(20) C. W. Whitworth and E. R. Carter, *ibid.*, **58**, 1285(1969).
(21) M. Mezei, R. W. Sager, W. D. Stewart, and A. L. deRuyter, *ibid.*, **55**, 584(1966).

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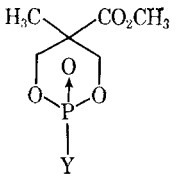
1,3,2-Dioxaphosphorinane 2-Oxides IV: Preparation of Some 2-Substituted-5-carbomethoxy-5-methyl-1,3,2-dioxaphosphorinane 2-Oxides as Potential Antitumor Agents

JOHN H. BILLMAN and GERALD R. ROEHRIG

Abstract □ Twenty-two of the title compounds, in which the substituents are chloro, alkylamino, dialkylamino, arylamino, hydroxy, and amine salts, as well as the pyrophosphate, have been synthesized and submitted for antitumor evaluation.

Keyphrases □ 1,3,2-Dioxaphosphorinane 2-oxides—synthesis □ Antitumor agents—synthesis, 1,3,2-dioxaphosphorinane 2-oxides □ IR spectrophotometry—structure, analysis

Previous work in the authors' laboratory (1) has led to consideration of the dioxaphosphorinane 2-oxides as potential antitumor agents. Synthesis and evaluation of compounds of Type I are described at this time.

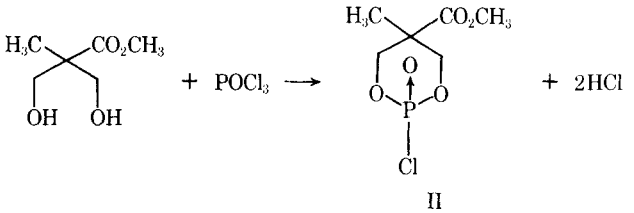


I

Y = —Cl, —NHR, —NR_2, —NHAr, —OH, -amine salts and the pyrophosphate

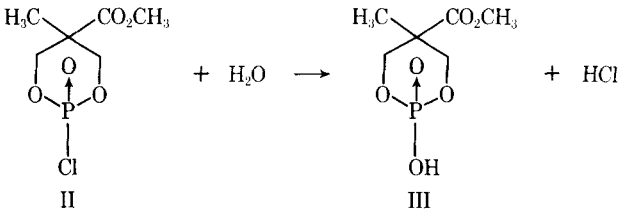
The starting point for the preparation of these compounds was the phosphochloridic acid II, which was prepared according to Scheme I. Compound II can formally be considered as an acid chloride analogous to the more commonly encountered carboxylic acid chlorides; as such, one would expect that it might exhibit many of the same types of reactions as the acyl chlorides. Indeed, many of those reactions have been observed and used to advantage. Schemes II–IV are representative of those used for the preparation of the compounds cited in this paper.

The salts of the acid were prepared for two basic reasons. Since the majority of these compounds are relatively water insoluble, it was thought that a compound with considerably greater water solubility might exhibit a greater degree of antitumor activity. Also, by incorporating amines that exhibit biological activity, one could compare the activity of the salt with that of the free amine. At this point, insufficient data have been returned to clarify either of these points.



