g.; m.p. 286–291° (lit.[5] m.p. 290.5–292.5°); R_f 0.65 in solvent A; $\lambda_{max}^{0.1\ N\ NaOH}$ 243 (9100), 269 mμ (ε 9700); $\lambda_{max}^{0.1\ N\ HCl}$ 268 mμ (ε 17,500); $\lambda_{max}^{CH_3OH}$ 221 (30,600), 274 mμ (ε 14,600).

Anal. Calcd. for $C_6H_{10}N_4O$ (154): C, 46.7; H, 6.54; N, 36.3. Found: C, 46.8; H, 6.59; N, 36.5.

2-Dimethylamino-4-hydroxy-6-methylaminopyrimidine (XII).—2-Dimethylamino-4-hydroxy-6-aminopyrimidine (10.0 g., 0.065 mole) was refluxed in 120 ml. of methylammonium acetate in an oil bath for 2 hr. (internal temperature, 130–135°). The reaction mixture was chilled overnight, whereupon some crystals had come out. Additional crystals separated after agitation and further cooling; yield 6.5 g. (44%) of the acetate salt, m.p. 120–125°. A portion of this product was recrystallized from ethyl acetate for analytical purposes; melting point was raised to 128–130°; R_f 0.83 with trace of lower R_f spot in solvent A; dried at room temperature *in vacuo*.

Anal. Calcd. for $C_9H_{16}N_4O_3$(228): C, 47.4; H, 7.07; N, 24.6. Found: C, 47.3; H, 7.28; N, 25.2.

A small crop of the yellow, crystalline acetate salt was dried at 80° *in vacuo* over phosphorus pentoxide to give the free base; m.p. 201–203° (lit.[25] m.p. 198–200°); $\lambda_{max}^{0.1\ N\ HCl}$ 222 (13,000), 270 mμ (ε 22,500); $\lambda_{max}^{0.1\ N\ NaOH}$ 270 mμ (ε 10,800).

Anal. Calcd. for $C_7H_{12}N_4O$ (168): C, 50.0; H, 7.19; N, 33.3. Found: C, 50.0; H, 7.20; N, 33.6.

2-Methylamino-4-hydroxy-6-aminopyrimidine.—Two grams (13 mmoles) of 2,6-bis(methylamino)-4-hydroxypyrimidine was added to 15.0 g. of ammonium acetate and refluxed for 2 hr. The reaction mixture was diluted with 250 ml. of water and evaporated to an oily liquid *in vacuo*. After repeating this procedure the resulting oil was crystallized from 10 ml. of water; yield, 0.60 g., m.p. 219–221°, with previous wetting. The crude product was boiled in 12 ml. of ethanol, treated with charcoal, and filtered. The filtrate was cooled and the product was collected; yield, 0.44 g. (24%); m.p. 221–223°, after drying *in vacuo* over phosphorus pentoxide at 105° (lit.[5] m.p. 227–229°); R_f 0.63 in solvent A; $\lambda_{max}^{0.1\ N\ NaOH}$ 239 (6000), 267 mμ (ε 9900); $\lambda_{max}^{0.1\ N\ HCl}$ 265 mμ (ε 21,700).

Anal. Calcd. for $C_5H_8N_4O$ (140): C, 42.9; H, 5.8; N, 40.0. Found: C, 43.1; H, 5.8; N, 39.9.

2,4-Dihydroxy-6-ureidopyrimidine (XIII).—One gram (7.9 mmoles) of 2,4-dihydroxy-6-aminopyrimidine was added to 10 g. of urea and placed in an oil bath at 150°. The bath temperature increased to 160° over the first 15 min. and to 170° over the next 15 min. during which time complete solution took place. The reaction mixture was kept at 170° for an additional 15 min. during which time crystals appeared. The mixture was diluted with 20 ml. of water while still warm, then allowed to stand at room temperature overnight before collecting the crystals; yield, 1.4 g.; unmelted at 400°. The material was recrystallized from 200 ml. of 50% aqueous ethanol; yield, 1.0 g. (75%); R_f 0.50 with trace of lower R_f spot in solvent B; $\lambda_{max}^{0.1\ N\ NaOH}$ 262 mμ (ε 19,000); $\lambda_{max}^{0.1\ N\ HCl}$ 257 mμ (ε 20,700); $\lambda_{max}^{CH_3OH}$ 259 mμ (ε 19,200).

Anal. Calcd. for $C_5H_6N_4O_3$(170): C, 35.3; H, 3.6; N, 32.9. Found: C, 35.5; H, 3.7; N, 32.9.

2-Amino-4-hydroxy-6-ureidopyrimidine (XIV).—One gram (8.0 mmoles) of 2,6-diamino-4-hydroxypyrimidine was added to 10 g. of urea and heated in an oil bath for 1 hr. at 165°. The mixture was diluted with 20 ml. of water, then allowed to stand at room temperature overnight. The product was collected and dried; yield, 0.75 g. Recrystallization from aqueous ethanol gave 0.65 g. (43%), unmelted at 400°. For analytical purposes, a portion of this product was dried over phosphorus pentoxide for several hours, then allowed to equilibrate in air; $\lambda_{max}^{0.1\ N\ NaOH}$ 223 (28,000), 272 mμ (ε 16,800); $\lambda_{max}^{0.1\ N\ HCl}$ 260 mμ (ε 18,700); $\lambda_{max}^{CH_3OH}$ 222 (39,000), 269 mμ (ε 17,600).

