1,7,8,9,10,10-Hexachlorotetracyclo[5.2.1.0^{2,6}.0^{3,5}]dec-8-ene (XIII).—The thermal degradation of II was quantitatively carried out by dissolving 11 g. (0.03 mole) in 125 ml. of benzene and refluxing the solution for 2 hours. The product was recovered and recrystallized from aqueous methanol to yield 10 g. of XIII, m.p. 165°.

Anal. Calcd. for $C_{10}H_6Cl_6$: C, 35.4; H, 1.8; Cl, 62.8; mol. wt., 339; H_2 uptake, mole/mole, 0.0. Found: C, 35.4; H, 1.9; Cl, 62.5; mol. wt., 338; H_2 uptake, mole/mole, 0.0.

5,6,7,8,9,9-Hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanophthalazine 2-oxide (XIV).—Eleven and one-half grams (0.031 mole) of II was added to 244 g. of a chloroform solution containing 8.3 g (0.06 mole) of peroxybenzoic acid. The solution was allowed to stand at room temperature for 136 hours. Evaporation of the solvent left a solid which was recrystallized from ether–cyclohexane to yield 10.5 g. (91%) of pure N-oxide XIV, m.p. 256° dec. The infrared spectrum of XIV shows principal peaks at 6.25 μ (C=C–Cl) and at 6.60 μ (azoxy group).[16] Compound XIV heated at 110° for three hours did not produce a change in its melting point or analysis.

Anal. Calcd. for $C_{10}H_6Cl_6N_2O$: C, 31.3; H, 1.6; Cl, 55.6; N, 7.3. Found: C, 31.6; H, 1.7; Cl, 55.3; N, 7.4.

2,3-Diacetyl-5,6,7,8,9,9-hexachloro-1,2,3,4,4a,5,8,8a-octahydro-1,4,5,8-dimethanophthalazine (XXIV).—Fifty grams (0.11 mole) of VI was added to a mixture of 170 g. of acetic anhydride and 25 g. of sodium acetate to produce a vigorously exothermic reaction which was controlled at 0° by cooling. The reaction mixture was poured into water, and the precipitated solid was filtered and recrystallized from benzene–hexane to yield 15 g. (33%) of the diacetyl derivative XXIV, m.p. 204°. The infrared absorption spectra showed two strong carbonyl peaks at 5.88 and 5.96 μ in addition to the usual peak at 6.27 μ (C=C–Cl).

Anal. Calcd. for $C_{14}H_{12}Cl_6N_2O_2$: Cl, 47.0. Found: Cl, 47.2.

5,6,7,8,9,9-Hexachloro-3,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethano-2(1H)-phthalazinesulfonic Acid (XXV).—Eleven and three-tenths grams (0.03 mole) of VI was dissolved in 110 ml. of benzene and 7.0 g. (0.06 mole) of chlorosulfonic acid was added dropwise with stirring at room temperature. The precipitated product was collected by filtration. It melted at 233° with decomposition, and could not be purified due to its low solubility in common organic solvents and in water. The yield was 12.8 g. (94%). The infrared spectrum showed strong peaks at 3.13 μ (N–H), 6.26 μ (C=C–Cl), and also at 8.67, 9.65 and 14.36 μ, all probably due to the SO_3H group.

Anal. Calcd. for $C_{10}H_8Cl_6N_2SO_3$: N, 6.2; S, 7.1; neut. equiv., 449. Found: N, 5.8; S, 6.7; neut. equiv., 463.

5,6,7,8-Tetrachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanophthalazin-9-one Dimethyl Acetal (XXVI).—Thirty and two-tenths grams (0.06 mole) of XI was treated with 15.8 g. of 85% potassium hydroxide dissolved in 125 ml. of absolute methanol at room temperature over a period of four days. Work-up by ether extraction and recrystallization from ether–hexane yielded 12.8 g. (60%) of XXVI, m.p. 114°.

Anal. Calcd. for $C_{12}H_{12}Cl_4N_2O_2$: C, 40.0; H, 3.3. Found: C, 40.4; H, 2.8.

5,6,7,8-Tetrachloro-1,2,3,4,4a,8a-hexahydro-1,4-methanophthalazine Sulfate (XXVII).—Thirty and two-tenths grams (0.06 mole) of XI was added to 60 ml. of 95% sulfuric acid and the mixture was heated on the steam-bath until gas evolution ceased. The mixture was poured onto crushed ice and the precipitated solid was filtered and washed with benzene. The product XXVII amounted to 10.6 g. (46% yield), m.p. 200–203° dec.

Anal. Calcd. for $C_9H_{10}Cl_4N_2O_4S$: Cl, 36.9; S, 8.3; neut. equiv., 192. Found: Cl, 36.7; S, 8.0; neut. equiv., 189.

MODESTO, CALIF.

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

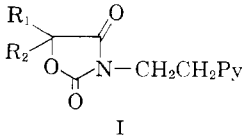
Pyridylethylated Oxazolidinediones. II[1]

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

RECEIVED AUGUST 11, 1958

An additional series of pyridylethylated 2,4-oxazolidinediones of the type I have been synthesized and screened for pharmacological activity. Significant responses found in animals include anti-convulsant activity, depression of motor activity and prolongation of Evipal sleeping time. The products of hydrolysis of the compound IV have been examined and found to have considerably less central nervous system depressant effect than the parent structure.

