2$	74.1	74.0	10.2	10.1	15.7	16.0
6A[y]	$C_6H_5CH_2$–	CH_3–	170	16.0	90							
6B	$C_6H_5CH_2$–	CH_3–	80–81	0.1	66	$C_{11}H_{18}N_2$	74.1	73.8	10.2	10.4	15.7	15.6
7A	$C_6H_5CH_2$–	$(CH_3)_2CH$–	98–100	.03	79	$C_{13}H_{18}N_2$	77.2	77.1	9.0	9.3	13.9	13.7
7B	$C_6H_5CH_2$–	$(CH_3)_2CH$–	76–82	.1	87	$C_{13}H_{22}N_2$					13.6	13.8
8A	C_9H_{11}–[g]	CH_3–	108–115	.1	85	$C_{13}H_{18}N_2$	77.2	76.9	9.0	9.1	13.9	14.3
8B	C_9H_{11}–[g]	CH_3–	100–104	.05	75	$C_{13}H_{22}N_2$	75.7	75.4	10.8	10.8	13.6	13.8
9A[z]	–C_8H_8–[h]		102–118	.07	94	$C_{11}H_{12}N_2$	76.7	76.4	7.0	6.9		
9B	–C_8H_8–[h]		92–100	.07	83	$C_{11}H_{16}N_2$	75.0	74.8	9.2	9.3	15.9	15.8

[a–m] These superscripts have the same significance as indicated in Tables I and II. [n] An "A" after compound number signifies the nitrile. [o] "B" after compound number signifies the amine. [p] Reported, J. Corse, J. T. Bryant and H. A. Shoule, THIS JOURNAL, **68,** 1906 (1946), b.p. 94–96°. [q] Reported, footnote *p*, b.p. 72–74° (32 mm.). [r] Reported, footnote *p*, b.p. 145–148° (40 mm.). [s] Reported, footnote *p*, b.p. 122–124° (24 mm.). [t] Reported, footnote *p*, no data given. [u] Reported, footnote *p*, b.p. 135–141° (32 mm.). [v] Reported, French Patent 747,827 (1937) [*C. A.*, **32,** 4608 (1938)], b.p. 125–135° (2 mm.). [w] Reported, F. C. Whitmore, *et al.*, THIS JOURNAL, **66,** 729 (1944), b.p. 171–172° (40 mm.). [x] Reported, French Patent 742,358 (1933) [*C.A.*, **27,** 3483 (1933)], b.p. 175–177° (17 mm.). [y] Reported, J. A. King and F. H. McMillan, THIS JOURNAL, **68,** 1468 (1946), b.p. 163–164° (14 mm.). [z] Reported, B. D. Astill and V. Boekelheide, *J. Org. Chem.*, **23,** 316 (1958), b.p. 129–133° (1 mm.), 87%.

reflux was treated successively with a charge of catalyst (0.2 g. of sodium in 4 ml. of ethanol), heated for 1 hour and the formed ethanol removed. The process was repeated three times. The reaction mixture was clarified by filtration, the volatile reactants removed and the product distilled to yield 5.6 g. at 108–109° (0.02 mm.). Redistillation gave 4.74 g. of product boiling at 106–108° (0.02 mm.), $n^{20}D$ 1.4144.

Anal. Calcd. for $C_9H_{16}O_5$: C, 52.9; H, 7.9. Found: C, 52.8; H, 7.8.

Ethyl α-(Carbethoxyoxy)-propionate (Compound VIII, R_1 = CH_3, R_2 = H) was prepared in 22% yield, b.p. 112–114° (18 mm.), $n^{20}D$ 1.4114 following the procedure above. It was more conveniently prepared as follows.

A mixture of 6.0 g. (0.051 mole) of ethyl lactate in 50 ml. of pyridine was cooled and maintained at 0° during addition dropwise (0.5 hour with stirring) of 7 ml. of ethyl chlorocarbonate. After 2 hours at 20°, 50 ml. of water was added and the reaction mixture acidified with hydrochloric acid, then extracted with four 25-ml. portions of benzene. The benzene extract was dried (sodium sulfate), the benzene removed and the product, 7.4 g. (77%), distilled at 80° (4 mm.).[17]

5-Methyl-3-([4-morpholino]-propyl)-1,3-oxazolidine-2,4-dione (Compound 111, Table II. Preparation *via* Path C, Scheme I).—A mixture of 4.82 g. (0.034 mole) of 3-(4-morpholino)-propylamine and 6.37 g. (0.034 mole) of ethyl α-(carbethoxyoxy)-propionate in 25 ml. of diethyl carbonate was allowed to react under conditions following the general procedure for compounds described for Table II above. The product, 5.0 g. (61%), was obtained, boiling at 124–126° (0.08 mm.), $n^{20}D$ 1.4851.

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[17] K. Freudenberg and M. Meister, *Ann.*, **518,** 86 (1935), report b.p. 93° (11 mm.).