

O,O-Diethyl hydrogen phosphorodithioate and its amine salts. Pyridine Salt-Mole Ratio 1:1. Pyridine (19.0 g., 0.25 mole) and 95 g. (0.5 mole) of the acid-ester⁴ in 100 ml. of benzene were refluxed for 6 hr. This reaction yielded 52.2 g. (97%) of *O,O,S*-triethyl phosphorodithioate, b.p. 56–48° at 0.2 mm., n_D^{25} 1.5038.

Anal. Calcd. for $C_6H_{15}O_2S_2P$: P, 14.46; S, 29.93. Found: P, 14.60; S, 29.90.

The gum-like product that separated from the reaction mixture weighed 39 g. It dissolved in water with decom-

position and was soluble in ethyl acetate but insoluble in acetone, petroleum ether (30–60°) and benzene.

Anal. Calcd. for $EtOPOS.C_2H_5N$: P, 15.20; S, 15.75. Found: P, 15.28; S, 15.77.

The yields obtained with other amines, and with the various acid-amine ratios employed, are shown in Table III.

Typical analyses of the esters obtained are shown in Table IV.

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Pyridyloxazolidinediones and Related Compounds

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In extension of our work with the pyridylethylated oxazolidinediones^{1,2} and in view of recent interest in pyridyl hydantoins,³ we have investigated

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the preparation of pyridyl, picolyl, quinoly, pyrimidyl, and imidazolylethyl oxazolidinediones of the type I. The compounds prepared have been described in Table I. In addition to the free bases, a number of methiodides of variants of I have been prepared.

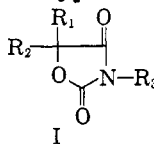
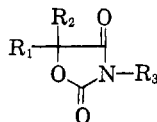


TABLE I. 3-PYRIDYL-OXAZOLIDINEDIONES AND RELATED COMPOUNDS



No.	$R_1^{a,b}$	M.P., ^c B.P. (Mm.), $R_1 = CH_3$, $R_2 = H$	R.S. ^d	Yield, ^e %	Formula	Analyses, % ^f					
						Carbon		Hydrogen		Nitrogen	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
1 ^o	2-Py	134 (0.2)		62	$C_9H_8N_2O_3$	56.3	56.3	4.2	4.4	14.6	14.4
2 ^b	3-Py	119–120	A	33	$C_9H_8N_2O_3$	56.3	56.4	4.2	4.3	14.6	14.4
3	^b	164–166	B	65	$C_{10}H_{11}IN_2O_3$	36.0	35.6	3.2	3.5	8.4	8.1
4	3-CH ₃ -2-Py	126–130 (0.2)		45	$C_{10}H_{10}N_2O_3$	58.3	58.2	4.9	5.5	13.6	13.9
5 ^t	4-CH ₃ -2-Py	88–89	A	32	$C_{10}H_{10}N_2O_3$	58.3	57.8	4.9	4.8	13.6	13.6
6	6-CH ₃ -2-Py	95–96	A	28	$C_{10}H_{10}N_2O_3$	58.3	58.5	4.9	4.9	13.6	13.6
7 ^j	2-Pc	104–108 (0.02)		54	$C_{10}H_{10}N_2O_3$	58.3	57.8	4.9	5.1	13.6	13.2
8	^b	178–180	B	52	$C_{11}H_{13}IN_2O_3$	37.9	37.9	3.8	3.9	8.0	8.4
9	3-Pc	125–128 (0.12)		73	$C_{10}H_{10}N_2O_3$	58.3	58.5	4.9	5.2		
10	^b	151–153	B	88	$C_{11}H_{13}IN_2O_3$	37.9	38.3	3.8	3.9	8.0	8.3
11	4-Pc	112–113	A	58	$C_{10}H_{10}N_2O_3$	58.3	57.9	4.9	4.9		
12	^b	168–171	B	86	$C_{11}H_{13}IN_2O_3$	37.9	38.2	3.8	3.7	8.0	8.3
13 ^k	Im	152–154 (0.4)		46	$C_{10}H_{14}N_2O_2$	53.3	53.4	6.7	7.2		
		$R_1 = CH_3 = R_2$									
14	2-Py	118–119	A	76	$C_{10}H_{10}N_2O_3$	58.3	58.8	4.9	5.2	13.6	13.9
15	^b	163–164	B	10	$C_{10}H_{13}IN_2O_3$	37.9	38.3	3.8	3.7	8.0	7.7
16	3-Py	147–148	A	77	$C_{10}H_{10}N_2O_3$	58.3	58.1	4.9	4.7		
17	^b	201–202	B	84	$C_{11}H_{13}IN_2O_3$	37.9	38.2	3.8	3.8	8.0	8.2
18	4-Py	133–134	A	52	$C_{10}H_{10}N_2O_3$	58.3	58.3	4.9	5.0	13.6	13.9
19	^b	241–244	B	93	$C_{11}H_{13}IN_2O_3$	37.9	38.2	3.8	3.9	8.0	8.4
20	4-CH ₃ -2-Py	178–179	A	76	$C_{11}H_{12}N_2O_3$	60.0	60.1	5.5	5.3	12.7	12.7
21 ^t	2-Pc	59–60	C	44	$C_{11}H_{12}N_2O_3$	60.0	60.4	5.5	5.7	12.7	12.6
22	3-Pc	117–120 (0.05)		86	$C_{11}H_{12}N_2O_3$	60.0	60.8	5.5	5.7	12.7	12.3
23	4-Pc	94–95	A	64	$C_{11}H_{12}N_2O_3$	60.0	60.2	5.5	5.6	12.7	12.7
24	Qn	164–166	A	71	$C_{14}H_{12}N_2O_3$	65.6	65.7	4.7	4.9	10.9	10.7
25	^b	217–218	B	72	$C_{15}H_{15}IN_2O_3$	45.3	45.8	3.8	4.0	7.0	7.0
26	Pm	94–95	C	18	$C_{11}H_{13}N_3O_3$	56.2	56.2	5.6	5.3	17.9	17.8

