New Compounds: Synthesis of Some Phosphorus–Nitrogen Compounds for Pharmacological Study II

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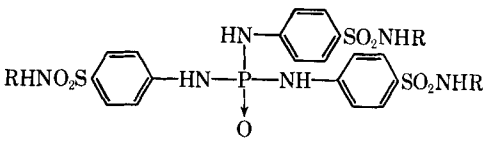
The synthesis of some *N*-substituted derivatives of phosphoric triamide and phosphorodiamidic acid *via* the condensation of phosphorus oxychloride with a number of sulfa drugs is described. Three moles of sulfanilamide, sulfacetamide, sulfapyridine, sulfathiazole, and sulfamerazine condensed with 1 mole of the oxychloride while with sulfisomidine and sulfadiazine 2 moles condensed with the acid chloride. In all the condensation reactions the molecular ratio of the reactants was 2 of the amino compound to 1 of the oxychloride.

IN A PREVIOUS PUBLICATION (1) it was reported that the condensation of phosphorus trichloride with a number of sulfa drugs afforded the *N*-substituted derivatives of phosphorus triamide and phosphorodiamidous acid. In the present investigation the work has been extended to include the phosphoric acid analogs of the previously reported compounds in order that the pharmacological activity of the two series of compounds may be compared. The fact that the phosphoric acid analogs were synthesized by condensing phosphorus oxychloride with the same sulfa compounds offered the opportunity to compare the reactivity of phosphorus trichloride and phosphorus oxychloride in these condensation reactions. With phosphorus trichloride the condensation was complete after 24 hr. except in the case of sulfanilamide where 12 hr. were sufficient. On the other hand, with phosphorus oxychloride a complete reaction was attained after 4 hr. with sulfanilamide and sulfacetamide and after 5 hr. with sulfadiazine, while with the rest of the amino compounds the reaction time never exceeded 12 hr. Moreover, the yields in the condensation reactions in which phosphorus trichloride was used ranged between 20–50%; those in which phosphorus oxychloride was used were much higher, *e.g.*, up to 94% yield was given with sulfapyridine and from 70 to 80% with the rest. In the condensation reactions 8 amino compounds were condensed with each acid chloride. With phosphorus oxychloride six out of the eight condensed in a manner that three molecules of the amino compound condensed with one molecule of the oxychloride. In the case of phosphorus trichloride four out of the eight condensed in this manner. Furthermore, while sulfamerazine failed to condense with phosphorus trichloride, it condensed readily with phosphorus oxychloride affording a 78% yield of the condensation product.

It can be seen from the foregoing that in these condensation reactions phosphorus oxychloride is more reactive than the trichloride.

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 and by their solubility in dilute alkali and their insolubility in dilute mineral acids.

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



Compd.	R	% Yield	Solvent of Crystallization[a]	M.p., °C.[c]	Formula	Anal.,[d] % Calcd.	Found
I	2-Thiazolyl	71	*A*	215–217[b] (260 dec.)	$C_{27}H_{24}N_9O_7PS_6$	N, 15.55	14.74
						S, 23.75	23.71
						P, 3.82	3.28
II	2-Pyridyl	94	*A*	180–183[b] (270 dec.)	$C_{33}H_{30}N_9O_7PS_3$	N, 15.78	14.82
						S, 12.14	13.08
						P, 3.91	3.32
III	4-Methyl-2-pyrimidinyl	78	*A*	186–190[b] (256 dec.)	$C_{33}H_{33}N_{12}O_7PS_3$	N, 20.08	19.39
						S, 11.49	12.49
						P, 3.70	3.24
IV	Acetyl	75	*B*	290 dec.	$C_{24}H_{27}N_6O_{10}PS_3$	N, 12.25	12.77
						S, 14.01	14.94
V	H	73	*A*	200–205[b] (256–260 dec.)	$C_{18}H_{21}N_6O_7PS_3$	N, 14.99	13.64
						S, 17.16	16.64

[a] *A*, aqueous ethanol; *B*, absolute ethanol. [b] Liquid crystal. [c] Melting points were performed by the capillary tube method and are uncorrected. [d] Analyses performed by Janssen Pharmaceutica, Beerse, Belgium.