Anal. Calcd. for $C_5H_7N_5O_2 \cdot H_2O$ (187): C, 32.1; H, 4.9; N, 37.4. Found: C, 32.3; H, 4.9; N, 37.4.

Acknowledgment.—We wish to thank Mr. L. Brancone and staff for the microanalyses and Mr. W. Fulmor and staff for the spectral data reported herein.

(25) W. Pfleiderer and K. Deckert, *Chem. Ber.*, **95**, 1597 (1962).

The Cyclization Reactions of Certain 5-Amino-4-chloro-6-hydrazinopyrimidines with Phosgene[1]

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The synthesis of 5-amino-4-chloro-6-hydrazinopyrimidine and its cyclization with phosgene gas is described. The initial product of the cyclization is shown to be the 9-aminopurin-8-ol III. Upon refluxing in ethanolic hydrogen chloride, 9-amino-6-chloropurin-8-ol (III) undergoes an acid-catalyzed ring expansion to yield the isomeric 5-chloro-1,2,3,4-tetrahydro-3-oxopyrimido[5,4-*e*]-*as*-triazine. Other phosgene cyclizations investigated include the preparation of 6-chloropurin-8-ol from 4,5-diamino-6-chloropyrimidine and the synthesis of 5-chloro-1,2,3,4-tetrahydro-1-methyl-3-oxopyrimido[5,4-*e*]-*as*-triazine from 5-amino-4-chloro-6-(1-methylhydrazino)pyrimidine. In addition, the preparation of the 8-thio analog of 9-amino-6-chloropurin-8-ol by the use of thiophosgene as the cyclizing reagent is described. In the course of the work described herein, the syntheses and reactions of a number of 4,5,6-trisubstituted pyrimidines were investigated. 4,6-Dimethoxy-5-nitropyrimidine was found to react readily with hydrazine to form 4,6-dihydrazino-5-nitropyrimidine in excellent yield; yet it was surprisingly unreactive with methylhydrazine yielding as the only isolable material an unknown product containing a degraded nitro substituent.

4,6-Dichloro-5-nitropyrimidine (I), first described by Boon and co-workers,[2] has been found to be a very useful intermediate due to the marked activity of the chloro substituents toward nucleophilic reagents.

During the course of a study involving the preparation of certain derivatives of this intermediate for screening purposes, I was found to yield an intractable material, undoubtedly polymeric in nature, when treated with an anhydrous alcoholic solution of hydrazine. Upon substituting the amino analog for I, 5-amino-4-chloro-6-hydrazinopyrimidine (II) was obtained in excellent yields. Attempts to cyclize II led to the discovery of some very interesting reactions which are the subject of this manuscript. The usual cyclization procedures[3] for the preparation of purines did not yield in isolable product, although Montgomery and Temple[4] recently did, indeed, effect the cyclization of 5-amino-4-chloro-6-hydrazinopyrimidine with formic acid to yield a crude product from which they obtained 9-aminohypoxanthine.

(1) Abstracted from a dissertation submitted by Mark Krakov to the faculty of Oregon State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Published with the approval of Monographs Publication Committee, Oregon State University, as Research Paper no. 455, Department of Chemistry, School of Science.

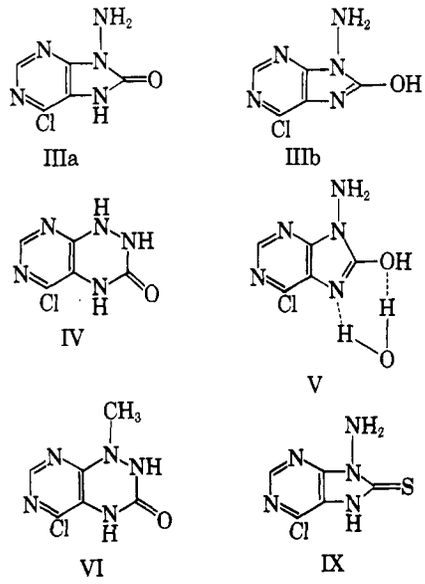
(2) W. R. Boon, W. G. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, **96**, (1951).

(3) R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Am. Chem. Soc.*, **75**, 263 (1953).

(4) J. A. Montgomery and C. Temple, Jr., *ibid.*, **82**, 4592 (1960).

CHART I

Fused Ring Compounds Derived from 5-Amino-4-chloro-6-hydrazinopyrimidine



For this reason cyclization was attempted by passing phosgene gas[5] into a slightly acidic solution of 5-amino-4-chloro-6-hydrazinopyrimidine. This precipitated a light tan solid, which on recrystallization from hot N,N-dimethylformamide gave a white crystalline solid. Analytical data obtained from this product indicated it to be $C_5H_4ClN_5O$ which suggested that the compound was either 9-amino-6-chloropurin-8-ol (III) or 5-chloro-1,2,3,4 - tetrahydro - 3 - oxopyrimido[5,4-*e*] - *as*-triazine (IV). (See Chart I, structures III and IV.)

