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A Novel Synthesis of Iminodipyrimidines[1]

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The reaction of 4-amino-6-hydroxy-2-methylpyrimidine with phosphorus oxychloride at 220—230° gave 6,6′-dichloro-2,2′-dimethyl-4,4′-iminodipyrimidine (I) in good yield. I was also obtained from 4-amino-6-chloro-2-methylpyrimidine under these conditions. The reaction was extended successfully to some other 4-aminopyrimidine derivatives to form the corresponding iminodipyrimidines. Reaction of either 4-amino-6-methoxy (or ethoxy)-2-methylpyrimidine or 6,6′-dimethoxy (or diethoxy)-2,2′-dimethyl-4,4′-iminodipyrimidine with phosphorus oxychloride at 220—230° proceeds anomalously to give I in quantitative yields. Replacement of the chlorine atoms in I by nucleophiles was carried out. Direct synthesis of 4,4′-dichloro-6,6′-dimethyl-2,2′-iminodipyrimidine was realized in the reaction of 2-amino-4-hydroxy-6-methylpyrimidine or 2-amino-4-chloro-6-methylpyrimidine with phosphorus oxychloride.

The 4,4′-iminodipyrimidine system is of interest because of its potential usefulness as an intermediate for several fused dipyrimido tricycles, and because of its potential physiological activity owing to the cyclic biamidine structure.[3] However, there have been no previous instances recorded in the literature for the synthesis of 4,4′-iminodipyrimidines, although in a few instances 2,2′-iminodipyrimidines are known.[4a,b] We now report a detailed account of our work on a novel synthesis of iminodipyrimidine, which was mentioned in part in our previous communication.[1]

During the conventional chlorination of 4-amino-6-hydroxy-2-methylpyrimidine (I)[5] with phosphorus oxychloride, we have observed the formation of trace of 6,6′-dichloro-2,2′-dimethyl-4,4′-iminodipyrimidine (IIIa) besides the main product, 4-amino-6-chloro-2-methylpyrimidine (IIa).[6] Since the formation of IIIa was surprising, a series of experiments was performed in the hope that more information might be obtained about this reaction. Thus it has been found that treatment of 1 part of I with 2 parts of phosphorus oxychloride at 220—230° for 5 hr gave IIIa in 65% yield along with a small amount of IIa. When the reaction was carried out at 180°, the main product was IIa (70%) and the yield of IIIa decreased to 10%. The structure of IIIa was assigned on the basis of the following evidence. Compound IIIa shows the presence of chlorine atoms in the Beilstein test. Its infrared spectrum shows a secondary amino stretching absorption band at 3220 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum (CF_3COOH) of IIIa shows sharp, unsplit singlets at 3.03 (CH_3) and 8.35 ppm (C_5H in pyrimidine). The mass spectrometry reveals a parent ion (*m/e* 269), M+2 ion and M+4 ion, which suggests that two chlorine atoms may be contained in the molecule. The assigned structure was confirmed with the information from its elemental analysis. The compound IIIa was also obtained in the reaction of IIa with phosphorus oxychloride at 220—230° for 5 hr in 64% yield.

1) Previous communication: S. Nishigaki, K. Senga, K. Ogiwara and F. Yoneda, *Tetrahedron Letters*, **1969**, 539.
2) Location: 35, *Shinanomachi, Shinjuku-ku, Tokyo.*
3) For a recent review on amidines in medicinal chemistry, see A. Kreutzberger in "Fortshritte der Arzneimettelforshung," Vol. 5, ed. by E. Jucker, Birkhäuser Verlag, Basel, 1968, p. 356.
4) *a*) F.H.S. Curd, W. Graham and F.L. Rose, *J. Chem. Soc.*, **1948**, 594; *b*) W. Broadbent, L.A. McArdle and F.L. Rose, *J. Chem. Soc.* (*C*), **1969**, 689.
5) A. Maggiolo, A.P. Phillips and G.H. Hitchings, *J. Am. Chem. Soc.*, **73**, 106 (1951).
6) Z. Fördi, G.V. Fodor, I. Demjen, H. Szeker and I. Halmos, *Chem. Ber.*, **75**, 755 (1942).