EXPERIMENTAL

N-Substituted Derivatives of Phosphoric Triamide and Phosphorodiamidic Acid—Compounds I–VII were prepared by the gradual addition of phosphorus oxychloride (0.01 mole) in pyridine–chloro-

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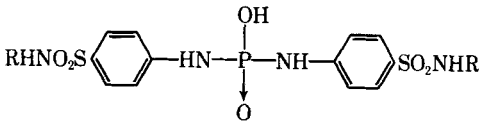
The products at present are under preliminary screening for possible antineoplastic action or any useful pharmacological activity.

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



Compd.	R	% Yield	Solvent of Crystallization[a]	M.p.,[b] °C.[c]	Formula	Anal.,[d] % Calcd.	Found
VI	2-Pyrimidinyl	80	*A*	190–193 (270 dec.)	$C_{20}H_{19}N_8O_6PS_2$	N, 19.92 S, 11.41	19.18 12.40
VII	4,6-Dimethyl-2-pyrimidinyl	70	*A*	195–196 (260 dec.)	$C_{24}H_{27}N_8O_6PS_2$	N, 18.11 S, 10.36	17.45 11.56

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

form (20 ml.) to the sulfa compound (0.02 mole) dissolved in the same solvent (150 ml.). For complete reaction the mixture was refluxed 12 hr. in all except with sulfanilamide, sulfacetamide, and sulfadiazine in which case refluxing for 4 and 5 hr. was sufficient. Then the solvent was distilled *in vacuo*, and 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 product after being dried was crystallized from the appropriate solvent. (See Tables I and II.)

N,N',N''-tri-β-Naphthylphosphoric Triamide—This compound was prepared by condensing β-naphthylamine with phosphorus oxychloride according to the above general procedure. The product which was obtained in 75% yield melted at 237–238° after being crystallized from aqueous ethanol.

Anal.—Calcd. for $C_{30}H_{24}N_3OP$: N, 8.88 Found: N, 9.07.

N,N',N'' - tri[N - (2 - Pyrimidinyl) - p - sulfamoylphenyl] Phosphorus Triamide—This compound was prepared by condensing sulfadiazine with phosphorus trichloride adopting the general method reported in the previous paper. The product which was obtained in 20% yield melted at 196–200° (255° dec.) (liquid crystal) (2) after being crystallized from absolute ethanol.

Anal.—Calcd. for $C_{30}H_{27}N_{12}O_6PS_3$: P, 3.98. Found: P, 3.56.

N,N'-di(α-Naphthyl) Phosphorodiamidous Acid and N,N'-di(β-Naphthyl) Phosphorodiamidous Acid—These were prepared by condensing the naphthylamine with phosphorus trichloride adopting the general method reported in the previous paper. The yield in both cases was 30% and the product crystallized from aqueous ethanol. The former compound melted at 228–230°.

Anal.—Calcd. for $C_{20}H_{17}N_2OP$: C, 72.26; H, 5.15; N, 8.40. Found: C, 71.41; H, 5.07; N, 8.61.

The latter compound melted at 240–243°.

Anal.—Calcd. for $C_{20}H_{17}N_2OP$: N, 8.40. Found: N, 8.61.

REFERENCES

(1) Abou-Moustafa, A., Khalifa, M., and El-Mangowri, H., *J. Pharm. Sci.*, **56**, 1357(1967).
(2) *Cf.* Willstatter and Benz, *Ber.*, **40**, 1582(1907).

Keyphrases

Phosphorus–nitrogen compounds
N-Substituted phosphoric triamide, phosphorodiamidic acid derivatives—synthesis
Condensation—phosphorus oxychloride, sulfa compounds