The infrared spectrum of the compound (see Table I) did not provide an unequivocal basis for structure assignment but indicated that structure III was more likely, and on these grounds a tentative structural assignment was made. The most striking feature of the spectrum is the presence of two very strong and well defined peaks (1745 and 1713 cm.$^{-1}$) in what is normally considered as the C=O absorption region. The peak at 1745 cm.$^{-1}$ may be assigned to the amide-I absorption band. This is a considerably higher frequency than that normally assigned to amide-I absorptions but is in keeping with observations that the amide-I bands of cyclic amides in fused five-membered rings are often shifted upwards to frequencies in the neighborhood of 1700–1750 cm.$^{-1}$ [6-8]; *e.g.*, Mason[9] has reported that purin-8-ol and its 7-methyl and 9-methyl homologs all show carbonyl stretching frequencies in the region of 1740–1745 cm.$^{-1}$. A six-membered cyclic amide, such as in structure IV, would not be expected to absorb at this high frequency.

The strong absorption at 1713 cm.$^{-1}$ still remains to be considered. Inasmuch as cyclic amides do not normally exhibit an amide-II band[6,7,10] and, in addition, the amide-II band is normally located at considerably lower frequencies, this does not appear to be a likely explanation for the presence of this band. This absorption is also at a much higher frequency than that normally attributed to C=C and C=N in the pyrimidine ring, the strong band at 1622 cm.$^{-1}$ being a more likely assignment for these vibrations. The most satisfactory explanation of the 1713-cm.$^{-1}$ band is that III consists of a tautomeric mixture of IIIa and IIIb, (see Chart I) the higher frequency being supplied by the carbonyl group in III and the lower band being the contribution of the enol form IIIb. This view finds support in that Gagnon, *et al.*,[11,12] have attributed absorptions in the range of 1670–1700 cm.$^{-1}$ to cyclic C=N vibrations in certain pyrazolones.

9-Amino-6-chloropurin-8-ol (III) is insoluble in nonpolar solvents and only slightly soluble in boiling water, dilute aqueous acids, or ethanol; it is quite soluble in dilute alkali. The chloro substituent appears to be surprisingly inert by comparison to 6-chloropurine; *e.g.*, 9-amino-6-chloropurin-8-ol failed to react when attempts were made to synthesize the morpholino derivative. This inertness of the 6-position toward nucleophilic reagents had been noted by Robins in the case of 6-chloropurin-8-ol-2-sulfonic acid.[13]

Upon solution in dilute aqueous base, the material can be recovered as a monohydrate V if the solution is immediately re-acidified; if the basic solution is allowed to stand, decomposition rapidly ensues. This hydrated material V was also obtained upon recrystallization of III from solutions buffered at pH 5 and pH 7. The hydrate can be quantitatively reconverted to III by sublimation or azeotropic distillation with toluene.

The infrared spectrum of V (see Table I) is similar to that of III but shows some major differences, such as the complete elimination of the strong absorption band which the anhydrous material exhibits at 1745 cm.$^{-1}$ and the strengthening and broadening of the band at 3460 cm.$^{-1}$. These spectral changes suggest that the structure III·H_2O involves the complete conversion of the heterocycle into its enol form, possibly with the water molecule bonded to the molecule as shown in structure V (see compound V, Chart I). The strengthening and broadening of the band at 3460 cm.$^{-1}$ can be attributed to superimposition of O—H stretching frequencies contributed by bound water. The C=O absorption at 1745 cm.$^{-1}$ would, of course, be eliminated.

When III was refluxed in a 0.33 *M* alcoholic solution of anhydrous hydrogen chloride, a new compound was obtained in 55% yield. Carbon–hydrogen–nitrogen analysis of this substance indicated that the new compound was isomeric with III while its infrared and ultraviolet spectra were markedly different (see Tables I and II). Although the general physical properties of the two compounds were similar, the second compound was far less soluble in the same solvents and had a considerably higher decomposition point (above 320°), as compared to III (285–295° dec.). The structure tentatively assigned to it was 5-chloro-1,2,3,4-tetrahydro-3-oxopyrimido[5,4-*e*]*as*-triazine (IV). This was

(5) L. F. Cavalieri and A. Bendich, *J. Am. Chem. Soc.*, **72**, 2587 (1950).
(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 214.
(7) H. W. Thompson, "Chemistry of Penicillin," H. T. Clarke, *et al*, Ed., Princeton University Press, Princeton, N. J., 1949, p. 390.
(8) H. H. Wasserman, F. M. Precopio, and Tien-Chuan Liu, *J. Am. Chem. Soc.*, **74**, 4093 (1952).
(9) S. F. Mason, *J. Chem. Soc.*, 4874 (1957).
(10) R. Gompper and H. Herlinger, *Ber.*, **89**, 2825 (1956).
(11) P. E. Gagnon, *et al.*, *Can. J. Chem.*, **32**, 823 (1954).
(12) P. E. Gagnon, J. L. Boivin, and R. J. Paquin, *ibid.*, **31**, 1025 (1953).
(13) R. K. Robins, *J. Org. Chem.*, **26**, 447 (1951).

