1,3,2-Dioxaphosphorinane 2-Oxides II. Preparation and Antitumor Activity of Some 2-Alkylamino and 2-Arylamino-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-Oxides

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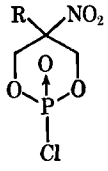
A series of 2-substituted-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxides consisting of 2-alkylamino and 2-arylamino types have been prepared and submitted for antitumor screening.

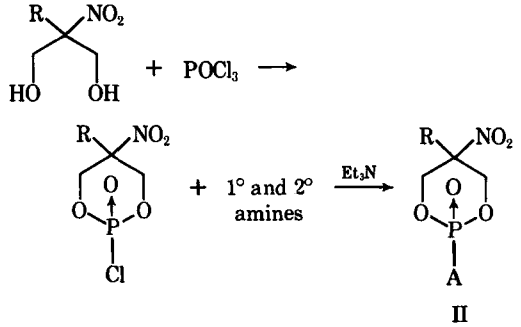
IN THE first publication of this series (1) the authors discussed several miscellaneous 2-substituted derivatives of 2-chloro-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxides (I).



I

In view of the fact that different atoms or groups can change the electronic density about the phosphorus atom and by so doing affect the antitumor activity of the 1,3,2-dioxaphosphorinane 2-oxides, it was decided that a desirable grouping to introduce into the 2-position would be substituted amines. Twenty-seven such amides have been prepared and are listed in Tables I and II.

The reaction sequence leading to the preparation of the phosphoramides, II, is shown in Scheme I.



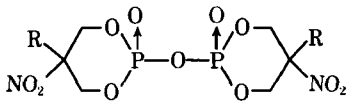
II

R = —CH_3, —CH_2CH_3

A = —NHR, —N⌒$(CH_2)_n$, —NHAr, *etc.*

Scheme I

The aliphatic amines react with the phosphochloridic acids, I, at 0°, whereas the aromatic amines which are less basic require heating. Also, the aliphatic amines form the amides in very good yields while the aromatic ones give poor yields owing to the production of the pyrophosphate, III, the formation of which is described in the first article of this



III

series (1). It appears that whenever the reaction time is greater than 0.5 hr. the pyrophosphate III is formed to a greater extent.

Biological Results—Preliminary antitumor screening data indicated that some of these compounds are exceedingly active towards Walker carcinosarcoma 256 (intramuscular). Upon rescreening one of these compounds, it failed to measure up to the previous high activity. Additional rescreening data are being sought for the other compounds to corroborate the original findings.

EXPERIMENTAL[1]

General Method for the Synthesis of 2-Alkylamino and 2-Arylamino-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-Oxides (Method A)—The preparation of 2-aziridino-5-methyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxide. The 2-chloro-2-methyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxide, 5 g. (0.0232 mole) was dissolved in 125 ml. of acetone and cooled to 0°. To this mixture aziridine, 1.32 g. (0.0232 mole), and triethylamine, 4.68 g. (0.0464 mole), were added dropwise with stirring. The solid hydrochloride formed at once and was removed by filtration. The filtrate was evaporated to dryness *in vacuo* yielding 5.0 g. (97.0% yield) of white solid. Recrystallization from ethanol gave 4.2 g. (82.0% yield) of pure solid product (m.p. 154–156°).

Anal.—Calcd. for $C_6H_{11}N_2O_5P$: N, 12.61; Found: N, 12.86.