In continuation[1] of our study of structural analogs of the pyridylethylated oxazolidinediones (I), we have examined additional variants[2] of R_1,R_2 for effect on pharmacological activity. The compounds are reported in Table I.



I

In general, synthetic procedures similar to those previously described were used.[1,3] The majority of the syntheses involved preparation of the cyanohydrin which was converted to the hydroxyamide through the pyrolysis of the imino ester hydrochloride. The hydroxyamide was cyclized to the 5,5-R_1,R_2-1,3-oxazolidine-2,4-dione which, in turn, upon condensation with the vinylpyridines yielded the required pyridylethylated oxazolidinediones (Table I).

In the preparation of the structures R_1 = cyclohexyl, R_2 = CH_3 (compounds 6–9, Table I), the synthesis was effected through cyclization of ethyl α-cyclohexyl-α-hydroxypropionate with urea. The requisite ester was prepared conveniently by reaction of one equivalent of cyclohexylmagnesium chloride and ethyl pyruvate.

Structures in which R_1 embodied a tertiary hydroxyl onto the 5-alkyl substituent was of interest, particularly with variants containing a *t*-hydroxyl function and indicated preparation of compounds 31–33 of Table I.

(1) Paper I of this series, S. L. Shapiro, I. M. Rose, E. Roskin and L. Freedman, THIS JOURNAL, **80**, 1648 (1958).

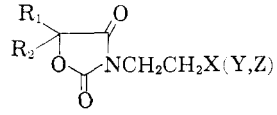
(2) (a) In ref. 1 it had been established that those structures wherein R_1 = C_2H_5, R_2 = CH_3 were good potentiators of Evipal sleeping time (E.s.t.) and suggested the preparation of compounds 1–6 of Table I. The high anti-convulsant response in the absence of a potentiation of the response in the E.s.t. test with the 5,5-substituted-3-methylpentamethylene series indicated exploration of compounds 6–18 of Table I; (b) variation of groups in the 5-position using structures analogous to the active barbiturates reflected examinations of compounds 19–30 of Table I. F. J. Marshall, *J. Org. Chem.*, **23**, 503 (1958), had successfully applied this approach to the study of 3,3-disubstituted-2-pyrrolidinones; (c) introduction of hydroxyl groups

(3) J. W. Clark-Lewis, *Chem. Revs.*, **58**, 63 (1958).

