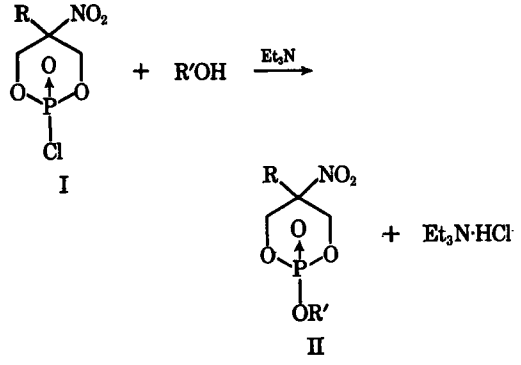
1,3,2-Dioxaphosphorinane 2-Oxides I. Preparation of Some 2-Alkoxy, 2-Acyl, and 2-Hydroxy-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-Oxides as Potential Antitumor Agents

By JOHN H. BILLMAN, RALPH F. MAY, and JANE E. HEARD

A series of compounds consisting of 2-alkoxy, 2-acyl, and 2-hydroxy-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxides has been prepared. Several amine salts of the 2-hydroxy compounds have been isolated. All of the compounds prepared were submitted for antitumor evaluation.

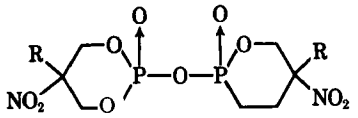
In an earlier publication (1) a report was made from this laboratory concerning the synthesis of phosphorochloridic acids I as possible intermediates leading to some potential antitumor agents.



Scheme I

Recently, several different derivatives of Compound I were prepared in order to determine what type of moiety in the 2 position might lend antitumor activity to the compound.

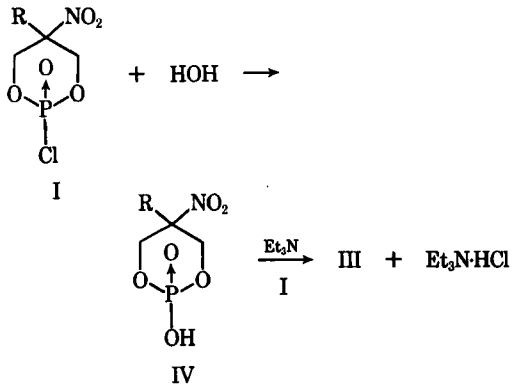
Three 2-alkoxy substituted compounds of Type II were prepared according to Scheme I. Although this synthesis appears to be straightforward, some



III

of the phosphorochloridic acid I failed to react as expected. Instead, a fairly large amount of the pyrophosphate III was produced thereby reducing the yield of the desired ester II.

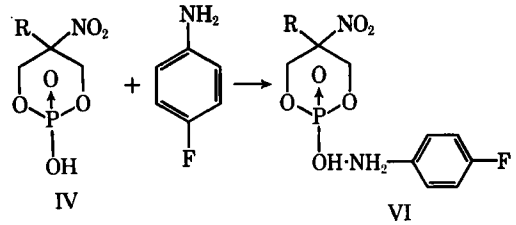
Since the 2-hydroxy Compound IV is readily prepared by refluxing the corresponding chloridic acid I in a 1 : 1 mixture of acetone–water, it was decided that Compound III was the result of traces of moisture in the reaction system. Once formed, Compound IV could then react with the phosphorochloridic acid I as is shown in Scheme II to yield the pyrophosphate III.



Scheme II

In order to prove that Scheme II is a possible pathway to the pyrophosphates, it has now been shown that a phosphorochloridic acid I and a 2-hydroxy compound of Type IV yield the expected anhydride in the presence of triethylamine.

Several amine salts of the 2-hydroxy-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxide IV were prepared, not only to improve the hydrolytic properties of the acid but to introduce some amines into the molecule which reportedly have antitumor activity. These salts were prepared as in Scheme III.



Scheme III

Three mixed anhydrides of Type VII were prepared as illustrated in Scheme IV. In view of the fact that these compounds are anhydrides and therefore, should be very active, it is expected that

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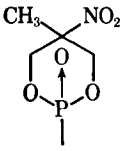
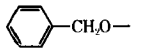
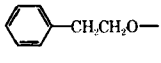
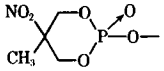
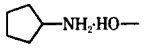
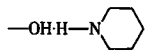
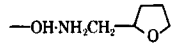
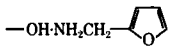
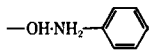
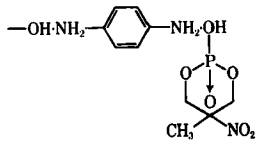
This is part of a Ph.D. thesis submitted to the Graduate School, Indiana University, 1967, and part of a M.A. thesis submitted to the Graduate School, Indiana University, 1968.