2 - (3′ - Chloroanilinium) - 5 - methyl - 5 - nitro-1,3,2-dioxaphosphorinane 2-Oxide (Method B)—Ten grams (0.0464 mole) of 2-chloro-5-methyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxide and 200 ml. of benzene were placed in a 500-ml. three-necked,

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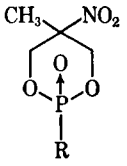
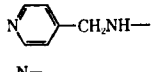
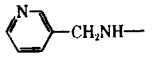
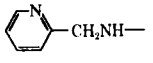
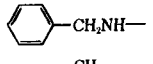
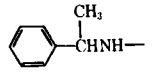
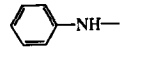
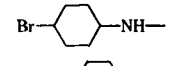
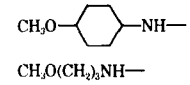
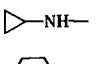
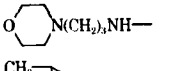
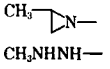
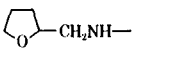
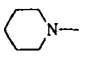
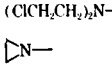
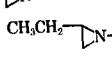
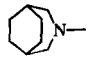
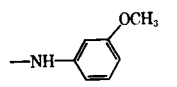
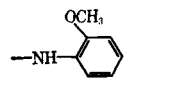
The authors wish to thank the Commercial Solvents Corporation for samples of the diols used in this research.

[1] All melting points were taken on a Thomas-Hoover device and are corrected. The infrared data were obtained from spectra prepared on a Perkin-Elmer Infracord. The elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

TABLE I—2-SUBSTITUTED AMINO DERIVATIVES OF 2-CHLORO-5-METHYL-5-NITRO-1,3,2-DIOXAPHOSPHORINANE 2-OXIDE



Compd. No.	R	Formula	Yield (pure), %	M.p., °C.	%N Calcd.	%N Found	Infrared Assignment, μ		
1		$C_{10}H_{19}N_2O_5P$	93.0	187–189	10.07	10.03	7.95	9.30	12.25
2		$C_9H_{16}N_2O_5P$	40.6	148–150	10.65	10.32	8.05	9.40	12.25
3		$C_{10}H_{14}N_3O_5P$	45.0	189–191	14.67	14.96	7.95	9.28	12.26
4		$C_{10}H_{14}N_3O_5P$	87.0	175–177	14.67	14.79	7.91	9.34	12.21
5		$C_{10}H_{14}N_3O_5P$	75.5	140–142	14.67	14.48	7.92	9.36	12.34
6		$C_{11}H_{16}N_2O_5P$	75.0	146–148	9.80	9.49	8.10	9.40	12.10
7		$C_{12}H_{17}N_2O_5P$	57.4	169–171	9.35	9.44	8.12	9.40	12.20
8		$C_{10}H_{12}N_2O_5P$	59.4	173–175	10.30	10.15	8.16	9.45	12.00
9		$C_{10}H_{12}BrN_2O_5P$	30.7	208–210	8.00	7.73	7.91	9.43	12.10
10		$C_{11}H_{16}N_2O_6P$	42.6	159–161	9.28	9.19	7.96	9.41	12.05
11	$CH_3O(CH_2)_3NH$—	$C_8H_{17}N_2O_6P$	71.0	105–107	10.45	10.36	8.02	9.40	12.30
12		$C_7H_{13}N_2O_5P$	80.0	147–149	11.89	11.96	8.05	9.30	12.20
13		$C_{11}H_{22}N_3O_6P$	33.3	152–154	13.00	12.99	8.00	9.30	12.45
14		$C_7H_{13}N_2O_6P$	91.2	113–115	11.85	11.88	7.88	9.50	12.50
15	CH_3NHNH—	$C_6H_{13}ClN_3O_5P$	74.2	154–156	16.09	16.19	7.83	9.41	12.25
16		$C_9H_{17}N_2O_6P$	76.0	120–122	10.00	9.76	7.91	9.38	12.31
17		$C_9H_{17}N_2O_5P$	73.5	246–248	10.60	10.58	7.98	9.40	12.30
18	$(ClCH_2CH_2)_2N$—	$C_8H_{15}Cl_2N_2O_5P$	67.0	251–253	8.70	8.43	7.70	9.30	12.63
19		$C_6H_{11}N_2O_5P$	82.0	154–156	12.61	12.86	8.10	9.50	12.30
20		$C_8H_{15}N_2O_5P$	51.5	131–133	11.20	10.94	7.85	9.30	12.20
21		$C_{12}H_{21}N_2O_5P$	85.0	216–218	9.21	9.33	7.95	9.40	12.30
22		$C_{11}H_{16}N_2O_6P$	36.6	181–182.5	9.28	9.36	8.05	9.4, 9.8	12.0
23		$C_{11}H_{16}N_2O_6P$	67.4	141.5–143.5	9.28	9.32	8.1	9.5, 10.0	12.1