TABLE I

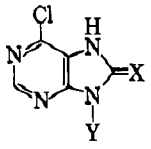
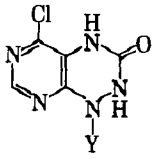
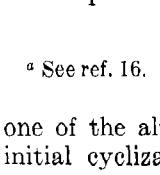
SUMMARY OF INFRARED DATA FOR CONDENSED RING COMPOUNDS

Compound	Hydrogen stretching vibrations,[a] 3000–4000 cm.$^{-1}$				Double-bond vibrations,[a] 1500–1750 cm.$^{-1}$					
III	3460 m	3330 m	3200 s	3090 m	1745 s	1713 s		1622 s	1556 s	1540 m
V	3460 s[b]	3310 m	3200 m	3080 m		1705 vs	1647 m	1611 s	1556 m	1529 m
VIII			3125 s	2995–3035 m[b]		1707 vs	1632 s	1592 s		
IX	3450 s	3305 s	3200 m	3095 s				1622 s	1551 s	1520 m
IV	3370 w	3315 s	3175 vs			1704 m	1660 m	1620 vs	1585 m	1550 m
VI			3190 m	3100 s		1715 vs[b]		1590 s	1579 s	1538 w
XIII		3320 w	3240 m	3040 m			1666 vs	1625 m		1547 w

[a] w, weak; m, medium; s, strong; vs, very strong. [b] Broad.

TABLE II

ULTRAVIOLET SPECTRAL DATA FOR CONDENSED RING COMPOUNDS

Ring System	Compound	X	Y	pH	λ_{max} mμ			ε × 10^{-3}		
	VIII[a]	O	H	4.5	277,	241		13.7,	4.0	
				1.0	279,	243		13.3,	3.8	
				11.0	289,			13.6,		
	III	O	NH_2	4.5	320,	274,	210	6.1,	10.9,	2.7
				Ethanol	325,	276,	212	6.4,	11.2,	1.5
	IX	S	NH_2	4.5	340,	291,	243	>7.4	>10.5	>6.7[b]
				Ethanol	347,	296,	248	8.5	12.5	6.2
	IV		H	4.5	305,[c]	275,	242	4.0,	8.3	31.6
	VI		CH_3	4.5	322,		218	5.5		19.1

[a] See ref. 16. [b] A portion of the sample remained undissolved. [c] A very slight shoulder.

one of the alternate structures for the product of the initial cyclization and its formation from III would have to involve a ring expansion. Recently, Taylor and co-workers[14] have reported another instance of this type of ring expansion in which mild acid hydrolysis of 6-methyl-9-N-formylaminopurine yielded 5-methyl-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine.

The absorption band at 1704 cm.$^{-1}$ in the infrared spectrum of IV (see Table I) can be assigned to the C=O stretching vibrations of an amide in a six-membered ring. This frequency is ordinarily high for such an assignment but it has been reported that values as high as 1715 cm.$^{-1}$ have been observed in certain substituted anilides.[15]

5 - Amino - 4 - chloro - 6 - (1 - methylhydrazino)-pyrimidine also was cyclized with phosgene to yield 1,2,3,4 - tetrahydro - 1 - methyl - 3 - oxopyrimido-[5,4-*e*]-*as*-triazine (VI) whose structure should be unequivocal. The product was quite similar in its physical properties to IV and, like III and IV, very labile when dissolved in dilute alkali.

A comparison of the infrared and ultraviolet spectra of IV and VI (see Tables I and II) revealed differences greater than one would expect solely as a result of the substitution of a methyl group in the 1-position. However, a similarly unexpected large variation was noted between the infrared spectra of 5-amino-4-chloro-6-hydrazinopyrimidine (II) and 5-amino-4-chloro-6-(1-methylhydrazino)pyrimidine (VII).

Because of its structural similarity to III, the synthesis of 6-chloropurin-8-ol by the same cyclization procedure was also investigated. Robins[16] had previously prepared the compound by the acid hydrolysis of 6,8-dichloropurine but had reported no infrared data for the compound. By treating 4-chloro-5,6-diaminopyrimidine in an alkaline medium with phosgene, 6-chloropurin-8-ol (VIII) was obtained in 35% yield; its ultraviolet spectrum agreed very well with that reported by Robins[16] (see Table II). VIII had the expected high decomposition point but its infrared spectrum was rather surprising in that it gave a strong band at 1707 cm.$^{-1}$ rather than a C=O absorption in the region of 1740–1745 cm.$^{-1}$ (see compound VIII, Table I). This may indicate that VIII exists completely in the enol form.

Inasmuch as all efforts to chlorinate III, IV, or VI were unsuccessful, the thio analog of III was prepared for purposes of chlorination *via* the new procedure reported by Robins[13] in 1961. The synthesis was achieved by the use of thiophosgene in a procedure analogous to that employed in the preparation of III. The product IX was a pale yellow solid which melts with decomposition at 280–290°. It was less soluble in

(14) E. C. Taylor, J. W. Barton, and W. W. Paudler, *J. Org. Chem.*, **26**, 4961 (1961).

(15) R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1248 (1947).

(16) R. K. Robins, *J. Am. Chem. Soc.*, **80**, 6671 (1958).

