# SYNTHESIS AND PROPERTIES OF 1,3-DIAZA-2-PHOSPHOLO[4,5-d]PYRIMIDINES

N. V. Sazonov and A. A. Kropacheva

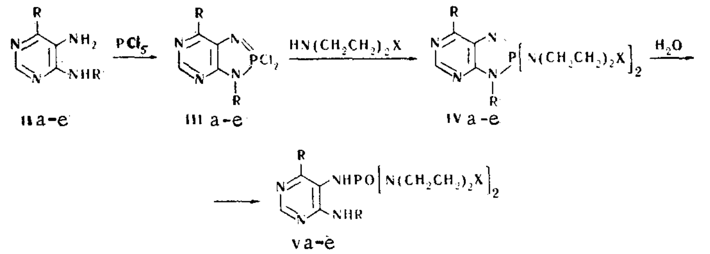
UDC 547.857+546.185'131

Reaction of 5-amino-4-alkyl(aryl or aralkyl)aminopyrimidines with $PCl_5$ gives 2,2-dichloro-3-alkyl(aryl or aralkyl)-1,3-diaza-2-phospholo[4,5-d]pyrimidines, which on treatment with piperidine or morpholine are converted into the corresponding 2,2-diamino derivatives. The latter, on boiling in water or aqueous alcohol, give the dipiperidides or dimorpholides of the corresponding 5-pyrimidylamidophosphoric acids.

This paper deals with the synthesis and properties of 1,3-diaza-2-phospholo[4,5-d]pyrimidines, which are phosphorus analogs of purine.

The synthesis of 1,3-diaza-1,3-dihydro-2-phospholo[4,5-d]pyrimidines (I) is described in the literature [1,2], starting from 4,5-diaminopyrimidines (II) and alkyl(aryl)phosphonic acid amides. An attempt to obtain I by a reaction between II and phenylphosphonyl dichloride was not successful [3].

We have synthesized 2,2-dichloro-1,3-diaza-2-phospholo[4,5-d]pyrimidines (III) as follows.



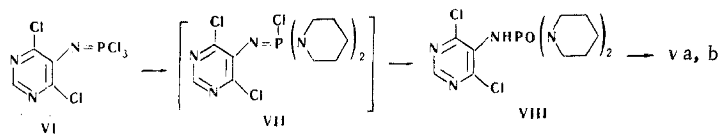
a R = Cl, R' = $C_6H_5$, X = $CH_2$; b R = Cl, R' = $CH_2C_6H_5$, X = $CH_2$; c R = Cl, R' = n-$C_4H_9$, X = O; d R = H, R' = $C_6H_5$, X = $CH_2$; e R = H, R' = $CH_2C_6H_5$, X = $CH_2$

The structure of III was confirmed by IR spectra (absence of bands due to primary and secondary amine groups). Compounds IIIa and IIIb react slowly with water under the usual conditions, while IIId and IIIe react extremely vigorously. On heating with water, III is hydrolyzed to the starting compound II.

Reaction of III with piperidine and morpholine gives the amino derivatives as colorless, crystalline compounds which are soluble in organic solvents, but insoluble in water. On heating IV with dilute HCl hydrolysis occurs to give II. Compounds IVa and IVb are stable under normal conditions, but IVd and IVe are converted on standing into 5-pyrimidylamidophosphoric diamides (V). Compounds V are readily prepared by heating IV in water or 96% alcohol. The structure of V was confirmed by independent synthesis, starting from 5-trichlorophosphazo-4,6-dichloropyrimidine (VI) [4,5]. Reaction of VI with piperidine yields 5-(dipiperidochlorophosphazo)-4,6-dichloropyrimidine (VII), which was converted without isolation into (4,6-dichloro-5-pyrimidyl)amidophosphoric acid dipiperidide (VIII). The latter, when reacted with aniline and benzylamine, yielded Va and Vb, identical with those obtained from IVa and IVb.

---

Ordzhonikidze All-Union Pharmaceutical Chemistry Scientific Research Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 5, pp. 710-712, May, 1970. Original article submitted October 14, 1968.



Catalytic dehalogenation of Vb gave Ve, identical with that obtained from IVe.

## EXPERIMENTAL

2,2,7-Trichloro-3-phenyl-1,3-diaza-2-phospholo[4,5-d]pyrimidine (IIIa). A suspension of 2 g (9.07 mmole) of IIa and 1.89 g (9.07 mmole) of $PCl_5$ in 30 ml of chlorobenze was heated with stirring in a current of nitrogen at 120-125° C (in a bath) for 2 hr (until the evolution of HCl ceased). The reaction mixture was cooled, and the solid was filtered off and washed with benzene and ether to give 2.34 g (81%) of product. For analysis, IIIa was washed with water, acetone, and ether, mp 311° C (decomp.) Found, %: Cl 33.31, 33.70. Calcualted for $C_{10}H_6Cl_3N_4P$, %: Cl 33.29.