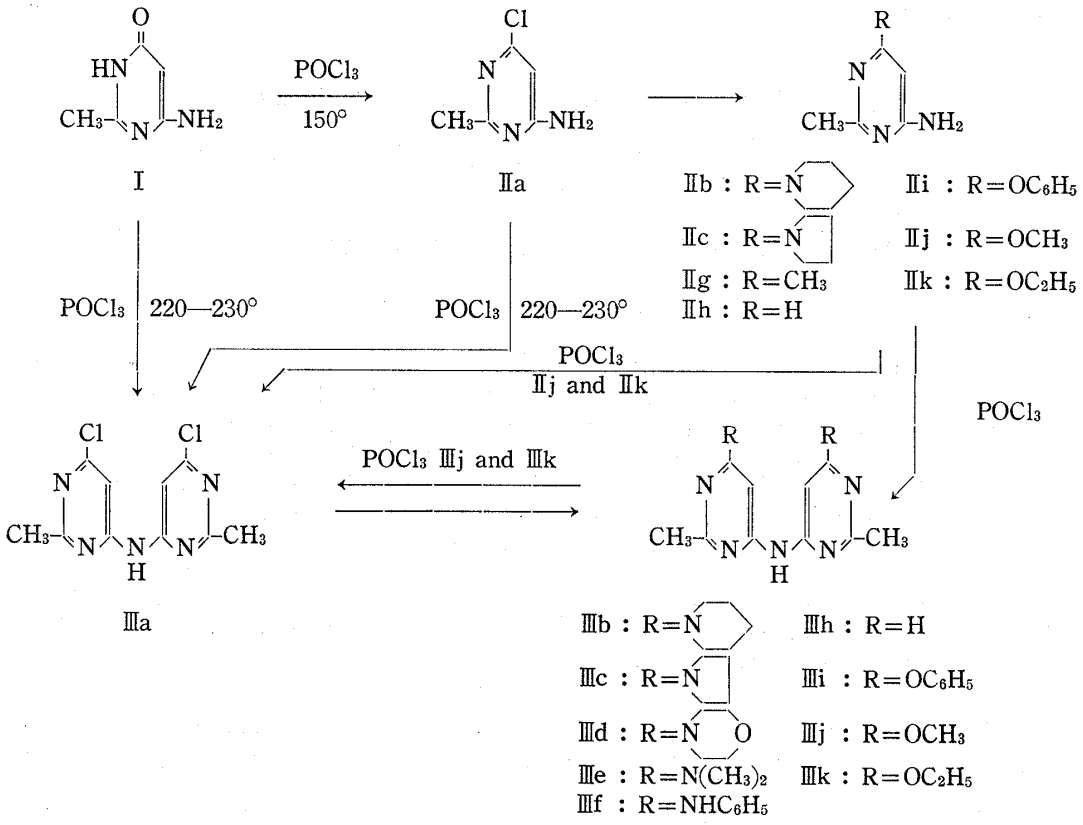

Chart 1

Other reagents usually employed in the thermal condensation were used to confirm the action of phosphorus oxychloride; concentrated hydrochloric acid, acetic acid, phosphoric acid, and polyphosphoric acid all were without effect. Heating of IIa in either diphenylether or sulfolane was also not effective in the absence of phosphorus oxychloride. Furthermore, no desired iminodipyrimidine could be obtained in the fusion of I with phosphorus pentachloride. The reaction appears to proceed only with phosphorus oxychloride as far as we have examined.