TABLE III

ULTRAVIOLET SPECTRAL DATA FOR CERTAIN 4,5,6-TRISUBSTITUTED PYRIMIDINES

4	5	6	pH	λ_{max} mμ		$\epsilon \times 10^{-3}$		Ref.
Cl	NH_2	NH_2	4.5	289,	254	7.5,	6.2	
			7	289,	253.5	8.9,	7.5	*a*
Cl	NH_2	$NHNH_2$	4.5	288,	266	8.0,	7.2	
			1	292,	225	7.7,	6.0	*b*
			7	289,	257	5.3,	5.7	*b*
Cl	NH_2	$N(CH_3)NH_2$	4.5	303,	272	9.7,	7.0	
			1	303,	249.5	7.3,	7.0	*b*
			7	304,	273.5	9.1,	7.1	*b*
Cl	NH_2	Cl	4.5	305,	245	6.1,	9.3	
Cl	NO_2	Cl	4.5	319,	255	2.5,	3.0	
Cl	NO_2	OCH_3	4.5	254,	212	2.8,	12.8	
OCH_3	NO_2	OCH_3	4.5	268,	215	>2.3	>10.3[c]	
OCH_3	NH_2	OCH_3	4.5	266		11.5		
$NHNH_2$	NO_2	$NHNH_2$	4.5	357,	217	8.0,	21.0	

[a] J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956). [b] See ref. 4. [c] A portion of the sample remained undissolved.

water than the oxo analog, although more soluble in ethanol, and unlike III did not form a hydrate upon crystallization from water.

Based upon our work with III and that of Montgomery and Temple[4] with regard to the cyclization of 5-amino-4-chloro-6-hydrazinopyrimidine, IX was assigned the structure 9-amino-6-chloropurine-8-thiol.

The C=S frequency in thioamides, thioureas, and related compounds is extremely variable so that it is not possible to assign this vibration to a specific band in the infrared spectrum of IX. It is interesting to note, however, the striking similarity of the hydrogen stretching regions in the spectra of III and IX (see Table I). This gives further support to the hypothesis that the two ring systems are the same. A comparison of the ultraviolet spectra of the two analogs III and IX (see Table II) shows a similarity with regard to the number of absorption maxima and their relative intensities. A pronounced bathochromic shift of 20–30 mμ is evident for all three peaks, an effect predicted by Pullman for thiosubstituted purine.[17]

Although the reaction of 4,6-dichloro-5-nitropyrimidine with anhydrous hydrazine gave largely a polymeric product, it gave excellent yields of 4,6-dimethoxy-5-nitropyrimidine with sodium methoxide. 4,6-Dimethoxy-5-nitropyrimidine (X) in turn reacted much more smoothly with anhydrous hydrazine to give 4,6-dihydrazino-5-nitropyrimidine (XI) in good yield, and easily was reduced to 5-amino-4,6-dimethoxypyrimidine (XII).

In the course of the work described thus far, the syntheses and reactions of a number of 4,5,6-trisubstituted pyrimidines were investigated; a summary of certain of these reactions is presented in Chart II with the ultraviolet data given in Table III.

As is well known, the presence of a strongly electron attracting nitrogroup at the 5-position of a pyrimidine ring imparts relatively high reactivity with respect to nucleophilic substitution at positions 4 and 6. This effect is readily understandable when one considers that in 4,6-dichloro-5-nitropyrimidine the electronic effect of the nitro group is reinforced by a like effect due to the ring nitrogens. The extremely low electron density on the carbon atoms 4 and 6 facilitates the displacement of the chloro substituents. It is for this reason that the substitution of hydrazine for the methoxyl groups in 4-chloro-6-methoxy-5-nitropyrimidine and 4,6-dimethoxy-5-nitropyrimidine (X) cannot be considered unusual. The methoxyl groups of these compounds should resemble closely in chemical behavior the alkoxyl group of a simple ester. Synthesis of XI from the dimethoxynitropyrimidine provides the best yields (over 95%) of the three routes investigated.

The marked deactivation of the 4- and 6-positions following the reduction of the 5-nitro group to the corresponding amine has been mentioned. The electron-releasing effect of the amine is such that 5-amino-4,6-dichloropyrimidine is inert to all but the most powerful nucleophiles and the aminodimethoxypyrimidine XII will not react with even so strong a nucleophile as ethanolic hydrazine. In the aminochlorohydrazinopyrimidines (*e.g.*, VII), the presence of the hydrazino substituent provides additional electron release and reinforces the deactivating effect of the amino group. The 4-chloro substituent in 5-amino-4-chloro-6-hydrazinopyrimidine is so inert that this compound underwent no reaction even with sodium methoxide. (In this last instance, it was necessary to conduct the experiment in an atmosphere of carefully scrubbed nitrogen; even traces of oxygen will cause considerable oxidation of the hydrazino moiety under these highly basic conditions.)

Hydrazines carrying electron-attracting substituents, which decrease the nucleophilicity of the hydrazino group (*e.g.*, formylhydrazine and phenylhydrazine) undergo no reaction with XIII.

