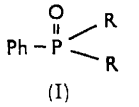
Synthesis and Properties of 1,3-Diaza-1,3-dihydro-2-phospholo(4,5-*d*)-pyrimidine 2-oxides

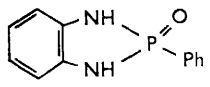
By J. H. Lister and G. M. Timmis

Condensations of 4,5-diaminopyrimidines and phosphonic diamides in a high-boiling solvent produce diaza-phospholopyrimidine oxides. These are hydrolytically unstable and give rise to derivatives of *N*-pyrimidinyl-phosphonamidic acid.

BECAUSE of the general similarity of the molecular architecture of 1,3-diaza-1,3-dihydro-2-phospholo(4,5*d*)-pyrimidine 2-oxides (III) to that of purine the possibility that such compounds might show antipurine activity in biological systems has been explored. An attempt [1] to prepare such compounds in which phenylphosphonic dichloride (I; R = Cl) and 4,5-diaminopyrimidines were



(I)



(II)

allowed to react was unsuccessful, but the corresponding benzodiazaphospholo-oxide (II) was obtained when *o*-phenylenediamine was used in place of the pyrimidine The same compound (II) was later prepared[2] by use of phenylphosphonic diamide (I; R = NH_2)[3] in place of the more reactive dichloride. The latter route also suggested a method for the preparation of diaza-phospholopyrimidines and had the advantage that the ammonia produced would be rapidly removed under the reflux conditions employed.

This method was successful,[4] some hours' heating in bromobenzene being required before evolution of ammonia ceased. The products usually crystallised well in good yields on cooling. Owing to the hydrolytic

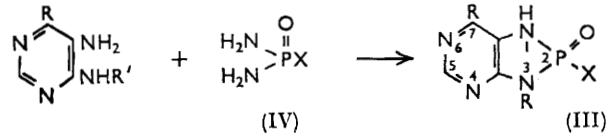
[1] R. L. Dannley and P. L. Wagner, *J. Org. Chem.*, 1961, **26**, 3995.

[2] V. Gutmann, D. E. Hagen, and K. Utvary, *Monatsh.*, 1962, **93**, 627.

[3] A. Michaelis, *Annalen*, 1896, **293**, 215.

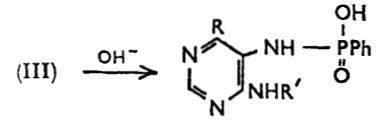
[4] J. H. Lister and G. M. Timmis, *Chem. and Ind.*, 1963, 819.

instability of this type of derivative recrystallisation was precluded and elementary analyses were carried out on the product after removal of traces of solvent by washing with hot dry ether and light petroleum (b. p. 60—80°) and drying in air at 110°. Two series



(IV) (III)

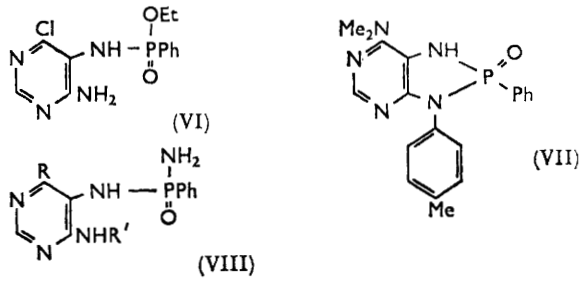
were prepared, one in which the phosphorus atom carried an aryl group (phenyl) and in the other an alkyl group (methyl). Phenylphosphonic diamide (IV; X = Ph) and the methyl [5] analogue (IV; X = Me) were the respective starting materials. Both series (Table 1) of condensation products decomposed above 200° and were extremely susceptible to hydroxyl ions, the methyl series being the more sensitive. Fission of the diazaphosphole ring at the P–N(3) bond occurred readily but in some cases the ring completely broke down with the formation of 4,5-diaminopyrimidines. The ease with which this can happen is shown in the case of (III; R = SH, R′ = Me, X = Me) which, on gentle warming in aqueous solution, rapidly precipitated 5-amino-4-methylamino-6-thiopyrimidine. Cold, dilute alkali was usually adequate for causing hydrolysis to the appropriate phenyl-*N*-(4-aminopyrimidin-5-yl) phosphoramidic acid (V) (Table 2). Subsequently atmospheric



(III) (V)

moisture was found to produce the same effect; after standing for some weeks the diazaphospholes were converted into the phosphonamidic derivatives. Attempted crystallisation of (III; R = Cl, R′ = H, X = Ph) from ethanol gave rise, by alcoholysis, to the ethyl ester (VI). The fission products are formulated with the phosphonamide group at the 5- rather than the 4-position by analogy with opening of the imidazole ring in the purines which leads to 5-acylamidopyrimidines. The hydrolytic instability is consistent with the effect of the electron-attracting functions, *i.e.*, the pyrimidine ring nitrogen atoms and phosphoryl group, on the phosphorus-containing ring. This postulate is supported by the fact that instability of the above type can be induced in the more stable benzodiazaphospholes (II) by the insertion of electron-attracting groups, *e.g.*, nitro or carboxyl, into the benzene ring.[1] Introduction of the *p*-tolyl group (VII) did not improve the hydrolytic stability. Although the phosphonamidic acid derivatives (V) themselves were relatively stable, suitable crystallising solvents were not found and they were purified by precipitation with acetic acid from alkali.