The synthetic procedure used was the direct synthesis⁴ of the oxazolidinedione from the amine, the α -hydroxy ester in an excess of the reactant, and diethyl carbonate under sodium alkoxide catalysis. Unlike our previous series,⁴ the amines herein evaluated, on occasion gave incomplete conversion to the required dione I, with isolation of the intermediate ethyl urethane derived from reaction of the ethyl carbonate with the hetero amine. In one instance (compound 5) the symmetrical bis-urea was also isolated and may have resulted from transient formation of the pyridyl isocyanate,^{5,6} followed by reaction with the reactant amine.

Selected compounds in this series proved to be mildly effective as anti-inflammatory agents⁷ (com-

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(7) See S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc., (Sci. Ed.)*, **46**, 333 (1957), for method of testing.

← Footnotes to Table I

^a The following abbreviations are used for the heterocyclic substituent: Py = pyridyl; Pc = picolyl; Im = 2-[1-(2-methyl-2-imidazolyl)]ethyl; Qn = 3-quinolyl; Pm = 2,6-dimethyl-4-pyrimidyl. ^b The compounds so marked are methiodides of the compounds immediately above. ^c The melting points are uncorrected and were established on a Fisher-Johns melting point block. ^d R.S. = recrystallizing solvent; A = ethyl acetate-hexane; B = ethanol; C = hexane. ^e Yields are based on recrystallized or distilled product. ^f Analyses are by Weiler and Strauss, Oxford, England. ^g After the removal of the formed ethanol of reaction a 13% yield of the ethyl urethane of 2-aminopyridine precipitated, m.p. 105–106°, not depressing the melting point of the authentic urethane prepared from 2-aminopyridine and ethyl chloroformate [R. L. Shriner and R. G. Child, *J. Am. Chem. Soc.*, **74**, 549 (1952), report m.p. 104–105°]. ^h When the mother liquor obtained after filtration of the product was evaporated and the residue recrystallized (hexane) there was obtained 5% yield of the ethyl urethane of 3-aminopyridine, m.p. 90–92° [*J. Am. Chem. Soc.*, **74**, 549 (1952) report m.p. 91–92°]. ⁱ After the removal of the formed ethanol of reaction 4.2 g. of a mixture of solids, m.p. 120–210° precipitated and was treated with boiling hexane. The hexane insoluble portion proved to be bis(4-methyl-2-pyridyl)urea m.p. 225°. An authentic sample prepared from 2-amino-4-methylpyridine and ethyl chloroformate melted at 228.5° (ethyl acetate). *Anal.* Calcd. for C₁₃H₁₄N₄O: C, 64.4; H, 5.8; N, 23.1. Found: C, 64.5; H, 5.1; N, 23.3. The hexane solution on standing gave the ethyl urethane of 2-amino-4-methylpyridine m.p. 128–131°, not depressing the melting point of the authentic urethane (prepared from 2-amino-4-methylpyridine and ethyl chloroformate), m.p. 130–131° (hexane). *Anal.