In order to extend the reaction some 6-substituted 4-amino-2-methylpyrimidines were treated with phosphorus oxychloride under the same conditions. As shown in Table I,

Table I. Reaction of 4-Amino-2-methylpyrimidines with Phosphorus Oxychloride

Starting material	Reaction Time (hr)	Reaction Temp. (°C)	Product	Yield (%)	Recrystn. solvent[a]	mp (°C)[b]	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	5	220—230	IIIa	65	C	245—246	$C_{10}H_9N_5Cl_2$	44.44	3.22	25.96	44.74	3.37	25.67
IIa	5	220—230	IIIa	64									
IIb	3	230	IIIb	52	A	174—175	$C_{20}H_{29}N_7$	65.36	7.95	26.68	65.50	7.81	26.59
IIc	3	230	IIIc	22	E	194—196	$C_{18}H_{25}N_7$	63.69	7.42	28.89	63.43	7.66	28.62
IIg	10	210—220	IIIg	68	EA	215—217	$C_{12}H_{15}N_5$	62.86	6.60	30.55	63.12	6.33	30.57
IIh	5	240—250	IIIh	54	B	216—218	$C_{10}H_{11}N_5$	59.68	5.51	34.81	59.60	5.46	34.90
IIi	5	220	IIIi	63	E	220	$C_{22}H_{19}O_2N_5$	68.56	4.97	18.17	68.75	5.03	17.88
IIj	2	230	IIIa	90									
IIk	3	230	IIIa	80									

a) C, chloroform; A, acetonitrile; E, ethanol; EA, ethyl acetate; B, benzene
b) All melting points were uncorrected.

6-piperidino- (IIb),[7] 6-pyrrolidino- (IIc) and 6-phenoxy-4-amino-2-methylpyrimidine (IIi), and 4-amino-2,6-dimethylpyrimidine (IIg)[8] were converted to the corresponding 2,2′-dimethyl-4,4′-iminodipyrimidines in moderate to good yields. In analogy with the above results, reaction of 4-amino-2-methylpyrimidine (IIh)[9] with phosphorus oxychloride gave 2,2′-dimethyl-4,4′-iminodipyrimidine (IIIh), which was identical with the product prepared by the catalytic dechlorination of IIIa over palladium-on-charcoal in methanol.

It will be noted that the 6-lower membered alkoxy 4-amino-2-methylpyrimidines were converted unexpectedly in IIIa in excellent yield in this reaction. Furthermore, a quantitative conversion of 6,6′-dimethoxy (or diethoxy)-2,2′-dimethyl-4,4′-iminodipyrimidine to IIIa was realized with phosphorus oxychloride. There seem to be no instances in the literature for the chlorination with replacement of the lower membered alkoxy group which is attached at the aromatic ring, and this reaction may represent an interesting precedent.[10] Displacement of the chlorine in IIIa by secondary amino, anilino, phenoxy and lower membered alkoxy group was accomplished. The reaction conditions required, yields and the physical and analytical data are summarized in Table II.

Table II. Preparation of 6,6′-Disubstituted 2,2′-Dimethyl-4,4′-iminodipyrimidines from IIIa

Reactant	Reaction		Product	Yield (%)	Recrystn. solvent[a]	mp (°C)[b]	Formula	Analysis (%)					
	Time (hr)	Temp. (°C)						Calcd.			Found		
								C	H	N	C	H	N
Piperidine	2	150—160	IIIb	88	A	174—175	—[c]	—	—	—	—	—	—
Pyrrolidine	2	100—120	IIIc	48	E	194—196	—[c]	—	—	—	—	—	—
Morpholine	2	150—160	IIId	88	E	181—183	$C_{18}H_{25}O_2N_7$	58.27	6.74	26.42	58.57	6.90	26.68
20% $(CH_3)_2$-NH in MeOH	5	120	IIIe	74	M	160—162	$C_{14}H_{21}N_7$	58.51	7.37	34.12	58.29	7.44	34.20
Aniline, a few drops of HCl	2	170—180	IIIf	56	E	189—191	$C_{22}H_{21}N_7$	68.91	5.53	25.57	68.83	5.24	25.72
H_2, Pd–C in MeOH		25	IIIh	81	B	216—218	—[c]	—	—	—	—	—	—
Phenol, K_2CO_3 in DMF	4	160—170	IIIi	87	E	219—221	—[c]	—	—	—	—	—	—
NaOMe in MeOH	2	90	IIIj	93	B	167—168	$C_{12}H_{15}O_2N_5$	55.16	5.79	26.81	54.98	5.78	26.72
NaOEt in EtOH	2	90	IIIk	89	A	142—143	$C_{14}H_{19}O_2N_5$	58.11	6.62	24.21	58.08	6.67	24.21

a) A, acetonitrile; E, ethanol; M, methanol; B, benzene
b) All melting points were uncorrected.
c) see Table I.