TABLE I

PYRIDYLETHYLATED OXAZOLIDINEDIONES

X =2-pyridyl
Y = 5-ethyl-2-pyridyl
Z = 4-pyridyl



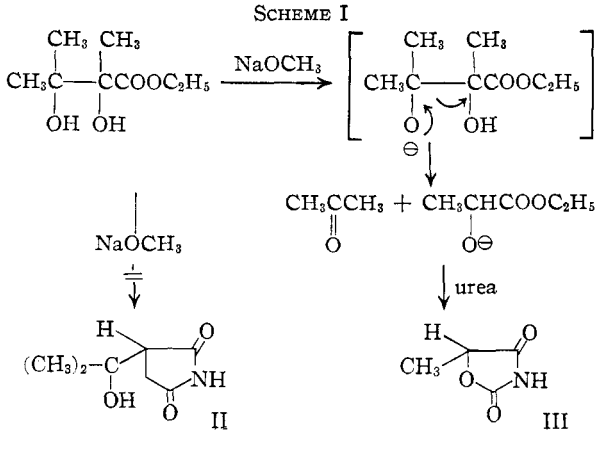
No.	R_1	R_2	X, Y or Z	M.p.,[a,e] °C., or b.p.[f] (mm.)	Yield,[g] %	Formula	Analyses[h] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	$(CH_3)_2CH-$	CH_3-	X	160–164 (0.1)	82	$C_{14}H_{18}N_2O_3$	64.1	64.3	6.9	7.5	10.7	10.4
2	$(CH_3)_2CH-$	CH_3-	Y	160–166 (.03)	82	$C_{16}H_{22}N_2O_3$	66.2	66.0	7.6	7.8	9.7	9.8
3	$(CH_3)_2CH-$	CH_3-	Z	160–167 (.03)	65	$C_{14}H_{18}N_2O_3$	64.1	64.5	6.9	7.2	10.7	10.3
4	$C_3H_5-^i$	CH_3-	X	148–156 (.05)	90	$C_{14}H_{16}N_2O_3$	64.6	64.7	6.2	6.1	10.8	10.5
5	$C_3H_5-^i$	CH_3-	Y	158–168 (.05)	89	$C_{16}H_{20}N_2O_3$					9.7	9.8
6	$C_3H_5-^i$	CH_3-	Z	37–42 170–174 (.05)	82	$C_{14}H_{16}N_2O_3$					10.8	10.5
7	$C_6H_{11}-^j$	CH_3-	X	58–60[b]	83	$C_{17}H_{22}N_2O_3$	67.5	67.3	7.3	6.9	9.3	9.1
8	$C_6H_{11}-^j$	CH_3-	Y	176–178 (0.05)	76	$C_{19}H_{26}N_2O_3$	69.1	69.2	7.9	8.2	8.5	8.6
10	$-(CH_2)_2CHCH_3CH_2-$		X	175–184 (.15)	86	$C_{15}H_{18}N_2O_3$					10.2	10.1
11	$-(CH_2)_2CHCH_3CH_2-$		Y	178–188 (.90)	88	$C_{17}H_{22}N_2O_3$	67.5	67.7	7.3	7.6	9.3	9.0
12	$-(CH_2)_2CHCH_3CH_2-$		Z	58–59[b]	77	$C_{15}H_{18}N_2O_3$	65.7	65.7	6.6	6.3	10.2	10.5
13	$-(CH_2)_4CHCH_3-$		X	170–178 (0.05)	79	$C_{16}H_{20}N_2O_3$	66.6	66.4	7.0	7.1	9.7	9.5
14	$-(CH_2)_4CHCH_3-$		Y	186–194 (.05)	79	$C_{18}H_{24}N_2O_3$	68.3	68.6	7.7	7.6		
15	$-(CH_2)_4CHCH_3-$		Z	69–70[b]	60	$C_{16}H_{20}N_2O_3$	66.6	67.1	7.0	7.0	9.7	9.9
16	$-(CH_2)_3CHCH_3CH_2-$		X	79–84	30	$C_{16}H_{20}N_2O_3$	66.6	66.7	7.0	6.9	9.7	9.5
16a	$-(CH_2)_3CHCH_3CH_2-$		X	[k]		$C_{16}H_{20}N_2O_3$	66.6	65.7	7.0	7.2	9.7	9.7
17	$-(CH_2)_3CHCH_3CH_2-$		Y	102–106[b]	20	$C_{18}H_{24}N_2O_3$	68.3	68.6	7.7	7.8	8.9	8.6
17a	$-(CH_2)_3CHCH_3CH_2-$		Y	[k]		$C_{18}H_{24}N_2O_3$	68.3	67.7	7.7	7.8	8.9	8.5
18	$-(CH_2)_3CHCH_3CH_2-$		Z	77–111[b]	61	$C_{16}H_{20}N_2O_3$	66.6	67.0	7.0	6.8	9.7	9.7
19	C_6H_5-	C_2H_5-	X	188–196 (0.03)	76	$C_{18}H_{18}N_2O_3$	69.7	69.4	5.9	5.8	9.0	8.6
20	C_6H_5-	C_2H_5-	Y	190–198 (.08)	74	$C_{20}H_{22}N_2O_3$	71.0	70.8	6.6	6.7	8.3	8.0
21	C_6H_5-	C_2H_5-	Z	198–206 (.10)	80	$C_{18}H_{18}N_2O_3$	69.7	69.8	5.9	5.9	9.0	9.0
22	$4\text{-Cl—}C_6H_4-$	CH_3-	X	69–70[b]	66	$C_{17}H_{15}ClN_2O_3$	61.7	61.7	4.6	4.9	8.5	8.1
23	$4\text{-Cl—}C_6H_4-$	CH_3-	Y	52–53[b]	66	$C_{19}H_{19}ClN_2O_3$	63.6	63.5	5.3	5.6	7.8	7.4
24	$4\text{-Cl—}C_6H_4-$	CH_3-	Z	77–78[b]	50	$C_{17}H_{15}ClN_2O_3$	61.7	62.2	4.6	4.6	8.5	8.6
25	$C_6H_5CH_2CH_2-$	CH_3-	X	198 (0.08)	83	$C_{19}H_{20}N_2O_3$					8.6	8.5
26	$C_6H_5CH_2CH_2-$	CH_3-	Y	210 (.08)	78	$C_{21}H_{24}N_2O_3$					8.0	7.8
27	$C_6H_5CH_2CH_2-$	CH_3-	Z	207 (.08)	86	$C_{19}H_{20}N_2O_3$					8.6	8.4
28	$C_6H_5CH{=}CH-$	CH_3-	X	202–210 (.10)	54	[l]						
29	$C_6H_5CH{=}CH-$	CH_3-	Y	212 (.05)	54	[m]						
30	$C_6H_5CH{=}CH-$	CH_3-	Z	104–107	89	$C_{19}H_{18}N_2O_3$	70.8	71.4	5.6	5.7		
31	$(CH_3)_2C(CH_2OH)-$	H	X	202–206 (0.10)	79	$C_{14}H_{18}N_2O_4$[n]	60.4	59.3	6.5	6.7	10.1	9.4
32	$(CH_3)_2C(CH_2OH)-$	H	Y	73–74	61	$C_{16}H_{22}N_2O_4$	62.7	63.0	7.2	6.7	9.1	9.4
33	$(CH_3)_2C(CH_2OH)-$	H	Z	92–93	78	$C_{14}H_{18}N_2O_4$	60.4	60.0	6.5	6.4	10.1	9.8