The authors wish to thank the Commercial Solvent Corporation for samples of the nitroalcohols they furnished for this project.

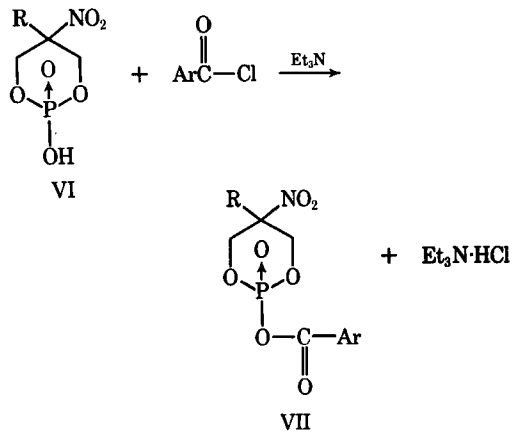
TABLE I—2-ACYL AND 2-HYDROXY-5-METHYL-5-NITRO-1,3,2-DIOXAPHOSPHORINANE 2-OXIDES



Compd. No.	R	Formula	Yield (pure), %	M.p., °C.	% N Calcd.	% N Found	Infrared Assignment, μ	
1	HO—	$C_4H_8NO_6P$	77.6	169–171	7.12	7.13	8.20	9.80
2	CH_3CH_2O—	$C_6H_{12}NO_6P$	86.5	99–100	6.22	6.27	7.82	9.50
3		$C_{11}H_{14}NO_6P$	15.0	152–154	4.89	4.84	7.80	9.62
4		$C_{12}H_{16}NO_6P$	64.5	105–107	4.66	4.65	7.80	9.40
5		$C_8H_{14}N_2O_{10}P_2$	64.5	250–252	7.30	7.44	7.52	10.00
6		$C_9H_{19}N_2O_6P$	99.2	248–250	9.94	9.92	8.12	9.45
7		$C_9H_{19}N_2O_6P$	83.8	204.5–206.5	9.93	9.93	8.2	9.4, 10.05
8		$C_9H_{19}N_2O_7P$	73.3	213–215	9.40	9.30	8.15	9.4, 10.05
9		$C_9H_{15}N_2O_7P$	75.5	204–206	9.52	9.67	8.2	9.3, 10
10		$C_{10}H_{15}N_2O_6P$	68.0	225–227	9.65	9.45	8.3	9.5
11		$C_{14}H_{24}N_4O_{12}P_2$	90.5	243–245	11.16	10.88	8.15	9.3, 9.98

they might act as phosphorylating and/or acylating agents. If this turns out to be the case, such compounds might very well interfere with biological systems involving the chemistry of RNA, DNA, *etc.* Compounds are given in Tables I and II.

Biological Results—To date, no biological data are available on any of the above compounds. All testing is being carried out by the Cancer Chemotherapy National Service Center (CCNSC), Bethesda, Md.



Scheme IV

EXPERIMENTAL[1]

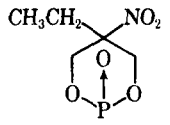
2-Alkoxy-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-Oxide—The synthesis of these compounds is typified by the procedure for 2-benzoxy-5-methyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxide. The benzyl alcohol 2.5 g. (0.0232 mole) and triethylamine 4.7 g. (0.0464 mole) mixture in acetone was added dropwise to a 200-ml., stirring, acetone solution of the phosphorochloridic acid 5 g. (0.0232 mole). The solution was allowed to reflux overnight resulting in a precipitate of amine hydrochloride. The solid was removed, and the acetone was evaporated *in vacuo* to afford an oil. The expected product was extracted from this oil with ethyl acetate and collected as a solid when the solvent was removed under reduced pressure. The material was recrystallized from 2-propanol to give 1 g. (15.0% yield) of pure product (m.p. 152–154°).