* Calcd. for C₉H₁₂N₂O₂: N, 15.6. Found: N, 15.7. ^j A forerun in the distillation 1.6 g. (9%), b.p. 95–97° (0.02 mm.), n_D^{20} 1.5140 gave analyses indicative of impure ethyl urethane of 2-picolylamine. ^k The required initial reactant 2-[1-(2-methyl-2-imidazolyl)] ethylamine was obtained from the National Aluminate Corp., Chicago, Ill., and was purified by distillation, b.p. 62–80° (0.04 mm.), n_D^{20} 1.5119. ^l A forerun in the distillation, 3.37 g. (19%), b.p. 98–100° (0.08 mm.), n_D^{20} 1.5162 gave analyses indicative of impure ethyl urethane of 2-picolylamine. The oxazolidinedione product boiled 103–104° (0.05 mm.), n_D^{20} 1.5183, and crystallized on standing.

pounds 1, 2, 5, 9, 20, 22, 23, and 24). Compounds 9–11, and 23 were effective potentiators of Evipal sleeping time.⁸

EXPERIMENTAL

General procedure (Table I). A solution of 0.2 g. of sodium in 4 ml. of ethanol was added to a solution of 0.1 mole of the amine, 0.1 mole of the ethyl α -hydroxy ester and 37 ml. of diethyl carbonate, and the stirred mixture was heated under reflux. When the internal temperature had dropped approximately 20°, the formed ethanol was removed and measured. If the quantity of ethanol was substantially less than theoretical, an additional charge of catalyst was added and the reflux and removal of formed ethanol were repeated as described above. Upon standing, or after removal of most of the diethyl carbonate, the product crystallized and was separated. Liquid products were distilled.

The methiodides were prepared by treating 0.01 mole of the free base with 2 ml. of methyl iodide in 40 ml. of ethanol and were obtained after the reaction mixture had been stored at room temperature for 7 to 10 days.

2-[N-(4-Methyl-2-pyridyl)carbamoyloxy]propionic acid. Alkaline hydrolysis of compound 5 and work-up as previously described² afforded the title compound in 68% yield, m.p. 144–148° (ethanol).

Anal. Calcd. for C₁₀H₁₂N₂O₄: C, 53.6; H, 5.4; N, 12.5. Found: C, 53.9; H, 5.6; N, 12.8.

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(8) See ref. (1) for method of testing.

Antihypertensive Agents. II. Tropine Quaternaries¹

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A series of tropine quaternaries (Table I) have been prepared for pharmacological screening. Synthesis was effected by treating a mixture of the quaternizing halide with tropine in a polar solvent such as acetonitrile.²

Whereas bis-tropinium salts (compounds 9–12) formed readily, methylene iodide yielded the iodo-methyltropinium iodide, suggesting that steric factors prevent two tropinium nitrogens from being linked by a single methylene unit.^{3,4}

(1) For Paper I of this series, see S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958).

(2) C. J. Cavallito, A. P. Gray and E. E. Spinner, *J. Am. Chem. Soc.*, **76**, 1862 (1954).

(3) For a related work see W. C. Davies, E. B. Evans and F. L. Hulbert, *J. Chem. Soc.*, 412 (1939).

(4) The failure for the conversion to the bis-quaternary may be associated with the "neopentyl-like" structure of the iodomethyl quaternary and its relative inactivity in S_N² reactions, see J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1956, page 157.