2,2,7-trichloro-3-benzyl-1,3-diaza-2-phospholo[4,5-d]pyrimidine (IIIb), was obtained in a similar manner. Yield 80%, mp 276-277° C (decomp). Found, %: Cl 31.90. Calculated for $C_{11}H_8Cl_3N_4P$, %: Cl 31.89. Compounds III were colorless, crystalline solids which were sparingly soluble in inert organic solvents.

7-Chloro-2,2-dipiperidino-3-phenyl-1,3-diaza-2-phospholo[4,5-d]pyrimidine (IVa). To a suspension of 2 g (6.27 mmole) of IIIa in 50 ml of benzene was added with stirring 2.15 g (25.1 mmole) of piperidine in 10 ml of benzene. The reaction mixture was heated for 1 hr at 70° C, then cooled, the piperidine hydrochloride was filtered off and washed with benzene, and the filtrates were combined. The benzene was distilled off in vacuo, and the residue was washed with ether to give 2.35 g (90%) of product. For analysis, the compound was dissolved in the minimum amount of benzene, shaken with charcoal, the charcoal filtered off, the benzene removed in vacuo until the volume had been reduced to 1/3, and ether was added. On standing, IVa separated, mp 228-230° C (decomp). Found, %: C 57.27; H 6.40; Cl 8.29; N 19.83. Mol wt 417. Calculated for $C_{20}H_{27}ClN_6P$, %: C 57.48; H 6.51; Cl 8.48; N 20.11. Molt wt 418.

7-Chloro-2,2-dipiperidino-3-benzyl-1,3-diaza-2-phospholo[4,5-d]pyrimidine (IVb). A suspension of 5 g (21.3 mmole) of IIb and 4.43 g (21.3 mmole) of $PCl_5$ in 70 ml of chlorobenzene was heated with stirring in a stream of nitrogen at 135° C for 2 hr 30 min. The reaction mixture was cooled to 20° C, and a solution of 7.25 g (85.2 mmole) of piperidine in 20 ml of benzene was added. The mixture was stirred for 1 hr at 70° C, cooled, the piperidine hydrochloride was filtered off and washed with benzene, and the combined filtrates were concentrated in vacuo. The residue was washed with ether to give 7.34 g (80%), mp 196-197° C (from absolute alcohol). Found, %: C 58.91; H 6.70; Cl 8.40; N 19.74; P 7.20. Mol wt 432. Calculated for $C_{21}H_{28}ClN_6P$, %: C 58.53; H 6.55; Cl 8.23; N 19.50; P 7.19. Mol wt 431.

7-Chloro-2,2-dimorpholino-3-n-butyl-1,3-diaza-2-phospholo[4,5-d]pyrimidine (IVc). A suspension of 5 g (24.9 mmole) of IIc and 5.17 g (24.9 mmole) of $PCl_5$ in 80 ml of benzene was boiled with stirring in a current of nitrogen for 4 hr 30 min (until the evolution of HCl ceased). The mixture was cooled to 8-10° C, and a solution of 8.7 g (100 mmole) of morpholine in 20 ml of benzene was added with stirring over 45 min. After stirring for an additional 2 hr at 20° C, the mixture was kept until the following day. Compound IVc was obtained in the same manner as IVb, yield 5.56 g (56%), mp 201-203° C (from benzene). Found, %: C 47.45; H 6.33; Cl 8.95; N 20.52; P 7.68. Calculated for $C_{16}H_{26}ClN_6O_2P$, %: C 47.94; H 6.54; Cl 8.85; N 20.97; P 7.73.

2,2-Dipiperidino-3-phenyl-1,3-diaza-2-phospholo[4,5-d]pyrimidine (IVd). A suspension of 2.5 g (13.4 mmole) of IId and 2.8 g (13.4 mmole) of $PCl_5$ in 30 ml of chlorobenzene was boiled for 2 hr with stirring in a stream of nitrogen (unitl evolution of HCl ceased). The mixture was cooled to 8-10° C, and a solution of 4.6 g (53.6 mmole) of piperidine in 10 ml of benzene was added with stirring, then the mixture was stirred for 2 hr at 20° C. Further treatment, which was the same as for IVb, gave IVd, 4.4 g (86%), mp 236-239° C (from benzene). Found, %: C 63.24; H 7.20; N 21.73; P 8.02. Calculated for $C_{20}H_{27}N_6P$, %: C 62.81; H 7.12; N 21.98; P 8.10.

2,2-Dipiperidino-3-benzyl-1,3-diaza-2-phospholo[4,5-d]pyrimidine (IVe) was obtained in a similar manner, yield 86%, mp 184-186° C (from benzene). Found, %: C 64.0; H 7.49; N 21.15; P 8.0. Calculated for $C_{21}H_{29}N_6P$, %: C 63.61; H 7.37; N 21.20; P 7.81.