[a] Recrystallizing solvent for melting points was ethyl acetate–hexane unless otherwise specified in this column. [b] Hexane. [c] Ethyl acetate–methanol. [d] Ethyl acetate. [e] Melting points are not corrected and were established on a Fisher–Johns melting point block. [f] All liquid compounds were isolated by short path distillation. [g] Yields are based on pure product. [h] Analyses by Weiler and Strauss, Oxford, England. [i] C_3H_5- = cyclopropyl. [j] $C_6H_{11}-$ = cyclohexyl. [k] Liquid residue of other isomer, not distilled. [l] Also characterized as the hydrochloride, m.p. 137–148° (ethyl acetate). *Anal.* Calcd. for $C_{19}H_{19}ClN_2O_3$: C, 63.4; H, 5.3; N, 6.7. Found: C, 63.3; H, 5.5; N, 7.1. [m] Characterized as the hydrochloride, m.p. 160–175° (ethyl acetate). *Anal.* Calcd. for $C_{21}H_{23}ClN_2O_3$: C, 65.2; H, 5.9; N, 6.2. Found: C, 65.7; H, 6.3; N, 6.8. [n] An acceptable analysis was not obtained on this sample.

droxyl function[2c] were not successfully synthesized when ethyl α,β,β-trimethylglycerate was condensed with urea in the presence of sodium methoxide in the attempt to prepare the corresponding dione II. There was obtained 5-methyl-1,3-oxazolidine-2,4-dione (III) in 61% yield. This probably resulted through formation of ethyl lactate from the glycerate ester by a reverse Claisen reaction.[4,5] These reactions are shown in Scheme I.

In the case of the structures obtained from 2-methylcyclohexanone, one form of the cyanohydrin was isolated (compound 4, Table II). The hydroxyamide (compound 14, Table II), the un-

SCHEME I

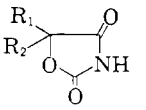


(4) C. R. Hauser and B. E. Hudson, Jr., THIS JOURNAL, **62**, 62 (1940).

(5) R. C. Huston, G. L. Goerner and H. H. Gyorgy, *ibid.*, **70**, 389 (1948).

TABLE II

INTERMEDIATE COMPOUNDS

No.	R_1	R_2	M.p.,[a,e] °C., or b.p.[f] (mm.)	Yield,[g] %	Formula	Analyses[h] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
			Cyanohydrins $R_1R_2C(OH)CN$[n]								
1[s]	$(CH_3)_2CH-$	CH_3-	82 (10)	69							
2[t]	C_3H_5-[i]	CH_3-	70–72 (3)	67							
3[u]	$-(CH_2)_2CHCH_3CH_2-$		64 (0.08)	56							
4[v]	$-(CH_2)_4CHCH_3-$		52–56[b]	46							
5[w]	$-(CH_2)_3CHCH_3CH_2-$		110 (7)	78							
6[s]	C_6H_5-	C_2H_5-	80 (0.08)	86[p]	$C_{10}H_{11}NO$	74.5	74.6	6.9	6.9		
7	4-Cl—C_6H_4-	CH_3-	92–94[b]	35	C_9H_8ClNO	59.5	59.1	4.4	4.4		
8	$C_6H_5CH_2CH_2-$	CH_3-	106 (0.22)	90[q]	$C_{11}H_{13}NO$	75.4	75.9	7.5	7.6		
9	$C_6H_5CH{=}CH-$	CH_3-		72[r]							
10	$(CH_3)_2C(OH)-$	CH_3-	66–67	70	$C_6H_{11}NO_2$	55.8	56.1	8.6	8.6		
			90–97 (0.05)								
			α-Hydroxyamides $R_1R_2C(OH)CONH_2$								
11[x]	$(CH_3)_2CH-$	CH_3-	84–85	90							
12	C_3H_5-[i]	CH_3-	78–84[c]	80	$C_6H_{11}NO_2$[ad]	52.2	52.2	8.8	8.6	10.1	10.0
13	$-(CH_2)_2CHCH_3CH_2-$		118–119[d]	82	$C_7H_{13}NO_2$	58.7	59.2	9.2	9.1	9.8	9.8
14	$-(CH_2)_4CHCH_3-$		120–121	74	$C_8H_{15}NO_2$	61.1	61.6	9.6	9.8		
15[y]	$-(CH_2)_3CHCH_3CH_2-$		87–95	70							
16[z]	C_6H_5-	C_2H_5-	93–95	70	$C_{10}H_{13}NO_2$	67.0	67.1	7.3	7.1	7.8	7.8
17	4-Cl—C_6H_4-	CH_3-	116–117	83	$C_9H_{10}ClNO_2$	51.1	51.3	5.1	5.2	7.0	6.9
18	$C_6H_5CH_2CH_2-$	CH_3-	106	98	$C_{11}H_{15}NO_2$					7.3	7.1
19	$C_6H_5CH{=}CH-$	CH_3-	97–99	58	$C_{11}H_{13}NO_2$	69.1	69.2	6.9	6.8	7.3	7.3
20[aa]	$(CH_3)_2C(OH)-$	CH_3-	98 (15)	30	$C_8H_{16}O_4$	54.5	54.8	9.2	9.1		
21[ab]	$(CH_3)_2C(CH_2OH)-$	H	131–132	91							
			Oxazolidinediones 								
22	$(CH_3)_2CH-$	CH_3-	111 (0.35)	83	$C_7H_{11}NO_3$					8.9	8.7
23	C_3H_5-[i]	CH_3-	93–96 (0.03)	63	$C_7H_9NO_3$	54.2	53.9	5.9	6.0	9.0	9.0
24	$C_6H_{11}-$[j]	CH_3-	75–76[b]	37	$C_{10}H_{15}NO_3$	60.9	61.2	7.7	7.6	7.1	7.3
25	$-(CH_2)_2CHCH_3CH_2-$		92 (0.01)	83	$C_8H_{11}NO_3$	56.8	56.9	6.6	6.8		
26	$-(CH_2)_4CHCH_3-$		93–94[b]	50	$C_9H_{13}NO_3$	59.0	58.9	7.2	6.9	7.7	7.8
27	$-(CH_2)_3CHCH_3CH_2-$		117–123 (0.10)	85	$C_9H_{13}NO_3$	59.0	58.7	7.2	7.6	7.7	7.6
28[a,c]	C_6H_5-	C_2H_5-	134 (0.03)	77	$C_{11}H_{11}NO_3$					6.8	6.6
29	4-Cl—C_6H_4-	CH_3-	110–111	67	$C_{10}H_8ClNO_3$	53.2	53.1	3.6	3.7	6.2	6.0
30	$C_6H_5CH_2CH_2-$	CH_3-	96–97	84	$C_{12}H_{13}NO_3$	65.7	65.8	6.0	5.9	6.4	6.2
31	$C_6H_5CH{=}CH-$	CH_3-	99–100	85	$C_{12}H_{11}NO_3$	66.4	65.8	5.1	5.2	6.5	6.4
32	$(CH_3)_2C(CH_2OH)-$	H	82–87	60	$C_7H_{11}NO_4$	48.6	48.9	6.4	6.4	8.1	7.7
			156–164 (0.08)								