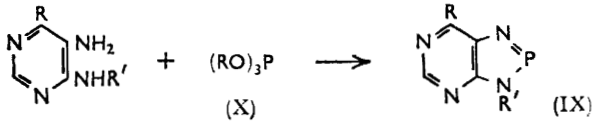
In some cases the reaction between diamine and phosphonic diamide did not produce cyclised products as only one of the amide nitrogens appeared to be involved. The products are formulated as the type (VIII) (Table 3) on analytical evidence and the known easy condensation of the 5-amino-group in 4,5-diaminopyrimidines with amides. All are considerably hydrated (2—6 water



(VI) (VII) (VIII)

molecules per unit, which are not removed at 105° *in vacuo*), consistent with the strong hydrogen bonding expected in such molecules. Attempts to crystallise them, as with the cyclised derivatives, profoundly changed the infrared spectra.

The attempted preparation of the parent pyrimidodiazaphospholes of the type (IX), in which structures directly comparable with the purines are possible, did not succeed. Condensation of the diaminopyrimidine



(X) (IX)

with triethyl phosphite (X; R = Et) or triphenyl phosphite (X; R = Ph) gave only unidentifiable products or starting material, whereas *o*-phenylenediamine under similar conditions gives benzo-1,3,2-diazaphospholes.[6] None of the above compounds showed either antimetabolite or antitumour activity.

EXPERIMENTAL

Melting points are corrected.

Condensation of a 4,5-Diaminopyrimidine with Phosphonic Diamides.—A hot solution of the 4,5-diaminopyrimidine (0·1 mole) in dry, freshly distilled bromobenzene (40 ml.) was filtered and the phosphonic diamide (0·11 mole) added. The mixture was heated under reflux for some hours. The product which crystallised on cooling was filtered off (large crystals were ground up). Contaminants and traces or solvent were removed by several washings with hot ether and light petroleum (b. p. 60—80°), the *product* being then dried at 110° (see Tables 1 and 3).

Hydrolysis of 1,3-Diaza-1,3-dihydro-7-dimethylamino-2-phenyl-2-phospholo[4,5-d]pyrimidine 2-oxide (III; R = NMe_2, R′ = H, X = Ph).—The diazophospholopyrimidine (0·25 g.) was suspended in 0·1N-sodium hydroxide (11 ml.) and shaken at room temperature until it dissolved (10 min.). After filtration, acetic acid was added to bring the pH to 6 and the highly crystalline precipitate filtered

[5] R. Rätz, *J. Amer. Chem. Soc.*, 1955, **77**, 417.
[6] K. Pilgrim and F. Korte, *Tetrahedron*, 1963, **19**, 137.

TABLE 1

1,3-Diaza-1,3-dihydro-2-phospholo(4,5-*d*)pyrimidine 2-oxides (III)

R	R′	X	Reflux time (hr.)	Found (%) C	H	N	Formula	Required (%) C	H	N	M. p.[c]
NMe_2	H	Me	8	38·3	5·4	30·9	$C_7H_{12}N_5OP,\frac{1}{2}H_2O$	37·8	5·9	31·5	>250°
NMe_2	H	C_6H_5	25	52·0	5·4	25·5	$C_{12}H_{14}N_5OP$	52·4	5·1	25·4	>250
NMe_2	Me	C_6H_5	23	53·9	5·4	22·0	$C_{13}H_{16}N_5OP$	53·9	5·6	24·2	>200
NMe_2	C_6H_4Me	C_6H_5	21	60·5	5·2	18·2	$C_{19}H_{20}N_5OP,\frac{1}{2}H_2O$	60·9	5·5	19·2	>200
Cl[a]	H	C_6H_5	22	44·3	2·9	20·2	$C_{10}H_8ClON_4P,\frac{1}{2}H_2O$	43·6	3·3	20·3	200
2,4-Cl_2[b]	H	C_6H_5	22	35·3	2·4	16·8	$C_{10}H_7Cl_2N_4OP,2H_2O$	35·6	3·3	16·6	>250
SH	Me	Me	22	29·3	4·9	22·8	$C_6H_9N_4OPS,1\frac{1}{2}H_2O$	29·6	5·0	23·0	>200
SH	Me	C_6H_5	19	46·0	4·4	18·8	$C_{11}H_{11}N_4OPS,\frac{1}{2}H_2O$	46·0	4·2	19·5	>200

[a] Found: Cl, 13·0. Req.: 12·9%. [b] Found: Cl, 22·0. Req.: Cl, 21·1%. [c] All with decomposition.