(Continued on next page.)

TABLE I (*Continued.*)

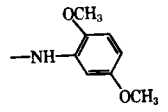
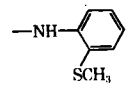
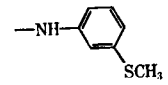
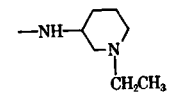
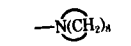
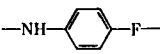
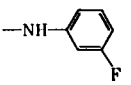
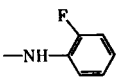
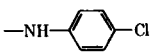
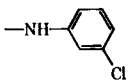
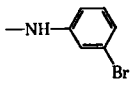
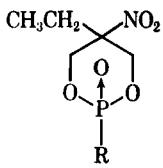
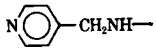
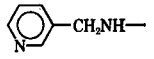
Compd. No.	R	Formula	Yield (pure), %	M.p., °C.	%N Calcd.	%N Found	Infrared Assignment, μ		
24		$C_{12}H_{17}N_2O_7P$	62.5	161–163	8.43	8.54	8.1	9.6, 10.05	
25		$C_{11}H_{15}N_2O_5PS$	49.1	127–128	8.80	8.98	8.0	9.4, 9.95	12.1
26		$C_{11}H_{15}N_2O_5P$	29.9	185–187	8.80	8.61	8.15	9.45, 10.0	12.05
27		$C_{11}H_{21}N_3O_5P$	31.5	110–112	13.69	13.64	8.08	9.60, 10.0	12.42
28		$C_{12}H_{23}N_2O_5P$	62.0	184–186	9.15	9.27	8.3	9.7, 10.2	12.5
29		$C_{10}H_{12}FN_2O_5P$	55.0	164–166	9.65	9.93	8.0	9.5, 10.0	12.25
30		$C_{10}H_{12}FN_2O_5P$	39.6	179–181	9.65	9.90	8.15	9.5	12.13
31		$C_{10}H_{12}FN_2O_5P$	56.5	162–164	9.65	9.56	8.07	9.45, 9.95	12.21
32		$C_{10}H_{12}ClN_2O_5P$	44.7	202–204	9.14	9.38	8.20	9.5, 9.9	12.1
33		$C_{10}H_{12}ClN_2O_5P$	57.5	171.5–173.5	9.14	9.30	8.13	9.50, 9.87	12.10
34		$C_{10}H_{12}BrN_2O_5P$	57.5	185–187	8.00	8.13	8.15	9.5, 10.0	12.1

TABLE II—2-SUBSTITUTED AMINO DERIVATIVES OF 2-CHLORO-5-ETHYL-5-NITRO-1,3,2-DIOXAPHOSPHORINANE 2-OXIDE



Compd. No.	R	Formula	Yield (pure), %	M.p., °C.	%N Calcd.	%N Found	Infrared Assignment, μ		
1		$C_7H_{13}N_2O_5P$	56.8	118–120	11.88	12.20	7.80	9.69	12.45
2		$C_8H_{15}N_2O_5P$	80.0	106–108	11.20	11.42	7.86	9.70	12.50
3		$C_9H_{17}N_2O_5P$	86.5	119–121	10.60	10.74	7.90	9.65	12.40
4		$C_{11}H_{16}N_3O_5P$	47.2	196–198	13.96	13.86	8.00	9.60	12.28
5		$C_{11}H_{16}N_3O_5P$	44.6	173–175	13.96	13.88	8.00	9.61	12.26
6	NH_2—	$C_5H_{11}N_2O_5P$	87.0	204–206	13.31	13.37	7.91	9.25	