[a–n] Have same significance as in Table I. [g] Unless otherwise stated, yields of cyanohydrin are based on reactant ketone, amides on imino ester hydrochloride which was pyrolyzed, and oxazolidinediones on amides. [p] Yield based on unrecovered ketone. [q] The compound suffered extensive decomposition when distillation was attempted. Yield shown is based on a dried residue. The boiling point and analyses shown were obtained by distillation of a small sample. [r] Yield shown is based on a dried residue. The compound could not be distilled without extensive decomposition. [s] Reported but not characterized; D. P. Evans and J. R. Young, *J. Chem. Soc.*, 1313 (1954). [t] T. W. Wood, U. S. Patent 2,433,500 (1948), reports b.p. 70° (5 mm.) (93%). [u] B. Tchoubar, *Bull. soc. chim. France*, 162 (1949), reports b.p. 120–121° (15 mm.). [v] *Ibid.*, reports m.p. 53–54°. [w] *Ibid.*, reports b.p. 135–140° (21 mm.). [x] J. Verhulst, *Bull. soc. chim. Belg.*, **39**, 563 (1930), reports m.p. 89–90°. [y] Obtained as a mixture of isomers and not analyzed. For the preparation of a pure isomer, m.p. 128°, see M. Godchot and G. Cauquil, *Compt. rend.*, **203**, 1042 (1936). [z] A. McKenzie and A. Ritchie, *Ber.*, **70B**, 23 (1937), report m.p. 91–91.5°. [aa] The compound is the ethyl ester, not the amide. It had previously been prepared but not characterized by R. Adams, B. L. Van Duuren and B. H. Braun, THIS JOURNAL, **74**, 5608 (1952). [ab] J. Madinaveitia, A. R. Martin, F. L. Rose and G. Swain, *Biochem. J.*, **39**, 85 (1945), report m.p. 127–128° (62%). [ac] R. W. Stoughton, THIS JOURNAL, **63**, 2378 (1941), reports b.p. 174–176° (3 mm.). [ad] The calculated analyses are for the molecule plus 0.5 mole of water of crystallization and represent the form in which the compound was characterized.

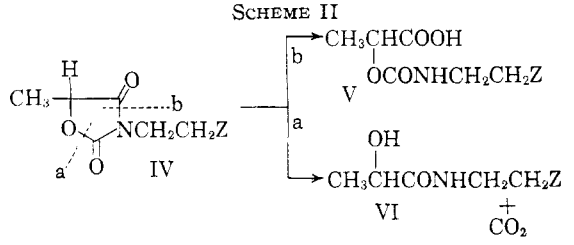
substituted cyclized structure (compound 26, Table II) and the corresponding pyridylethylated adducts (compounds 13-15, Table I) were obtained as but one of the two possible diastereoisomers. Alternatively, with 3-methylcyclohexanone, partial separation was effected in the final state, in the instance of compounds 16 and 16a, and 17 and 17a, while the 4-pyridylethylated product, compound 18, was retained as a mixture of diastereoisomers (Table I).