The reaction of XIII with 1,1-dimethylhydrazine was found to yield 5-amino-4-chloro-6-(1-methylhydrazino)pyrimidine (VII) instead of the expected product, 5-amino-4-chloro-6-(2,2-dimethylhydrazino)pyrimidine. The identity of this product was established by elemental analysis, by a positive reaction with sodium pentacyanoaminoferroate,[18] and by a comparison of the infrared spectrum of this material with that of VII which has been prepared from methylhydrazine.

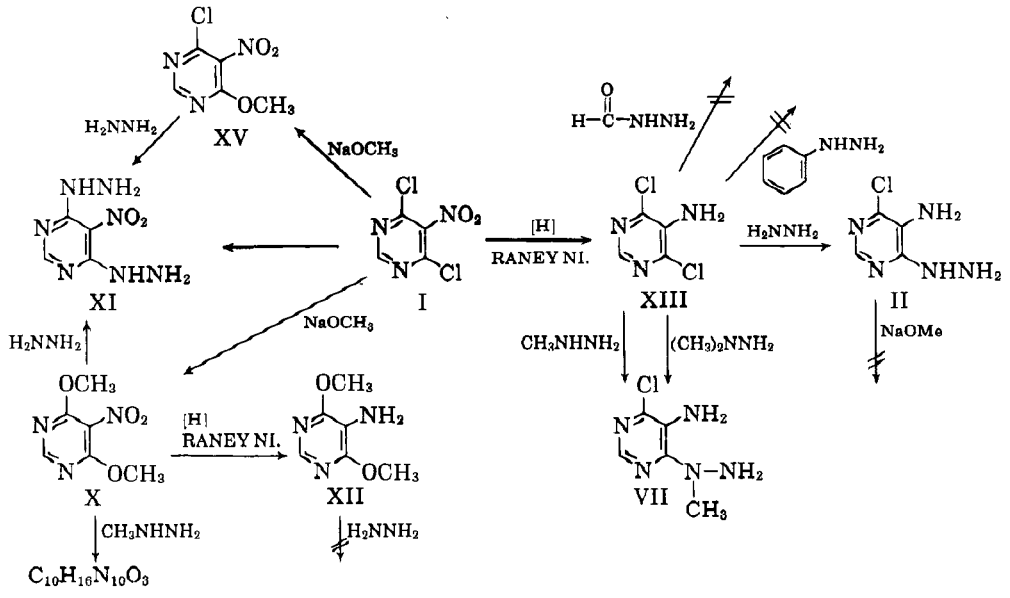
One other reaction which deserves some discussion is the reaction of 4,6-dimethoxy-5-nitropyrimidine (X) with methylhydrazine. By analogy to its reaction with hydrazine, one would expect X to yield 4,6-di(1-methylhydrazino)-5-nitropyrimidine in good yield. Instead, after two hours' refluxing with methylhydrazine

(17) A. Pullman, *Bull. soc. chim. France*, 641 (1958).

(18) F. Feigl, "Spot Tests in Organic Analysis," 5th Ed., Elsevier Publishing Co., New York, N. Y., 1956, p. 616.

CHART II

Some Reactions of 4,5,6-Trisubstituted Pyrimidine



in ethanol, there was isolated from the reaction mixture a large amount of starting material and a few milligrams of an unknown crystalline product XIV which melted with decomposition at 240–260°. This reaction was repeated using 1-butanol as a solvent in order to obtain a higher reflux temperature. Under these conditions, the yield of XIV was increased considerably. Carbon–hydrogen–nitrogen analysis of XIV indicates that the reaction is not straightforward but leads to a complex product (or products) in which the nitro substituent has been partially reduced.

Experimental

All melting points were taken on a Fisher-Johns melting point apparatus. The infrared spectra were obtained with a Perkin-Elmer Model 21 infrared spectrophotometer using a sodium chloride prism, with samples in the form of Nujol mulls. The ultraviolet absorption spectra were determined with a Beckman Model DB spectrophotometer.

9-Amino-6-chloropurin-8-ol (III).—The apparatus employed for the phosgene cyclization reactions consisted of a three-necked flask fitted with a magnetic stirrer and gas inlet and outlet tubes. A series of trap bottles containing 20% sodium hydroxide solution was connected to the outlet tube in order to absorb excess phosgene. When used with a good hood, this arrangement permitted the reactions to be carried out conveniently and without danger.

5-Amino-4-chloro-6-hydrazinopyrimidine (12.8 g., 0.08 mole) was dissolved in 200 ml. of water containing 8 ml. of concentrated hydrochloric acid. Phosgene gas was then introduced into this solution with stirring for 50 min.; a light tan solid material precipitated. After flushing the unchanged phosgene out of the system, the precipitate was filtered, washed well with water, and dried; yield 10.1 g.

This crude material was most easily purified by two recrystallizations from approximately 10% hot N,N-dimethylformamide. However, the purest samples were obtained by sublimation (210°, 0.02 mm.), the sublimate being a white crystalline material, decomposing at 285–295°. Sublimation must be performed by use of a long sublimation tube because the brown residual material is extremely light and fluffy and tends to fly upwards onto the sublimate.

Anal. Calcd. for $C_5H_4ClN_5O$: C, 32.4; H, 2.17; N, 37.7; Cl, 19.1. Found: C, 32.4; H, 2.20; N, 37.5; Cl, 19.2.