TABLE 2

Phenyl-*N*-(pyrimidin-5-yl)phosphonamidic acids (V)

R	R′	Found (%) C	H	N	Formula	Required (%) C	H	N	M. p.
NMe_2	H	49·3	5·3	23·9	$C_{12}H_{16}N_5O_2P$	49·1	5·5	23·9	245—247°
NMe_2	Me	49·9	5·7	22·2	$C_{13}H_{18}N_5O_2P$	49·4	6·1	22·2	199—200
NMe_2	C_6H_4Me	59·8	6·0	18·0	$C_{19}H_{22}N_5O_2P$	59·5	5·8	18·3	180—182
Cl[a]	H	45·2	4·8	17·4	$C_{12}H_{14}ClN_4O_2P,\frac{1}{2}H_2O$	44·8	4·7	17·4	160—161
2,6-Cl_2	H	33·95	3·3	15·6	$C_{10}H_9Cl_2N_4O_2P,2H_2O$	33·8	3·7	15·8	185—188

[a] Ethyl phosphonamidic ester.

TABLE 3

N-(Pyrimidin-5-yl)phosphonic diamides (VIII)

R	R′	X	Found (%) C	H	N	P	Formula	Required (%) C	H	N	P	M. p.*
NMe_2	Me	Me	34·9	6·8	28·6	—	$C_8H_{17}N_5OP,2H_2O$	34·3	7·6	30·9	—	>150°
NH_2	Me	C_6H_5	40·0	5·2	26·1	9·2	$C_{11}H_{15}N_6OP,3H_2O$	39·8	6·4	25·3	9·3	>175
NHMe	Me	C_6H_5	36·7	5·9	23·5	7·2	$C_{12}H_{16}N_6OP,6H_2O$	36·0	7·3	21·0	8·0	>170
OMe	Me	C_6H_5	43·7	4·7	21·0	8·8	$C_{12}H_{16}N_5O_2P,2H_2O$	43·8	6·1	21·3	9·4	>190

* All with decomposition.

Also prepared by the same route: *phenyl*-N-(4-*amino*-1,3-*dimethyl*-2,6-*dioxopyrimidin*-5-*yl*)*phosphonic diamide*, m. p. 200° (decomp.) (Found: C, 37·0; H, 5·2; N, 18·2; P, 8·3. $C_{12}H_{16}N_5O_3P,4H_2O$ requires C, 37·8; H, 6·3; N, 18·4; P, 8·1%).

off. After washing with water, ethanol, and ether, and drying at 110° *phenyl*-N-(4-*amino*-6-*dimethylaminopyrimidin*-5-*yl*)*phosphonamidic acid* (V; R = NMe_2, R′ = H) (0·25 g.) was obtained as colourless prisms, m. p. 245—247°. See Table 2 for other *compounds*.

4-*Dimethylamino*-5-*nitro*-6-p-*toluidinopyrimidine*.—A solution of 4-chloro-6-dimethylamino-5-nitropyrimidine (3·7 g.) in ethanol (120 ml.) containing triethylamine (7 ml.) was treated slowly, with stirring, with a solution of *p*-toluidine (2·2 g.) in ethanol (50 ml.). After stirring for 3 hr. the solution was evaporated to dryness under reduced pressure and the solid triturated with water. The residue, on recrystallisation from ethanol, gave the *nitropyrimidine* (4·7 g.) as golden needles, m. p. 122—123° (Found: C, 57·3; H, 5·4; N, 25·7. $C_{13}H_{15}N_5O_2$ requires C, 57·1; H, 5·5; N, 25·6%).

5-*Amino*-4-*dimethylamino*-6-p-*toluidinopyrimidine*.—The above pyrimidine (4·7 g.) in methanol (400 ml.) was hydrogenated to completion over Raney nickel. After removal of catalyst and evaporation of solvent the residue was recrystallised from methanol giving the *triaminopyrimidine* (3 g.) as colourless plates, m. p. 189—190° (Found: C, 64·1; H, 6·6; N, 29·1. $C_{13}H_{17}N_5$ requires C, 64·2; H, 7·0; N, 28·8%).

5-*Amino*-4-*methoxy*-6-*methylaminopyrimidine*.—A methanolic solution of 4-methoxy-6-methylamino-5-nitropyrimidine (4 g.)[7] was reduced under the same conditions as above. Evaporation left a dark oil which crystallised on standing. Further crystallisation from cyclohexane gave colourless prisms of the *diaminopyrimidine* (2 g.), m. p. 139—140° (Found: C, 46·4; H, 6·1; N, 36·3. $C_6H_{10}N_4O$ requires C, 46·7; H, 6·4; N, 36·3%).

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[7] D. J. Brown, *J. Appl. Chem.*, 1957, **7**, 109.