Another objective of this work was the hydrolysis[6]

(6) In the instance of the anti-epileptic drug, 3,5,5-trimethyl-1,3-oxazolidine-2,4-dione, W. J. Wadell and T. C. Butler, *Proc. Soc. Exp. Biol., Med.*, **96**, 563 (1957), have reported that it is converted by

of 5-methyl-3-(2-[4-pyridyl]-ethyl)-1,3-oxazolidine-2,4-dione (IV). This compound was one of the more active structures reported in our previous work and, conceivably, its products of hydrolysis might reflect the pharmacological pattern observed. Treatment with a slight excess of dilute sodium hydroxide[7] at 20° resulted in the isolation of 52% of N-2-(4-pyridyl)-ethylcarbamoylolactic acid (V) through fission of IV at "b" and 12% of N-2-(4-pyridyl)-ethyllactamide (VI) through fission of VI at "a," followed by loss of carbon dioxide. The reactions are shown in Scheme II.[8] The physical characteristics of the urethan acid V indicate that it exists as a zwitterion probably of intramolecular type.

SCHEME II



Pharmacology.—The pharmacological screening of the compounds of Table I was performed in a manner similar to that previously described.[1] Good anti-convulsant action was noted with compounds 4, 11, 12 and 16a. Compound 11 showed a 4+ anti-convulsant response in the absence of any noted potentiation of Evipal sleeping time (E.s.t.).

As had been previously noted,[1] the 4-pyridylethyl group in the 3-position of the oxazolidinedione ring promotes a potentiating response of the E.s.t. The response with this substituent was usually greater than, and was rarely exceeded by, the other pyridylethyl substituents. A high order of activity was noted with compounds 4, 6, 21 and 33.

Significant depression of central nervous system activity was obtained with compounds 6, 16, 25 and 27.

With the hydrolysis products of compound IV, the urethan acid V had about 2+ anticonvulsant activity, slight potentiation of E.s.t. and no noted depression in the activity test. The N-(4-pyridylethyl)-lactamide (VI) showed no pharmacological effects other than a 140% increase in E.s.t. These findings suggest that the noted central nervous system depressant effects of 5-methyl-3-([4-pyridyl]-ethyl)-1,3-oxazolidine-2,4-dione (IV) are not associated with *in vivo* hydrolysis to the noted hydrolysis products.

Experimental[9]

Hydrolysis of 5-Methyl-3-(2-[4-pyridyl]-ethyl)-1,3-oxazolidine-2,4-dione (IV).—A solution of 25.6 g. (0.10 mole) of the hydrochloride of the above compound in 120 ml. of water containing 13.6 g. (0.34 mole) of sodium hydroxide was maintained at 20° for 20 hours.

N-2-(4-Pyridyl)-ethyllactamide (VI from Hydrolysis of IV).—The solution was saturated with sodium chloride and extracted repeatedly with chloroform (2.5 l.). The residue upon evaporation of the dried chloroform extracts yielded 2.28 g. (12%) of N-2-(4-pyridyl)-ethyllactamide, m.p. 131–135°. Recrystallization (ethyl acetate) raised the m.p. to 136–137°. A mixed m.p. with authentic N-2-(4-pyridyl)-ethyllactamide showed no depression (mixed m.p. 135–137°).

N-2-(4-Pyridyl)-ethylcarbamoylolactic Acid (V from Hydrolysis of IV).—After the chloroform extraction, the aqueous layer was neutralized with 20 ml. (0.24 mole) of hydrochloric acid and 1 liter of ethanol was added until no more sodium chloride precipitated. The sodium chloride was separated and the filtrate concentrated to 100 ml. *in vacuo*. The resultant slurry was boiled with 100 ml. of ethanol and the sodium chloride separated. As the filtrate cooled, sodium chloride was continuously removed until the product (effervescence with sodium bicarbonate) started to precipitate. Excess ethanol (200 ml.) was added and the pure product was separated, washed with ethanol and dried (7.45 g.), m.p. 157–158°.

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.5; H, 5.9; N, 11.8. Found: C, 55.6; H, 5.7; N, 12.1.

Evaporation of the mother liquor and washes on the steam-bath and drying *in vacuo* gave 10.17 g. of a solid which, after trituration (ethyl acetate) and recrystallization (ethanol), gave an additional 5.02 g. of product. The total yield was 12.4 g. (52%).

N-2-(4-Pyridyl)-ethyllactamide (VI).—A solution of 6.1 g. (0.05 mole) of 2-(4-pyridyl)-ethylamine[10] and 15 ml. of ethyl lactate was maintained at 20° for one week. On addition of 30 ml. of ether, the amide crystallized. After 24 hours the product was separated, 4.3 g. (44%), m.p. 135–136°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.8; H, 7.3; N, 14.4. Found: C, 61.9; H, 7.0; N, 14.1.