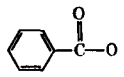
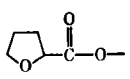
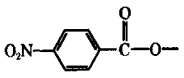
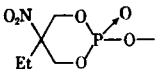
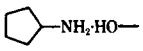
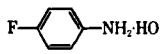
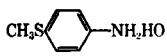
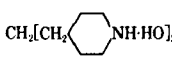
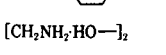
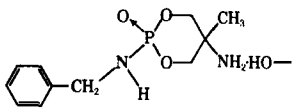
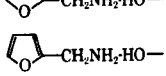
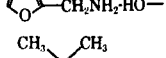
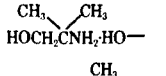
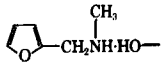
Anal.—Calcd. for $C_{11}H_{14}NO_6P$: N, 4.89. Found: N, 4.84.

2-Hydroxy-5-methyl-5-nitro-1,3,2-dioxaphos-

[1] All melting points were taken on a Thomas-Hoover device and are corrected. The analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

TABLE II—2-ALKOXY-5-ALKYL-5-NITRO-1,3,2-DIOXAPHOSPHORINANE 2-OXIDES



Compd. No.	R	Formula	Yield (pure), %	M.p., °C.	% N Calcd.	% N Found	Infrared Assignment, μ	
1	HO—	$C_5H_{10}NO_6P$	63.0	117–119	6.64	6.73	8.30	9.90
2		$C_{12}H_{14}NO_7P$	80.5	134–136	4.45	4.47	8.00	9.80
3		$C_{10}H_{12}NO_8P$	56.8	119–121	4.60	4.63	7.90	9.80
4		$C_{12}H_{13}N_2O_9P$	70.0	214–216	7.78	7.88	8.60	9.60
5		$C_{10}H_{18}N_2O_{11}P$	73.8	255–257	6.95	6.97	7.60	9.25
6	Na^+O^-—	$C_5H_9NNaO_6P$	90.6	300–302	6.01	6.10	7.98	9.22
7		$C_{10}H_{21}N_2O_6P$	98.1	222–224	9.45	9.48	8.15	9.30
8		$C_{11}H_{16}FN_2O_6P$	80.3	222–224	8.75	8.75	8.20	9.32
9		$C_{12}H_{19}N_2O_6PS$	85.5	188–190	8.00	8.01	8.28	9.31
10		$C_{22}H_{46}N_4O_{12}P_2$	87.0	227–229	8.81	8.74	8.20	9.33
11		$C_{12}H_{28}N_4O_{12}P_2$	79.0	257–258	11.62	11.80	8.15	9.25
12		$C_{16}H_{27}N_3O_9P_2$	78.5	206–208	9.00	9.12	8.20	9.30
13		$C_{10}H_{21}N_2O_7P$	69.0	183–185	9.00	8.99	8.12	9.35
14		$C_{10}H_{17}N_2O_7P$	85.0	185–187	9.08	8.91	8.12	9.22
15		$C_9H_{21}N_2O_7P$	85.8	211–213	9.34	9.12	8.00	9.35
16		$C_{11}H_{19}N_2O_7P$	95.6	124–126	8.70	8.59	8.20	9.20

phorinane 2-Oxide—This compound and the 5-ethyl product as well were prepared by a procedure similar to that of Edmundson (2).

Anal.—Calcd. for $C_4H_8NO_6P$: N, 7.12. Found: N, 7.13.

2-Hydroxy-5-methyl-5-nitro-1,3,2-dioxaphosphorinane 2-Oxide, Furfurylamine Salt—The following synthesis is typical of the procedure used for preparing salts. Five grams (0.025 mole) of 2-hydroxy-5-methyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxide was dissolved in 100 ml. of hot acetone. A mixture of 2.42 g. (0.025 mole) of furfurylamine and 10 ml. acetone was added slowly to the hot solution with constant stirring. The salt formed rapidly and was collected by filtration after cooling. Recrystallization in 2-propanol and water gave 5.6 g. (75.5% yield) of white crystalline material, m.p. 204–206°.

Anal.—Calcd. for $C_9H_{15}N_2O_7P$: N, 9.52. Found: N, 9.67.

2-Acyl-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-Oxide—The synthesis of this series of compounds is illustrated by the synthesis of 2-benzoyl-5-ethyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxide. The acetone solutions of the 2-hydroxy-5-ethyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxide 5 g. (0.0237 mole) and the benzoyl chloride 3.5 g. (0.0237 mole) were combined with no noticeable reaction. The triethylamine 4.8 g. (0.0474 mole) was added dropwise with stirring to give an immediate precipitate of

triethylamine hydrochloride. The solid was removed by filtration, and the filtrate was evaporated to dryness *in vacuo* to give a white solid. The material was recrystallized from acetonitrile to give 6 g. (80.5% yield) of pure product (m.p. 134–136°).