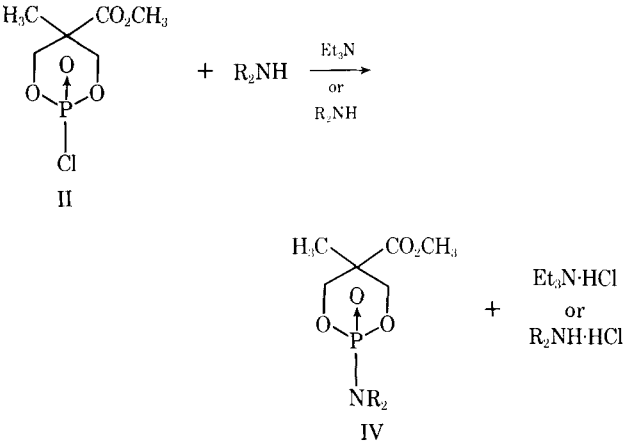
II

Scheme I



II III

Scheme II



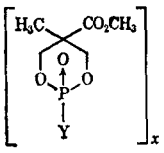
II IV

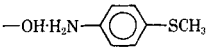
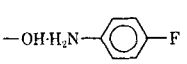
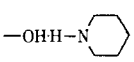
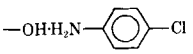
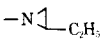
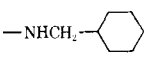
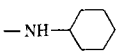
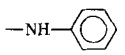
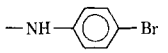
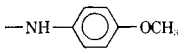
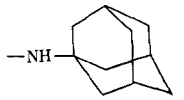
R = alkyl, aryl, or hydrogen

Scheme III

Tables I and II contain the data pertinent to the structures of the compounds under consideration.

Table I—2-Substituted-5-carbomethoxy-5-methyl-1,3,2-dioxaphosphorinane 2-Oxides



Compd. Number	Y	x	Formula	Pure Yield, %	M.p.	Procedure
1	—Cl	1	$C_6H_{10}ClO_5P$	41.3	108–109°	A
2	—OH	1	$C_6H_{11}O_6P$	52.7	182–184°	B
3		1	$C_{13}H_{20}NO_6PS$	79.4	174–176°	C
4		1	$C_{12}H_{17}FNO_6P$	94.5	150–151.5°	C
5		1	$C_{11}H_{22}NO_6P$	54.2	117–121°	C
6		1	$C_{12}H_{17}ClNO_6P$	54.6	135–136.5°	C
7	—O—	2	$C_{12}H_{20}O_{12}P_2$	20.0	186–187°	D
8		1	$C_8H_{14}NO_5P$	33.3	90–91°	E
9		1	$C_9H_{16}NO_5P$	59.0	b.p. 124–128° at 0.1–0.3 Torr.	E
10		1	$C_{10}H_{18}NO_5P$	59.1	47–49°	E
11		1	$C_{11}H_{20}NO_5P$	35.0	112–114°	E
12		1	$C_{13}H_{18}NO_5P$	33.1	100–101°	E
13		1	$C_{12}H_{22}NO_5P$	70.0	167.5–169.5°	E
14		1	$C_{10}H_{18}NO_5P$	50.0	85–86.5°	E
15		1	$C_{12}H_{22}NO_5P$	38.0	125.5–127.5°	E
16		1	$C_{12}H_{16}NO_5P$	49.4	165–166°	F
17		1	$C_{12}H_{15}BrNO_5P$	57.2	158.5–159.5°	F
18		1	$C_{13}H_{18}NO_6P$	56.9	140–141°	F
19		1	$C_{15}H_{26}NO_5P$	29.7	171.5–173°	E
20	—$NH(CH_2)_3NH$—	2	$C_{15}H_{28}N_2O_{10}P_2$	44.4	195–197°	E
21	—$NH(CH_2)_8NH$—	2	$C_{20}H_{38}N_2O_{10}P_2$	26.9	166–167.5°	E
22	—$NH(CH_2)_4NH$—	2	$C_{16}H_{30}N_2O_{10}P_2$	55.6	227.5–228.5°	E

BIOLOGICAL RESULTS

All biological testing was carried out by the Cancer Chemotherapy National Service Center (CCNSC), Bethesda, Md. Compounds I–VI, VIII–X, XII–XIX, XXI, and XXII were tested against L1210 lymphoma over a total dose range of 40–400 mg./kg. and found to be inactive. Compounds II, III, V, VI, X, XIII, and XV–XVIII were tested against Walker 256 carcinosarcoma over a total dose range of 100–400 mg./kg. and found to be inactive.

EXPERIMENTAL[1]

2-Chloro-5-carbomethoxy-5-methyl-1,3,2-dioxaphosphorinane 2-Oxide (II)—*Procedure A*—Phosphorus oxychloride (154.5 g., 1.01 moles) was added in small portions to stirring 2-carbomethoxy-2-methyl-1,3-propanediol (50.0 g., 0.337 mole) in a conical flask fitted with a drying tube. After the exothermic reaction had subsided, the stirring reaction mixture was heated to 90° for 4 hr. The reaction mixture was poured with stirring into 600 ml. of petroleum ether (90–120° b.p.) which had been cooled to 0° in an ice bath. White crystals of the phosphochloridic acid precipitated; they were filtered and washed with anhydrous ether, yielding 31.3 g. or 41.3%.

