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.

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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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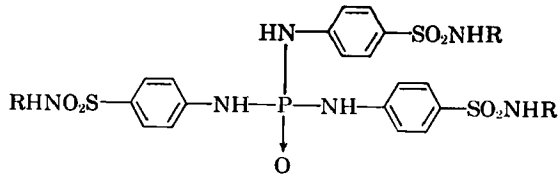
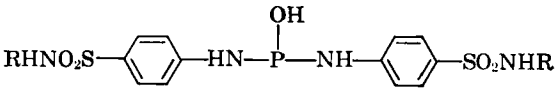
TABLE I—*N*-SUBSTITUTED DERIVATIVES OF PHOSPHORIC TRIAMIDE



Compd.	*R*	% Yield	M.p., °C.[a]	Formula	Anal.,[b] Calcd.	Found
I	6-Methoxy-3-pyridazinyl	76	219–222 265 dec.	$C_{33}H_{33}N_{12}O_{10}PS_3$	N, 18.99	19.49
II	2-Phenyl-3-pyrazolyl	88	170–174 242 dec.	$C_{45}H_{39}N_{12}O_7PS_3$	N, 17.02 C, 54.75 H, 3.98	16.67 54.18 4.06
III	2,4-Dimethoxy-6-pyrimidinyl	70	245–248 270 dec.	$C_{36}H_{39}N_{12}O_{13}PS_3$	N, 17.24	17.85

[a] Liquid crystal. Melting points were performed by the capillary tube method and are uncorrected. [b] Analyses performed by Janssen Pharmaceutica, Beerse, Belgium.

TABLE II—*N*-SUBSTITUTED DERIVATIVES OF PHOSPHORODIAMIDOUS ACID



Compd.	R	% Yield	M.p., °C.[a]	Formula	Anal.,[b] Calcd.	Found
IV	6-Methoxy-3-pyridazinyl	58	187–190 248 dec.	$C_{22}H_{23}N_8O_7PS_2$	N, 18.47	18.42
V	2-Phenyl-3-pyrazolyl	80	178–182 255 dec.	$C_{30}H_{27}N_8O_5PS_2$	N, 16.60	16.49
VI	5-Methoxy-2-pyrimidinyl	67	155–158 232 dec.	$C_{22}H_{23}N_8O_7PS_2$	N, 18.48	18.16

[a] Liquid crystal. Melting points were performed by the capillary tube method and are uncorrected. [b] Analyses performed by Janssen Pharmaceutica, Beerse, Belgium.

EXPERIMENTAL

***N*-Substituted Derivatives of Phosphoric Triamide and *N*-Substituted Derivatives of Phosphorodiamidous Acid**—*General procedure*—Compounds I–VI were prepared by the gradual addition of the acid chloride (0.01 mole) in pyridine–chloroform (20 ml.) to the sulfa compound (0.02 mole) dissolved in the same solvent (120 ml.). Reactions were completed after reflux periods of 12 (I–III) or 24 (IV–VI) hr. Then the solvent was distilled *in vacuo*, the residue suspended in dilute hydrochloric acid, filtered, and washed with water until the washings gave a negative chloride test with silver nitrate T.S. The dried products were crystallized from aqueous ethanol. (See Tables I and II.)

***N,N'*-di[*N*-(5-Methoxy-2-pyrimidinyl)-*p*-sulfamoyl Phenyl] Phosphorodiamidic Acid**—This compound was prepared by condensing sulfamethoxydiazine (8.5 g.) dissolved in pyridine–chloroform (160 ml.) with phosphorus oxychloride (2.33 g.) dissolved in 40 ml. of the same solvent. The reaction mixture was refluxed for 12 hr., the solvent distilled *in vacuo*, and the residue worked up in the usual manner. The product which was obtained in 76% yield melted at 225–227°, 260° dec. (liquid crystal) after being crystallized from aqueous ethanol.

Anal.—Calcd. for $C_{22}H_{23}N_8O_8PS_2$: N, 17.94. Found: N, 17.97.

***N,N',N''*-tri[*N*-(2,4-Dimethoxy-6-pyrimidinyl)-*p*-sulfamoyl Phenyl] Phosphorus Triamide and *N, N'*-Di [*N*-(2,4-Dimethoxy-6-pyrimidinyl)-*p*-sulfamoyl Phenyl] Phosphorodiamidous Acid**—These were prepared by condensing sulfadimethoxine (8.8 g.) dissolved in pyridine-chloroform (150 ml.) with phosphorus trichloride (1.94 g.) dissolved in 30 ml. of the same solvent. The reaction mixture was refluxed for 24 hr., then the solvent was distilled *in vacuo* and the residue was worked up as usual. Crystallization of the product thus obtained from (*ca.* 300 ml.) 70% aqueous ethanol yielded (5.85 g.) of a compound which on recrystallization from the same solvent melted at 290° dec. Concentration of the mother liquor afforded (1.87 g.) of a second compound which melted at 190–193°, 245–250° dec. (liquid crystal) after being recrystallized from 50% aqueous ethanol.

Former compound: *Anal.*—Calcd. for $C_{36}H_{39}N_{12}O_{12}PS_3$: N, 17.51. Found: N, 18.16.

Latter compound: *Anal.*—Calcd. for $C_{24}H_{27}N_8O_9PS_2$: N, 16.86. Found: N, 17.14.

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Keyphrases

Phosphorus-nitrogen compounds—synthesis
Sulfonamides-phosphorus tri- and oxychloride—condensation