III crystallized from aqueous solutions buffered at pH 5 and pH 7 in the form of a monohydrate V. The monohydrate was also obtained by acidification of a basic solution of III.

Anal. Calcd. for $C_5H_4ClN_5O \cdot H_2O$: C, 29.5; H, 2.97; N, 34.4. Found: C, 29.6; H, 3.04; N, 34.2.

Dehydration of V to give the original anhydrous material was accomplished by both (a) sublimation and (b) azeotropic distillation using toluene. A comparison of the infrared spectra demonstrated that the products obtained by these procedures were both identical to the original anhydrous compound, III.

5-Chloro-1,2,3,4-tetrahydro-3-oxopyrimido[5,4-*e*]-*as*-triazine (IV).—Two grams (0.0108 mole) of 9-amino-6-chloropurin-8-ol was suspended in 90 ml. of an approximately 0.33 *M* solution of anhydrous hydrogen chloride in absolute ethanol. The mixture was refluxed on a steam bath for 1 hr., during which time the suspended material turned bright yellow. After filtration from the cooled solution and drying, the crude product weighed 1.4 g. This material was then dissolved in 50–60 ml. of hot N,N-dimethylformamide, and the hot solution was filtered to remove a small amount of insoluble material. Upon addition of an equal volume of water to the cooled solution, IV precipitated as an almost white solid; dry weight, 1.1 g. (55%); m.p. > 320° dec.

A 150-mg. portion of the crude product was purified for analysis by sublimation at 210° (0.03 mm.); yield, 91 mg.

Anal. Calcd. for $C_5H_4ClN_5O$: C, 32.4; H, 2.17; N, 37.7. Found: C, 32.2; H, 2.22; N, 37.3.

5-Amino-4-chloro-6-(1-methylhydrazino)pyrimidine (VII).

A.—Into 140 ml. of an absolute ethanolic solution containing 8 g. (0.049 mole) of 5-amino-4,6-dichloropyrimidine was pipetted, with stirring, 6.4 ml. (0.13 mole) of methylhydrazine. After refluxing for 2 hr., the pale yellow solution was cooled, whereupon needle-like crystals appeared. These were filtered, washed with a little ethanol, and recrystallized from approximately 500 ml. of boiling water. After 2 to 3 hr. of refrigeration, 7.5 g. (89%) of well formed, white needles were collected and air-dried; m.p. 206–208° (lit.[4] m.p. 203–204°).

B.—One gram (0.0061 mole) of 5-amino-4,6-dichloropyrimidine was dissolved in 18 ml. of absolute ethanol contained in a flask fitted with a reflux condenser and magnetic stirrer. A solution of 1.2 ml. of 1,1-dimethylhydrazine in an equal volume of absolute ethanol was added, with stirring, to the refluxing solution. The mixture was maintained at reflux for 5 hr., during which time it changed from a yellow to a red color. Upon cooling, crystallization occurred. Recrystallization of the product from water yielded 400 mg. (38%) of 5-amino-4-chloro-6-(1-methylhydrazino)pyrimidine. A positive reaction with pentacyanoaminoferroate[18] established the presence of the $-N(CH_3)-NH_2$ substituent.

The infrared spectra of the samples prepared by methods A and B were identical.

Anal. Calcd. for $C_5H_8ClN_5$: C, 34.6; H, 4.65. Found: C, 34.8; H, 4.68.

5-Chloro-1,2,3,4-tetrahydro-1-methyl-3-oxopyrimido[5,4-*e*]-*as*-triazine (VI).—To a solution of 1.2 ml. of concentrated hydrochloric acid in 4.5 ml. of water was added 2 g. (0.011 mole) of 5-amino-4-chloro-6-(1-methylhydrazino)pyrimidine. Phosgene gas was then bubbled through the solution; a heavy white precipitate soon began to form. After approximately 25 min. the unchanged phosgene was flushed out of the system with nitrogen gas, and the precipitate was collected, washed well with water, and dried. The dry material (1.1 g.) was recrystallized from 50 ml. of hot N,N-dimethylformamide. The yield of the light gray material, which appears to be a very fluffy mat of tiny needles, was 0.9 g. (39.4%). A sample was purified for analysis by the sublimation technique described for III, yielding a white sublimate. On the melting point block, darkening commenced at about 295° and slowly progressed until the temperature reached 320°.

Anal. Calcd. for $C_6H_6ClN_5O$: C, 36.1; H, 3.03; N, 35.1. Found: C, 36.1; H, 3.18; N, 35.2.

6-Chloropurin-8-ol (VIII).—4,5-Diamino-6-chloropyrimidine[6] (4.0 g., 0.028 mole) was added to 240 ml. of 6% sodium hydroxide solution contained in a 500-ml. three-necked flask fitted with inlet and outlet tubes for delivery of phosgene gas, a magnetic stirrer, and a pressure-equalizing separatory funnel. Phosgene was then bubbled through the mixture. After about 2 hr., an additional 100 ml. of 6% sodium hydroxide solution was added through the separatory funnel. At the end of another hour, the flow of phosgene was interrupted and the pale yellow precipitate which had formed during the reaction was separated by filtration from the acidic filtrate. After refrigeration a small second crop of crystals was obtained from the filtrate. The combined crops, weighing 2.8 g., were triturated with approximately 30 ml. of dilute sodium hydroxide solution, and the insoluble starting material was removed by filtration. Acidification of the filtrate reprecipitated the 6-chloropurin-8-ol. This procedure was repeated again to ensure that all of the starting material was removed from the product. The yield of VIII was 1.5 g. (31.8%), m.p. 322° dec. A small portion of VIII was sublimed for analysis. The total recovery of starting material (from purification of the crude product and neutralization of the acidic filtrate from the reaction mixture) was 1.7 g. (42.5%).