The reaction was extended successfully to 4-amino-6-hydroxy-2-phenylpyrimidine (IVa),[11] 4-amino-6-chloro-2-phenylpyrimidine (IVb)[12] to give 6,6′-dichloro-2,2′-diphenyl-4,4′-iminodipyrimidine (IVc) in 41 and 53% yield, respectively.

7) F. Craveri and G. Zoni, *Boll. Sci. Fac. Chim. Ind. Bologna*, **16**, 126 (1958).
8) A.R. Ronzio and W.B. Cook, *Org. Syn.*, **24**, 6 (1944).
9) This compound was prepared from IIa by catalytic dechlorination over palladium-on-charcoal in methanol in good yield. Addition of small amount of aqueous ammonia gave better result rather than the procedure described in ref. 6.
10) The only previously recorded chlroination with group replacement is the conversion of 4,6-diamino-5-nitroso-2-phenylpyrimidine to 5-chloro-4,6-diamino-2-phenylpyrimidine by the action of phosphorus oxychloride. E.C. Taylor and C.W. Jefford, *J. Am. Chem. Soc.*, **84**, 3744 (1962).
11) F. Bergmann, A. Kalmus, H.U. Waron and H.K. Bovrin, *J. Chem. Soc.*, **1963**, 3729.
12) E.C. Taylor and J. Weinstock, Brit. Patent 951655 (1964) [*C.A.*, **61**, 4387 (1964)].

Rose and his coworkers[4a] have first reported the synthesis of 4,4′-dichloro-6,6′-dimethyl-2,2′-iminodipyrimidine (Vc). Their method consists of the chlorination of 4,4′-dihydroxy-6,6′-dimethyl-2,2′-iminodipyrimidine which was prepared by condensation of 2-guanidino-4-hydroxy-6-methylpyrimidine with ethyl acetoacetate. Recently, some 2,2′-iminodipyrimidine derivatives were prepared analogously by Rose, *et al.*[4b] We have attempted the synthesis of compound Vc[4a] based upon our method and realized a direct synthesis from 2-amino-4-hydroxy-6-methylpyrimidine (Va)[13] or 2-amino-4-chloro-6-methylpyrimidine (Vb)[13] and phosphorus oxychloride.

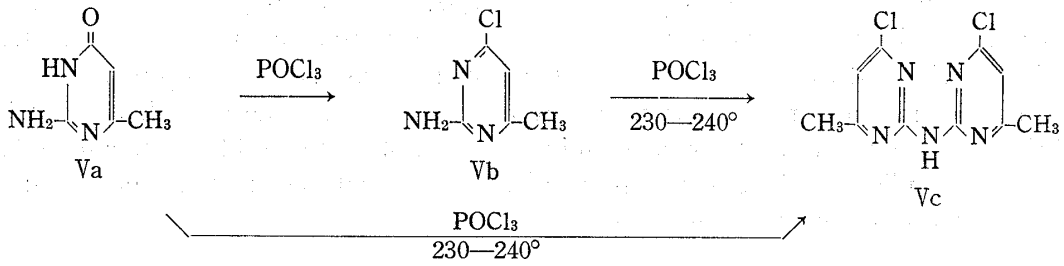

Chart 2

Finally, the preparation of a crossed iminodipyrimidine was tried by heating a mixture of I and Va in phosphorus oxychloride. The thin-layer chromatogram of the reaction product showed two spots which were attributed to IIa and Vb, respectively, and each spot had similar intensity; none of the iminodipyrimidine could be detected.

Experimental[14]

6,6′-Dichloro-2,2′-dimethyl-4,4′-iminodipyrimidine (IIIa)——Method A: A mixture of 10 g (0.08 mole) of 4-amino-6-hydroxy-2-methylpyrimidine (I) and 20 ml of $POCl_3$ was refluxed for 5 hr at 220—230°. The red-brown reaction mixture was poured into 500 ml of ice–H_2O. After standing overnight at room temperature, separated precipitates were collected by filtration, washed with H_2O and dried to give 7 g (65%) of yellow powder. Recrystallization from $CHCl_3$ gave colorless crystals.