(4,6-Dichloro-5-pyrimidyl)phosphoric Dipiperidide (VIII). A suspension of 4 g (24.4 mmole) of 5-amino-4,6-dichloropyrimidine and 5.07 g (24.4 mmole) of $PCl_5$ in 50 ml of benzene was stirred in a stream of nitrogen at 70° C for 1 hr 30 min. To the resulting solution of VI was added with ice water cooling 8.32 g (97.6 mmole) of piperidine in 20 ml of benzene, and the mixture was stirred for 2 hr with cooling, then for 1 hr at 20° C. The piperidine hydrochloride was filtered off and washed with benzene, and the combined filtrates were evaporated in vacuo. To the resulting oil was added 100 ml of 96% alcohol, whereupon the reaction mixture became warm. After standing at 20° C for one day, the alcohol was distilled off to dryness, and the residue washed with 50 ml of water, giving 7.12 g (78%) of VIII, mp 191-192° C (from methanol). Found, %: C 44.40; H 5.80; Cl 18.90; N 18.88; P 7.80. Calculated for $C_{14}H_{22}Cl_2N_5OP$, %: C 44.45; H 5.86; Cl 18.75; N 18.52; P 8.19.

(4-Chloro-6-n-butylamino-5-pyrimidyl)amidophosphoric Dimorpholide (Vc). Crystallization of 0.9 g of IVc from water give 0.74 g (79%) of Vc, mp 157-158° C. Found, %: C 45.40; H 6.79; Cl 8.28; N 20.00; P 7.38. Calculated for $C_{16}H_{28}ClN_6O_3P$, %: C 45.88; H 6.74; Cl 8.47; N 20.07; P 7.40.

(4-Chloro-6-benzylamino-5-pyrimidyl)amidophosphoric Dipiperidide (Vb). A) A 0.5-g quantity of IVb was boiled in 10 ml of water until the solid was no longer converted into an oil. The water was decanted, and the oil was dried and dissolved in 30 ml of ether to give, on standing, a precipitate of 0.35 g (67%) of Vb, mp 124.5-125° C (from ether). Found, %: C 56.49; H 6.89; Cl 7.66; N 18.84; P 6.95. Calculated for $C_{21}H_{30}ClN_6PO$, %: C 56.18; H 6.74; Cl 7.90; N 18.72; P 6.90.

B) A solution of 2.14 g (5.66 mmole) of VIII and 1.2 g (11.3 mmole) of benzulamine in 30 ml of absolute methanol was kept at 20° C for one day, the alcohol was distilled off to dryness, and the residue was treated with 50 ml of benzene. After filtration and removal of the benzene, the residual oil crystallized on standing to give 2.48 g (98%) of Vb, which gave no depression of mp on mixing with a sample of material obtained by method A).

Ve was obtained in a similar manner, in 92% yield.

(4-Chloro-6-anilino-5-pyrimidyl)amidophosphoric Dipiperidide (Va). A 0.95-g quantity of IVa was boiled for 30 min in 30 ml of 96% alcohol, and evaporated to dryness in vacuo, to give 0.83 g (84%) of Va, mp 168-169° C (from benzene). Found, %: C 55.30; H 6.60; Cl 8.27 N 19.15; P 6.95. Calculated for $C_{20}H_{29}ClN_6OP$, %: C 55.10; H 6.71; Cl 8.13; N 19.28; P 7.11.

(6-Benzylamino-5-pyrimidyl)amidophosphoric dipiperidide (Ve) was obtained in a similar manner, 92% yield, mp 166-166.5° C (from ethyl acetate). Found, %: C 60.67; H 7.68; N 19.85; P 7.12. Calculated for $C_{21}H_{31}N_6OP$, %: C 60.85; H 7.54; N 20.28; P 7.47. (6-Anilino-5-pyrimidyl)amidophosphoric dipiperidide (Vd) was obtained in a similar manner, 89% yield, mp 185-185.5° C (from ethyl acetate). Found, %: C 59.94; H 7.12; N 20.76; P 7.90. Calculated for $C_{20}H_{29}N_6OP$, %: C 59.98; H 7.30; N 20.99; P 7.74.

Dehalogenation of (4-chloro-6-benzylamino-5-pyrimidyl)amidophosphoric Dipiperidide. In a hydrogenation flask were placed 1 g of Vb, 0.23 g of triethylamine, 0.3 g of 5% Pd on BAU charcoal, and 50 ml of methanol. Dehalogenation was carried out at 20° C and atmospheric pressure; hydrogen uptake ceased after 1 hr 30 min. The catalyst was filtered off and washed with alcohol, the alcohol was evaporated to dryness, and the residue was treated with 50 ml of ethyl acetate. The mixture was brought to a boil, filtered, and evaporated to dryness to give 0.9 g (97%) of Ve.

## LITERATURE CITED

1. J. H. Lister and G. M. Timmis, Ind., 819,1963.
2. J. H. Lister and G. M. Timmis, J. Chem. Soc. (C), 1242,1966.
3. R. L. Danuley and P. L. Wagner, J. Org. Chem., 26, 3995,1961.
4. I. E. Mamaeva, N. V. Sazonov, and A. A. Kropacheva, KhGS[Chemistry of Heterocyclic Compounds], 521, 1969.
5. I. E. Mamaeva, N. V. Sazonov, and A. A. Kropacheva, Khim. farm. zh., 2, 31, 1968.