Anal.—Calcd. for $C_{12}H_{14}NO_7P$: N, 4.45. Found: N, 4.47.

Bis(5-alkyl-5-nitro-2-oxo-1,3,2-dioxaphosphorinanyl) Oxide—The synthesis of this type of compound is typified by the synthesis of the methyl derivative. The phosphorochloridic acid 20 g. (0.0928 mole) was dissolved in undried acetone, and the triethylamine 9.4 g. (0.0928 mole) was added. Within 10 min. the solid product began to form, and the reaction was complete in 2 hr. The solid was removed by filtration and dried, yielding 11.5 g. (64.5% yield) of pure product (m.p. 250–252°).

Anal.—Calcd. for $C_8H_{14}N_2O_{11}P_2$: N, 7.46. Found: N, 7.44.

REFERENCES

(1) Billman, J. H., Meisenheimer, J. L., and May, R. F., *J. Med. Chem.*, **9**, 772 (1966).
(2) Edmundson, R. S., *Tetrahedron*, **21**, 2379(1965).

Keyphrases

2-Alkoxy-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxides—synthesis
2-Acyl-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxides—synthesis
2-Hydroxy-5-alkyl-5-nitro-1,3,2-dioxaphosphorinane 2-oxides—synthesis
IR spectrophotometry—structure

New Compounds: Synthesis of Some Phosphorus-Nitrogen Compounds for Pharmacological Study III

By A. ABOU-MOUSTAFA and M. KHALIFA

Phosphorus-nitrogen compounds containing moieties of the so-called long-acting sulfonamides were prepared by reacting the sulfonamides with PCl_3 or $POCl_3$ in a 2:1 ratio. In the case of PCl_3 the condensation took place according to the above ratio with sulfaphenazole, sulfamethoxypyridazine, and sulfamethoxydiazine. With sulfadimethoxine two products were obtained: a derivative of phosphorus triamide and a derivative of diamidophosphorus acid; this corresponds to the condensation of 1 mole of the acid chloride with 3 moles and with 2 moles of the sulfonamide, respectively. In the $POCl_3$ condensations the ratio mentioned earlier was obeyed only with sulfamethoxydiazine while with the rest, 3 moles of the sulfonamide condensed with 1 mole of the oxychloride.

In continuation of the work which has been started in this laboratory on the condensation of a number of sulfa drugs with phosphorus trichloride and phosphorus oxychloride (1, 2), the so-called long-acting sulfonamides were condensed with the same acid chlorides for two reasons: to complete the picture required for the pharmacological study and to compare once more the reactivity of the two acid chlorides in these condensation reactions. This latter objective was dealt with in a previous publication (2) and from a consideration of the reaction time, the yields, and the mode in which the sulfa drug had condensed with the acid chloride, it was concluded that phosphorus oxychloride is more reactive than the trichloride. The results obtained from the present investigation conform with those obtained earlier and confirm the finding that phosphorus oxychloride is more reactive than the trichloride.

With the trichloride the condensation was complete after 24 hr. while with the oxychloride 12 hr. was sufficient. Moreover, higher yields were obtained with the oxychloride (70–88%) than with the trichloride (58–80%). Finally the manner in which the sulfa compound condensed with the acid chloride was significant. In three cases the sulfonamide–oxychloride condensation ratio was 3:1 while in the fourth only two molecules of the sulfonamide condensed with one molecule of the acid chloride. This latter mode was the rule in the phosphorus trichloride condensations except in the case of sulfadimethoxine where a mixture of the tri- and diamide derivatives was obtained with the former predominating.

The superior reactivity of phosphorus oxychloride to that of the trichloride is probably due to the fact that the phosphorus atom in the oxychloride is more electrophilic than that in the trichloride—a property which expectedly would render it more vulnerable to attack by nucleophilic reagents and this is in keeping with what has been reported earlier (3).

That the phosphorus atom in the synthesized compounds is linked to the N^4 of the sulfa drug was shown qualitatively by the failure of all the condensation products to diazotize, their solubility in dilute alkali, and their insolubility in dilute mineral acids.

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