Method B: A mixture of 1.75 g (0.012 mole) of 4-amino-6-chloro-2-methylpyrimidine (IIa) and 3.5 ml of $POCl_3$ was refluxed for 5 hr at 220—230°. After the reaction mixture was treated as described in Method A, 1.1 g (64%) of yellow powder were yielded.

Method C: A mixture of 0.5 g (0.0036 mole) of 4-amino-6-methoxy-2-methylpyrimidine (IIj) and 1 ml of $POCl_3$ was refluxed for 2 hr at 230°. By treatment of the reaction mixture as described in Method A, 0.45 g (90%) of yellow powder were obtained.

In complete analogy with the above result, reaction of 4-amino-6-ethoxy-2-methylpyrimidine (IIk) with $POCl_3$ gave IIIa in 80% yield.

Method D: A mixture of 0.5 g (0.0019 mole) of 6,6′-dimethoxy-2,2′-dimethyl-4,4′-iminodipyrimidine (IIIj) and 1 ml of $POCl_3$ was refluxed for 3 hr at 230°. The reaction mixture was treated as described in Method A and 0.5 g (98%) of yellow powder were obtained.

Similarly, reaction of 6,6′-diethoxy-2,2′-dimethyl-4,4′-iminodipyrimidine (IIIk) with $POCl_3$ yielded IIIa in 95% yield.

2,2′-Dimethyl-6,6′-dipiperidino-4,4′-iminodipyrimidine (IIIb)——Method A: A mixture of 0.5 g (0.0026 mole) of 4-amino-2-methyl-6-piperidinopyrimidine (IIb) and 2 ml of $POCl_3$ was heated under refluxed at 230° for 3 hr. After the excess of $POCl_3$ was evaporated under reduced pressure, the resulting gray solid was dissolved in 2N HCl and neutralized with 5% aqueous NH_3. After standing overnight at room temperature, precipitated crystals were collected by filtration, washed with H_2O and dried to give 0.25 g (52%) of gray-brown crystals. Recrystallization from CH_3CN gave colorless crystals.

2,2′-Dimethyl-6,6′-dipyrrolidino-4,4′-iminodipyrimidine (IIIc) were similarly prepared from 4-amino-2-methyl-6-pyrrolidinopyrimidine (IIc) and $POCl_3$ (see Table I).

13) S. Gabriel and J. Colman, *Chem. Ber.*, 32, 2921 (1899).

14) Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were determined on a Japan Spectroscopic Co., Ltd. spectrophotometer, Model IR-E, from samples mulled in Nujol. NMR spectra were taken at 60 Mc with a Japan Electron Optics Lab. Co., Ltd. Model JNM-C-60-H spectrometer using tetramethylsilane as the internal reference.

Method B: A mixture of 1 g (0.0037 mole) of IIIa and 0.94 g (0.0111 mole) of piperidine was heated for 2 hr at 150—160°. After cooling, the precipitated crystals were dissolved in 50 ml of EtOH with warming and neutralized with aqueous NH_3. The solution was evaporated to dryness under reduced pressure. The residue was collected by filtration, washed with boiling H_2O and dried to yield 1.2 g (88%) of IIIb.

Compound IIIc and IIId were prepared by the same method described above, treating IIIa with pyrrolidine and morphiline (see Table II).

4-Amino-2-methyl-6-pyrrolidinopyrimidine (IIc)——A mixture of 3 g (0.02 mole) of IIa and 4.5 g (0.06 mole) of pyrrolidine was heated for 2 hr at 140°. The reaction mixture was dissolved in 30 ml of 2N HCl, and neutralized with 5% of aqueous NH_3. The precipitated crystals were collected by filtration, washed with H_2O and dried to give 3.3 g (89%) of pale yellow crystals. Recrystallization from EtOH gave colorless plates, mp 252—253°. *Anal.* Calcd. for $C_9H_{14}N_4$: C, 60.65; H, 7.92; N, 31.44. Found: C, 60.37; H, 7.78; N, 31.06.