5-Methyl-1,3-oxazolidine-2,4-dione (III from Ethyl α,β,β-Trimethyl Glycerate).—Nine grams (0.15 mole) of urea was added to a refluxing solution of 3.5 g. (0.15 g. atom) of sodium metal in 60 ml. of methanol. When solution was complete, 26.4 g. (0.15 mole) of ethyl α,β,β-trimethylglycerate (compound 20, Table II) was added and reflux continued for 7 hours. After removal of the methanol on the steam-bath, the cooled residue was dissolved in 60 ml. of water, the solution saturated with sodium chloride, washed twice with 50 ml. of ether, acidified with concentrated hydrochloric acid and the product extracted with six 100-ml. portions of ether. The ether was removed on the steam-bath and the residue upon distillation yielded 10.5 g. (61%) of 5-methyl-1,3-oxazolidine-2,4-dione, b.p. 92–93° (0.15 mm.), $n^{20}D$ 1.4757. An authentic sample[11] had $n^{20}D$ 1.4757.

Further confirmation of the identity as 5-methyl-1,3-oxazolidine-2,4-dione was obtained by its reaction product with 2-vinylpyridine which melted at 59–61° (hexane) and did not depress the melting point of 3-(2-[2-pyridyl]-ethyl)-5-methyl-1,3-oxazolidine-2,4-dione, m.p. 59–61°, mixed m.p. 59–61°. This product, initially reported[1] as a liquid, crystallized on standing.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 60.0; H, 5.5; N, 12.7. Found: C, 60.0; H, 5.2; N, 12.3.

5-(Hydroxy-*t*-butyl)-1,3-oxazolidine-2,4-dione (Compound 32, Table II).—Pantoamide (compound 21, Table II, 28.2 g., 0.193 mole), dissolved in 50 ml. of hot methanol, was added in one portion to a refluxing solution of 4.6 g. (0.201 g. atom) of sodium metal in 50 ml. of methanol containing 26.2 g. (0.220 mole) of diethyl carbonate and reflux continued for 4 hours. After removal of the methanol on the steam-bath, the cooled residue was dissolved in 300 ml. of water, the solution saturated with sodium chloride, washed twice with 100 ml. of ether, acidified with concentrated hydrochloric acid, and the product extracted with six 100-ml. portions of ether. The ether was removed on the steam-bath and the residue distilled to yield 24.3 g. of product, b.p. 156–164° (0.08 mm.). The initially viscous oil solidified on trituration with benzene.

metabolic demethylation to 5,5-dimethyl-1,3-oxazolidine-2,4-dione. As one possibility of metabolic interest, the compound IV could similarly suffer loss of the 3-(4-pyridyl)-ethyl group, and yield 5-methyl-1,3-oxazolidine-2,4-dione. When evaluated pharmacologically, this unsubstituted dione showed none of the properties of the dione IV.

(7) Reference 3, pp. 85–90, describes hydrolyses of 2,4-oxazolidinediones.

(8) A report of a more extensive investigation of hydrolysis of substituted 2,4-oxazolidinediones by the authors is in preparation.

(9) Descriptive data shown in the tables are not reproduced in the Experimental section. Typical syntheses of products described in the tables are given.

(10) G. Magnus and R. Levine, THIS JOURNAL, **78**, 4128 (1956).

(11) R. W. Stoughton, *ibid.*, **63**, 2378 (1941).

3-(2-[2-Pyridyl]-ethyl)-3-aza-1-oxaspiro-7-methyl-[4,5]-decane-2,4-dione (Compounds 16 and 16a, Table I).—The dione (compound 27, Table II) (4.6 g., 0.025 mole) and 2.64 g. (0.025 mole) of 2-vinylpyridine were heated at 150° for 2 hours. A small portion of cooled melt, triturated with hexane, afforded seed crystals. The remainder was dissolved in 35 ml. of 0.85 *N* hydrochloric acid and the solution was washed with two 25-ml. portions of ether. After addition of excess saturated sodium bicarbonate solution and seeding, 3.23 g. of compound 16 was obtained and separated, m.p. 48–65°. An additional 0.75 g., m.p. 32–75°, was separated after storage of the filtrate at 10° for 24 hours. The combined yield of compound 16 was recrystallized (hexane–ethyl acetate). On standing, 1.7 g. separated, m.p. 79–84°, and was used as the analytical and testing sample. On concentration of the mother liquor, a second crop (0.45 g., m.p. 43–77°) was obtained. The aqueous filtrate was extracted with ether. This extract was combined with the mother liquor of the recrystallization, the solvents were removed and the residue so obtained designated as compound 16a is a mixture of the isomers.

In a similar manner, a separation was effected to give the pure isomer compound 17, and the mixture of isomers, compound 17a of Table I.

α-*p*-Chlorophenyl-α-hydroxypropionitrile (Compound 7, Table II).—To a cooled (5–10°) well-stirred mixture of 103 g. (0.666 mole) of *p*-chloroacetophenone, 60 ml. of ether, 100 ml. of water and 82 g. (1.67 moles) of sodium cyanide, concentrated hydrochloric acid (140 ml., 1.7 moles) was added dropwise over a period of 1.7 hours. Stirring was continued for 2 hours at 20°. The ether layer was separated, dried (magnesium sulfate), filtered and the ether removed. After trituration with hexane, there was obtained 50 g. (41%) of product, m.p. 82–85°.