Anal.—Calcd. for $C_6H_{10}ClO_5P$: C, 31.52; H, 4.41. Found: C, 31.35; H, 4.35.

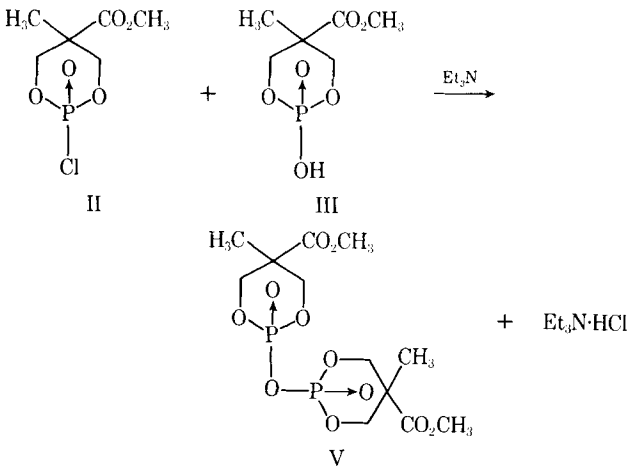
2-Hydroxy-5-carbomethoxy-5-methyl-1,3,2-dioxaphosphorinane 2-Oxide (III)—*Procedure B*—A stirring solution of II (42.50 g., 0.186 mole) in 100 ml. of 95:5 acetone–water was refluxed for 3.5 hr. and the reaction mixture was cooled overnight. The resulting white crystals of III were recrystallized from acetone, yielding 20.6 g. or 52.7%.

Anal.—Calcd. for $C_6H_{11}O_6P$: C, 34.25; H, 5.28. Found: C, 34.30; H, 5.41.

[1] All melting points were determined on a Thomas-Hoover capillary apparatus and are corrected. IR spectra were obtained from a Perkin-Elmer 137 infrared spectrophotometer. Analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind.

Table II—Analytical Data for 2-Substituted-5-carbomethoxy-5-methyl-1,3,2-dioxaphosphorinane 2-Oxides

Compd. Number	Anal., %: C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	IR Bands (cm.$^{-1}$): N—H	C=O	P→O	POC	POP	O ‖ CCH$_3$	OH
1	31.52	31.35	4.41	4.35	—	—	—	1735	1225	990	—	1360	—
2	34.25	34.30	5.28	5.41	—	—	—	1725	1245	1000	—	1350	3000–2000
3	—	—	—	—	4.01	3.99	2700–2200	1725	1200	1000	—	1345	—
4	—	—	—	—	4.36	4.40	2700–2100	1725	1200	1000	—	1350	—
5	—	—	—	—	4.74	5.03	3000–2100	1725	1210	1000	—	1375	—
6	—	—	—	—	4.15	3.97	2700–2100	1730	1200	1010	—	1350	—
7	35.83	35.91	5.01	5.16	—	—	—	1725	1235	990	960	1360	—
8	—	—	—	—	5.96	6.04	—	1725	1240	1000	—	1360	—
9	—	—	—	—	5.60	5.33	—	1725	1260	1000	—	1360	—
10	—	—	—	—	5.30	5.30	—	1725	1250	950–1050	—	1360	—
11	—	—	—	—	5.02	4.86	—	1725	1235	995	—	1365	—
12	—	—	—	—	4.68	4.75	3200	1730	1225	1000	—	1365	—
13	—	—	—	—	4.83	4.88	3200	1725	1215	995	—	1350	—
14	—	—	—	—	5.32	5.47	—	1730	1230	1010	—	1350	—
15	—	—	—	—	4.81	4.81	—	1730	1230	1000	—	1350	—
16	—	—	—	—	4.91	4.67	3150	1725	1220	990	—	1350	—
17	—	—	—	—	3.85	3.86	3100	1730	1220	990	—	1350	—
18	—	—	—	—	4.44	4.50	3300	1720	1220	1000	—	1370	—
19	—	—	—	—	4.23	4.23	3310	1725	1225	1000	—	1325	—
20	—	—	—	—	6.11	6.30	3240	1735	1225	1010	—	1325	—
21	—	—	—	—	5.30	5.45	3210	1730	1220	1000	—	1365	—
22	—	—	—	—	5.91	5.96	3200	1730	1230	1000	—	1320	—