2,2′-Dimethyl-6,6′-dimethylamino-4,4′-iminodipyrimidine (IIIe)——A solution of 1 g (0.0037 mole) of IIIa in 10 ml of 20% methanolic $(CH_3)_2NH$ solution was heated at 120° for 5 hr in a sealed tube. The resulting mixture was concentrated under reduced pressure. To the residue was added a 10% NaOH solution, and the solution was filtered. The filtrate was neutralized with AcOH to precipitate 0.8 g (74%) of yellow powder. Recrystallization from CH_3CN gave colorless crystals.

6,6′-Dianilino-2,2′-dimethyl-4,4′-iminodipyrimidine (IIIf)——A mixture of 1 g (0.0037 mole) of IIIa, 1 g (0.0111 mole) of aniline and 4 drops of conc. HCl was heated for 2 hr at 170—180°. The reaction mixture was dissolved in 100 ml of MeOH and neutralized with aqueous NH_3. After evaporation under reduced pressure, the residue was collected, washed with boiling H_2O and dried to give 0.8 g (56%) of pale yellow powder. Recrystallization from EtOH gave colorless needles.

2,2′,6,6′-Tetramethyl-4,4′-iminodipyrimidine (IIIg)——A mixture of 2 g (0.0082 mole) of 4-amino-2,6-dimethylpyrimidine (IIg) and 8 ml of $POCl_3$ was refluxed for 10 hr at 210—220°. After the excess of $POCl_3$ was evaporated under reduced pressure, the residue was dissolved in 30 ml of H_2O and neutralized with aqueous NH_3. The solution was extracted with $CHCl_3$. The extracts were dried (Na_2SO_4) and evaporated to dryness to provide 1.4 g (68%) of yellow powder. Recrystallization from EtOAc gave colorless plates.

2,2′-Dimethyl-4,4′-iminodipyrimidine (IIIh)——Method A: A mixture of 1 g (0.0092 mole) of IIh and 5 ml of $POCl_3$ was refluxed for 5 hr at 240—250°. After the excess of $POCl_3$ was removed under reduced pressure, the residue was dissolved in 30 ml of H_2O. The solution was neutralized with aqueous NH_3 and extracted with $CHCl_3$. After dryness (Na_2SO_4), the $CHCl_3$ solution was evaporated to give 0.5 g (54%) of yellow powder. Recrystallization from benzene gave colorless needles. The NMR spectrum (DMSO-d_6) exhibited a six-proton singlet at 2.53 ppm (CH_3), a two-proton doublet at 7.57 ppm (J=6.0 cps) (C_5H in pyrimidine), a two-proton doublet at 8.67 ppm (J=6.0 cps) (C_6H in pyrimidine), and a one-proton singlet at 10.48 ppm (NH).

Method B: A solution of 1.5 g (0.012 mole) of IIIa and 4 ml of conc. aqueous NH_3 in 50 ml of MeOH was subjected to hydrogenation in the presence of 0.1 g of 10% Pd-C at room temperature and atmospheric pressure. Hydrogenation was stopped when the theoretical volume of hydrogen was consumed. Removal of the catalyst left a pale yellow solution, which was evaporated to dryness. The residue was extracted with acetone with warming and the extract was evaporated to yield 0.9 g (81%) of pale yellow powder.

4-Amino-2-methyl-6-phenoxypyrimidine (IIi)——A mixture of 7.18 g (0.05 mole) of IIa, 4.7 g (0.05 mole) of phenol and 6.9 g (0.05 mole) of anhyd. K_2CO_3 in 50 ml of DMF was heated under refluxing for 3 hr. After cooling, the K_2CO_3 was filtered off, and the filtrate was evaporated under reduced pressure. The residue was crushed in H_2O and collected by filtration, washed with H_2O and dried to give 5.8 g (57%) of pale yellow crystals, which were recrystallized from benzene give colorless plates, mp 177—179°. *Anal.* Calcd. for $C_{11}H_{11}ON_3$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.42; H, 5.58; N, 20.55.