round-bottom flask equipped with a Dean-Stark trap, magnetic stirring bar, and heating mantle. After the benzene solution was refluxed for 0.5 hr. to remove all water from the system, 11.8 g. (0.0928 mole) of 3-chloroaniline was added dropwise to the reaction flask. White material precipitated. The reaction mixture was stirred at reflux temperature, overnight, then the reaction was interrupted and the hot solution was filtered immediately to remove the 3-chloroaniline hydrochloride. About 100 ml. of benzene was removed from the filtrate under reduced pressure causing a white precipitate to form. The solution was cooled in a refrigerator and 7.1 g. of crystals was collected by suction filtration. The solvent from the filtrate was evaporated to dryness under reduced pressure leaving a solid which was combined with the crystals previously collected and recrystallized from 2-propanol to give a total of 8 g. (57.5%) of the white crystalline 2-(3'-chloroanilinium)-5-methyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxide, m.p. 171.5–173.5°.

Anal.—Calcd. for $C_{10}H_{12}ClN_2O_5P$: N, 9.14. Found: N, 9.30.

REFERENCES

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

Keyphrases

2-Alkylamino-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxides—synthesis
2-Arylamino-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxides—synthesis
Antitumor activity—1, 3, 2-dioxaphosphorinane 2-oxides
IR spectrophotometry—structure

1,3,2-Dioxaphosphorinane 2-Oxides III. Preparation and Antitumor Evaluation of Some 3,9-Disubstituted-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]-undecane 3,9-Dioxide

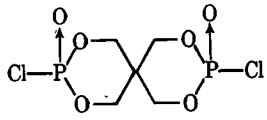
By JOHN H. BILLMAN and RALPH F. MAY

A series of 3,9-aminodisubstituted-2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5] undecane 3,9-dioxides has been prepared and screened for antitumor activity. Only one of these compounds showed activity toward Walker carcinosarcoma 256.

In view of the fact that some 2-alkylamino and 2-arylamino-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxides have been shown to possess some antitumor activity against Walker carcinosarcoma 256 (intramuscular) (1), one might expect that molecules containing two dioxaphosphorinane 2-oxide groupings would possess equal or greater activity than the single ring system.

Since Sweeting (2) had reported the synthesis of 3,9-dichloro-2,4,8,10-tetraoxa-3,9-diphosphaspiro [5.5] undecane 3,9-dioxide, I, it was decided that this dichloride would be an excellent starting material for making compounds that would fulfill the requirement of a double ring system. It was also felt that it would be of interest to see if the spirane moiety would act as a good carrier group and if in some way or other would have an effect on antitumor activities.

The desired amides were prepared by condensing the appropriate amines with the dichloride I in acetonitrile in the presence of triethylamine as outlined in Scheme I and as listed in Table I.



I

Biological Results—Only Compound 6 in Table I showed appreciable activity, and this was toward Walker carcinosarcoma 256. It showed an inhibition of 35% at a dose level of 25 mg./kg., 58% at 100 mg./kg., and 79% at 200 mg./kg. The activity of this compound is probably due to the alkylating groups in the molecule. Most of the other amides had an exceedingly high melting point and were very insoluble in most of the common organic solvents. The lack of antitumor activity for these diamides may be accounted for by their great insolubility.

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This paper represents part of a M.A. thesis submitted to the Graduate School, Indiana University, 1966.

The authors wish to thank Dr. O. J. Sweeting for supplying a large sample of 3,9-dichloro-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-dioxide (I) which was used in the early part of this work.