α-*p*-Chlorophenyl-α-hydroxypropionamide (Compound 17, Table II).—A solution of 55.4 g. (0.33 mole) of compound 7, Table II, in 550 ml. of ether containing 12 ml. of methanol was saturated with dry hydrogen chloride gas while maintaining the temperature below 0°. After 1 hour, 20 g. of imino ester hydrochloride separated, and after the second hour an additional 17.4 g. was obtained. The total yield was 37.4 g. (49%). Upon pyrolysis of the imino ester hydrochloride at 150° for 45 minutes and cooling, the amide crystallized. After solution in 100 ml. of ethyl acetate and filtration of ammonium chloride, addition of 240 ml. of hexane to the filtrate yielded 22 g. of amide, m.p. 116–117°.

5-*p*-Chlorophenyl-5-methyl-1,3-oxazolidine-2,4-dione (Compound 29, Table II).—Sodium metal (2.42 g., 0.15 g. atom), was dissolved in 25 ml. of refluxing methanol and 13.6 g. (0.115 mole) of diethyl carbonate added, followed by a solution of 19.95 g. (0.10 mole) of α-*p*-chlorophenyl-α-hydroxypropionamide (compound 17, Table II) in 25 ml. of methanol. After 4 hours under reflux the methanol was removed and the cooled residue was dissolved in 75 ml. of water. After washing with two 100-ml. portions of ether the product was precipitated by slow addition of excess 3 *N* hydrochloric acid. The product was separated, 18.2 g. (81%), m.p. 103–106°.

Ethyl α-Cyclohexyl-α-hydroxypropionate.—Magnesium turnings (5.35 g., 0.22 g. atom) were covered with 30 ml. of ether, 5 g. of cyclohexyl chloride was added and then a crystal of iodine. Without stirring, the mixture was heated gently until the iodine color disappeared and the reaction was self-sustaining. Ether (30 ml.) was added, and with stirring, an additional 20 g. (0.20 mole) of cyclohexyl chloride in 60 ml. of ether was admitted at a rate sufficient to maintain gentle reflux which was continued for 20 minutes after completion of the addition. The solution was filtered through glass wool into a dropping funnel and added with stirring to a solution of 23.2 g. (0.20 mole) of ethyl pyruvate in 150 ml. of benzene at −5 to 0° over 40 minutes, then stirred for an additional 40 minutes. The solution was poured onto 200 g. of crushed ice and acidified with dilute sulfuric acid. The aqueous phase was removed and extracted twice with ether. The combined organic phases were washed with dilute sodium bicarbonate, dried (magnesium sulfate) and the solvents removed. Upon distillation of the residue, 9.4 g. (24%) of product was obtained, b.p. 84–100° (1.1 mm.).

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 66.0; H, 10.1. Found: C, 66.0; H, 9.9.

5-Cyclohexyl-5-methyl-1,3-oxazolidine-2,4-dione (Compound 24, Table II).—To a solution of 1.02 g. (0.0445 g. atom) of sodium metal in 25 ml. of ethanol, 2.66 g. (0.0445 mole) of urea was added and dissolved under reflux. A solution of 8.9 g. (0.0445 mole) of the α-hydroxy ester described above in 5 ml. of ethanol was then added, and reflux continued for 6 hours. Ethanol was removed on the steam-bath, the cooled residue dissolved in 100 ml. of water and the solution washed twice with ether. The aqueous layer was acidified with 3 *N* hydrochloric acid and the oily product extracted with ether. The ether was removed on the steam-bath and the residue distilled to give 5.5 g. (63%) of product, b.p. 108–128° (0.08 mm.). When a solution of this material in 130 ml. of hot hexane was permitted to cool slowly, the product crystallized yielding 3.28 g. (37%).

3-(2-[2-Pyridyl]-ethyl)-5-*p*-chlorophenyl-5-methyl-1,3-oxazolidine-2,4-dione (Compound 22, Table I).—A mixture of 4.0 g. (0.0177 mole) of compound 29, Table II, and 2.04 g. (10% excess) of 2-vinylpyridine was heated at 150° for 2 hours. The acidified (hydrochloric acid) solution of the cooled residue was washed with ether. The product which precipitated on the addition of excess sodium bicarbonate was separated, 4.25 g. (73%), m.p. 67–68°.

3-(2-[2-(5-Ethyl)-pyridyl]-ethyl)-5-cyclopropyl-5-methyl-1,3-oxazolidine-2,4-dione (Compound 5, Table I).—A solution of 5.0 g. (10% excess) of compound 23, Table II, and 4.0 g. (0.03 mole) of 2-vinyl-5-ethylpyridine was heated at 150° for 2 hours. The acidified (hydrochloric acid) aqueous solution of the cooled residue was washed with ether. After the addition of excess sodium bicarbonate solution, the separated oily product was extracted with ether. On removal of the ether, the residue was fractionated by short path distillation and 7.7 g. (89%) of product was collected, b.p. 158–168° (0.05 mm.).

Acknowledgment.—The authors wish to thank Dr. G. Ungar and his staff for the pharmacological screening of the compounds.

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