2,2′-Dimethyl-6,6′-diphenoxy-4,4′-iminodipyrimidine (IIIi)——Method A: A mixture of 0.5 g (0.0025 mole) of IIi and 1 ml of $POCl_3$ was refluxed for 3 hr at 220°. After cooling, the reaction mixture was dissolved in diluted HCl and neutralized with aqueous NH_3. The separated precipitates were collected by filtration, washed with H_2O and dried to give 0.3 g (63%) of yellow powder. Recrystallization from EtOH gave colorless needles.

Method B: A mixture of 1 g (0.037 mole) of IIIa, 1 g (0.0111 mole) of phenol, and 1.5 g (0.0111 mole) of anhyd. K_2CO_3 in 5 ml of DMF was heated under refluxed for 4 hr at 160—170°. After cooling, the K_2CO_3 was filtered off and the filtrate was evaporated under reduced pressure. The residue was washed with H_2O and dried to give 1.2 g (87%) of IIIi.

6,6′-Dimethoxy-2,2′-dimethyl-4,4′-iminodipyrimidine (IIIj)——A suspension of 1 g (0.0037 mole) of IIIa in 10 ml of MeOH which contained 0.23 g (0.0111 mole) of $NaOCH_3$ was refluxed for 2 hr at 90°. After cooling, the NaCl which separated was filtered off and the filtrate was evaporated. The residue was washed with H_2O and dried to produce 0.9 g (93%) of pale yellow powder, which was recrystallized from benzene to give colorless plates. The NMR spectrum (DMSO-d_6) exhibited a six-proton singlet at 2.47 ppm (CH_3), a six-proton singlet at 3.90 ppm (OCH_3), a two-proton singlet at 7.00 ppm (C_5H in pyrimidine), and a one-proton singlet at 10.28 ppm (NH).

In similar fashion to the preparation of IIIj described above, 6,6′-diethoxy-2,2′-dimethyl-4,4′-iminodipyrimidine (IIIk) was obtained from IIIa and NaOEt in 89% yield (see Table II).

6,6′-Dichloro-2,2′-diphenyl-4,4′-iminodipyrimidine (IVc)——Method A: A mixture of 0.7 g (0.004 mole) of 4-amino-6-hydroxy-2-phenylpyrimidine (IVa) and 1.5 ml of $POCl_3$ was refluxed for 3 hr at 220—230°. After evaporation of the excess of $POCl_3$, the residue was crushed in 2N HCl. The crushed powder was dissolved in EtOH. The EtOH solution was neutralized with aqueous NH_3, the separated crystals were collected by filtration to produce 0.3 g (41%) of brown powder. Recrystallization from a mixture of H_2O and EtOH (4:1) gave colorless crystals, mp 170—172°. *Anal.* Calcd. for $C_{20}H_{13}N_5Cl_2$: C, 60.92; H, 3.32; N, 17.77. Found: C, 60.88; H, 3.34; N, 17.53.

Method B: A mixture of 0.8 g (0.004 mole) of 4-amino-6-chloro-2-phenylpyrimidine (IVb) and 2.5 ml of $POCl_3$ was heated for 3 hr at 220—230°. The reaction mixture was treated as described in Method A to yield 0.4 g (53%) of brown powder.

4,4′-Dichloro-6,6′-dimethyl-2,2′-iminodipyrimidine (Vc)——A mixture of 2 g (0.016 mole) of 2-amino-4-hydroxy-6-methylpyrimidine (Va) and 10 ml of $POCl_3$ was heated under refluxing for 10 hr at 230—240°. Excess of $POCl_3$ was removed under reduced pressure. The residue was dissolved in 100 ml of H_2O and neutralized with aqueous NH_3. The precipitated crystals were collected by filtration, washed with H_2O and dried to give 1 g (44%) of yellow crystals, which was identical with an authentic sample prepared by the method of Rose, *et al.*[4a]

Vc was also obtained from 2-amino-4-chloro-6-methylpyrimidine (Vb) in 48% yield under the same conditions.

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