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SYNTHESIS OF IMINODIPYRIMIDINES

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We wish to report a new reaction of 6-amino-2-methylpyrimidines with phosphorus oxychloride whereby they can be converted into 2,2'-dimethyl-4,4'-iminodipyrimidines. These compounds would be the useful intermediates for several fused dipyrimido tricycles.

Treatment of 1 part of 6-amino-4-hydroxy-2-methylpyrimidine (1) with 2 parts of phosphorus oxychloride at 220-230° (2) for 5 hr results in the formation of 6,6'-dichloro-2,2'-dimethyl-4,4'-iminodipyrimidine (I), which is isolated by evaporation of the phosphorus oxychloride and dilution with water. Compound I is also obtained from 6-amino-4-chloro-2-methylpyrimidine (3) under the same conditions. The structure of I was ascertained by elemental analysis (4), molecular weight determination (by mass spectrometry), IR spectra (presence of a secondary amino absorption) and NMR spectra (sharp, unsplit singlets at 3.03 and 8.35 ppm in CF_3COOH). Similarly, 4-phenoxy-, 4-piperidino- (5), and 4-pyrrolidino-6-amino-2-methylpyrimidine (5) were converted to corresponding 4,4'-iminodipyrimidines (see TABLE I).

It will be noted that the 4-lower membered alkoxy 6-amino-2-methylpyrimidines were converted to I in excellent yield under these conditions. Furthermore, a quantitative conversion of 6,6'-dimethoxy (or diethoxy)-2,2'-dimethyl-4,4'-iminodipyrimidine to I was realized. There seem to be no previous instances recorded in the literature for the chlorination with replacement of alkoxy group, and this reaction may represent an interesting precedent (6).

TABLE I

Reaction of 6-Amino-2-methylpyrimidines with Phosphorus Oxychloride

Starting Material	Reaction Time hr	Reaction Temp °C	Product	Yield %	M.p. °C	Recrystn solvent
6-amino-4-hydroxy-2-methylpyrimidine	5	220-230	6,6'-dichloro-2,2'-dimethyl-4,4'-iminodipyrimidine (I)	65	245-246	$CHCl_3$
6-amino-4-chloro-2-methylpyrimidine	5	210-220	I	64		
6-amino-2-methyl-4-phenoxypyrimidine	3	220	2,2'-dimethyl-6,6'-diphenoxy-4,4'-iminodipyrimidine	62.5	220	EtOH
6-amino-2-methyl-4-piperidinopyrimidine	3	230	2,2'-dimethyl-6,6'-dipiperidino-4,4'-iminodipyrimidine	52	174-175	CH_3CN
6-amino-2-methyl-4-pyrrolidinopyrimidine	3	230	2,2'-dimethyl-6,6'-dipyrrolidino-4,4'-iminodipyrimidine	22.2	194-196	EtOH
6-amino-4-methoxy-2-methylpyrimidine	2	230	I	90		
6-amino-4-ethoxy-2-methylpyrimidine	3	230	I	79.5		

Other conditions usually employed in thermal condensations were used to confirm the actions of phosphorus oxychloride; concentrated hydrochloric acid, acetic acid, phosphoric acid and polyphosphoric acid all were without effect. Heating in diphenylether or sulfolane was also not effective in the absence of phosphorus oxychloride. The reaction proceeds only by phosphorus oxychloride as far as we have examined and appears to be equally applicable to other 6-amino-pyrimidines (8).

Replacement of the chlorine in I with secondary amino, anilino, phenoxy and lower membered alkoxy group was accomplished as described in TABLE II.

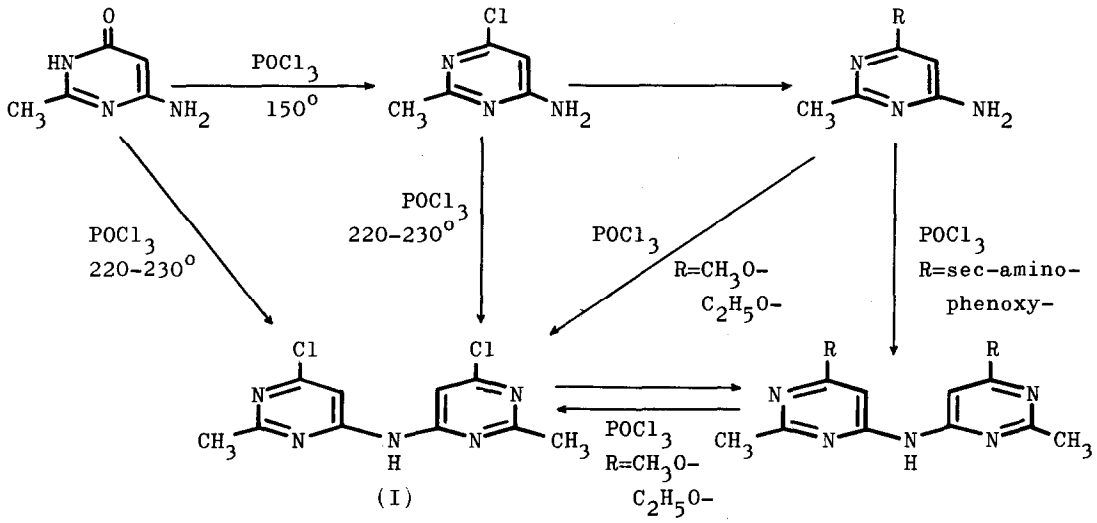

TABLE II

Preparation of 6,6'-Disubstituted 2,2'-Dimethyl-4,4'-iminodipyrimidines from I

Substituent	Reaction			Yield	M.p.	Recrystn
	Reactant (3 equiv)	Time hr	Temp °C	%	°C	solvent
piperidino-	piperidine	2	150-160	88.2	174-175	CH_3CN
morpholino-	morpholine	2	150-160	87.6	181-183	EtOH
pyrrolidino-	pyrrolidine	2	100-120	47.6	194-196	EtOH
anilino-	aniline, a few drops of HCl	2	170-180	56.3	189-191	EtOH
phenoxy-	phenol, K_2CO_3 in DMF	4	160-170	87.4	219-221	EtOH
methoxy-	NaOMe in MeOH	2	90	92.8	167-168	benzene
ethoxy-	NaOEt in EtOH	2	90	88.8	142-143	CH_3CN

REFERENCES AND NOTES

(1) A. Maggiolo, A. P. Phillips, G. H. Hitchings, J. Am. Chem. Soc., 73 106 (1951).

(2) When the reaction is carried out at 180°, the main product is 6-amino-4-chloro-2-methylpyrimidine (70%) and the yield of II decreases to 10%.

(3) Z. Fördi, G. V. Fodor, I. Demjen, H. Szekeres, I. Halmos, Chem. Ber., 75, 755 (1942).

(4) Satisfactory analytical data were obtained for all compounds reported.

(5) F. Craveri, G. Zoni, Boll. Sci. Fac. Chim. Ind. Bologna, 16, 126 (1958); Chem. Abstr., 53, 13161 (1959)

(6) The only previously recorded chlorination with group replacement is the conversion of 2-phenyl-4,6-diamino-5-nitrosopyrimidine to 2-phenyl-4,6-diamino-5-chloropyrimidine by the action of phosphorus oxychloride (7).

(7) E. C. Taylor, C. W. Jefford, J. Am. Chem. Soc., 84, 3744 (1962).

(8) Additional compounds prepared by this method were 2,2', 6,6'-tetrachloro-4,4'-iminodipyrimidine and 6,6'-dichloro-2,2'-diphenyl-4,4'-iminodipyrimidine.