Scheme IV

2-Hydroxy-5-carbomethoxy-5-methyl-1,3,2-dioxaphosphorinane 2-Oxide, 4-Methylmercaptoaniline Salt—*Procedure C*—This procedure is representative of those used in preparation of the salts. A solution of 4-methylmercaptoaniline (3.31 g., 23.8 mmoles) in 50 ml. of acetone was added dropwise to a stirring solution of III (5.00 g., 23.8 mmoles) in 25 ml. of acetone, and the resulting mixture was stirred for 1 hr. at room temperature. White crystals of the salt precipitated; they were washed with acetone and dried, yielding 6.60 g. or 79.4%.

Anal.—Calcd. for $C_{13}N_{20}NO_6PS$: N, 4.01. Found: N, 3.99.

Bis(5-carbomethoxy-5-methyl-2-oxo-1,3,2-dioxaphosphorinanyl)-pyrophosphate (V)—*Procedure D*—A solution of III (4.60 g., 21.9 mmoles) in 25 ml. of acetone was added dropwise to a stirring solution of II (5.00 g., 21.9 mmoles) in 25 ml. of acetone at room temperature. An excess of triethylamine in acetone was added to the reaction mixture, which was then stirred for 2 hr. at room temperature. Triethylamine hydrochloride precipitated; the reaction mixture was chilled and filtered. The solvent was removed from the filtrate *in vacuo;* the resulting white crystals of V were recrystallized from ethyl acetate–acetonitrile, yielding 1.75 g. or 20.0%.

Anal.—Calcd. for $C_{12}H_{20}O_{12}P_2$: C, 35.83; H, 5.01. Found: C, 35.91; H, 5.16.

2-Aziridino-5-carbomethoxy-5-methyl-1,3,2-dioxaphosphorinane 2-Oxide—*Procedure E*—This procedure is representative of those used in the preparation of the alkylamides of Type IV. A solution of aziridine (0.94 g., 21.7 mmoles) and an excess of triethylamine in 50 ml. of acetone was added dropwise to a stirring solution of II (5.00 g., 21.9 mmoles) in 25 ml. of acetone at 0°. Triethylamine hydrochloride precipitated immediately. The reaction mixture was filtered after precipitation was complete, and the solvent was evaporated from the filtrate *in vacuo*. The resulting white crystals of the amide were recrystallized from ether, yielding 1.70 g. or 33.3%.

Anal.—Calcd. for $C_8H_{14}NO_5P$: N, 5.96. Found: N, 6.04.

2-(4-Bromoanilino)-5-carbomethoxy-5-methyl-1,3,2-dioxaphosphorinane 2-Oxide—*Procedure F*—This procedure is representative of those used in the preparation of the arylamides of Type IV. A solution of 4-bromoaniline (15.04 g., 87.4 mmoles) in 50 ml. of benzene was refluxed with stirring for 1 hr. in an apparatus equipped with a Dean trap to remove moisture. A solution of II (10.00 g., 43.7 mmoles) in 50 ml. of benzene was added dropwise to the stirring reaction mixture, which was then refluxed for an additional 4 hr. 4-Bromoaniline hydrochloride precipitated; the reaction mixture was filtered while still hot and the filtrate was chilled. The resulting white crystals of the amide were recrystallized from benzene, yielding 9.1 g. or 57.2%.

Anal.—Calcd. for $C_{12}H_{15}BrNO_5P$: N, 3.85. Found: N, 3.86.

REFERENCE

(1) J. H. Billman and R. F. May, *J. Pharm. Sci.*, **57**, 1812(1968).

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