Anal. Calcd. for $C_5H_3ClN_4O$: C, 35.2; H, 1.77; N, 32.8. Found: C, 35.0; H, 1.80; N, 32.6.

9-Amino-6-chloropurine-8-thiol (IX).—5-Amino-4-chloro-6-hydrazinopyrimidine (4 g., 0.025 mole) was partially dissolved in 60 ml. of water containing 2.2 ml. of concentrated hydrochloric acid. To this mixture 4 ml. (0.0525 mole) of thiophosgene was added dropwise, with stirring, over a period of 35–40 min. After an additional 10 min. of stirring, the brown precipitate which formed was collected, washed well with ether to remove unchanged thiophosgene, and dried. Sublimation of the crude product at 210° (0.03 mm.) was a very slow process, requiring 2 days. A very light and fluffy residue, which tended to fly up onto the sublimate, probably as a result of degassing, necessitated the use of a 3-foot sublimation tube. Increasing the vacuum very gradually helped to reduce the degassing problem. The yield of sublimed product was 1.12 g. (22.2%). 9-Amino-6-chloropurine-8-thiol is a pale yellow, crystalline material, m.p. 280–290° dec.

Anal. Calcd. for $C_5H_4ClN_5S$: C, 29.8; H, 2.00; N, 34.7. Found: C, 29.7; H, 2.14; N, 34.2.

4,6-Dihydrazino-5-nitropyrimidine (XI).—**A.** 4,6-Dimethoxy-5-nitropyrimidine (X) was prepared by the method of Rose and Brown.[19] A warm solution of 2 g. (0.011 mole) of X in approximately 130 ml. of absolute ethanol was added portionwise to approximately 5 ml. of an ethanolic solution containing 1.4 g. (0.44 mole) of anhydrous hydrazine; a bright yellow solid immediately precipitated. The mixture was stirred for 1 hr. under gentle reflux, cooled, and filtered to yield 1.94 g. (97%) of XI, m.p. 202–203.5° dec.

Anal. Calcd. for $C_4H_7N_7O_2$: C, 26.0; H, 3.81; N, 53.0. Found: C, 25.7; H, 3.87; N, 52.6.

This material exploded violently in the combustion tube during carbon–hydrogen analyses. In order to obtain valid analytical results, it was necessary to mix the sample with an inert diluent (ignited Celite was used) and to use an oversized combustion boat.

B.—A solution of 2 g. (0.0106 mole) of 4-chloro-6-methoxy-5-nitropyrimidine[14] in 60 ml. of absolute ethanol was added dropwise, with stirring, to 5 ml. of an ethanolic solution containing 1.36 g. (0.042 mole) of anhydrous hydrazine; a heavy, orange precipitate formed immediately. After refluxing for 1 hr., the mixture was cooled and the precipitate collected. Recrystallization from approximately 200 parts of water yielded 1.48 g. (76%) of yellow-orange, needle-like crystals. The product was shown by infrared spectral analysis to be identical to that obtained by procedure A.

C.—One gram (0.0052 mole) of 4,6-dichloro-5-nitropyrimidine (I), prepared by the method of Boon, *et al.*,[2] was dissolved in 65 ml. of absolute ethanol. This solution was then added dropwise, with stirring, to a solution of 0.72 g. (0.022 mole) of hydrazine in 1 ml. of ethanol. After refluxing for 1 hr. the mixture was cooled, and the orange solid which formed was collected by filtration. This solid was suspended in approximately 150 parts of boiling water, and the brown, insoluble portion was removed by filtration from the hot solution. The clear filtrate was found to have a pH of 4.1. The solution was brought to pH 6 by the addition of 0.02 *N* sodium hydroxide solution, whereupon the formation of tiny, needle-like crystals was observed. At this point the solution was again brought to an incipient boil, and a small amount of undissolved material was removed by filtration. Upon cooling, the filtrate yielded 0.31 g. (32.5%) of long, red, needle-like crystals of 4,6-dihydrazino-5-nitropyrimidine. The identity of the compound was confirmed by elemental analysis and by its infrared spectrum.

The brown, insoluble material obtained was very intractable. Carbon–hydrogen analysis showed it to contain 29.9% C and 2.77% H. The infrared spectrum exhibited only very diffuse peaks. This material is probably polymeric in nature.

5-Amino-4,6-dimethoxypyrimidine (XII).—Three grams (0.016 mole) of 4,6-dimethoxy-5-nitropyrimidine[19] was dissolved in approximately 180 ml. of hot absolute ethanol, and to this solution was added approximately 2 g. (wet weight) of Raney nickel catalyst. The mixture was then shaken under an initial pressure of 20 p.s.i. of hydrogen for 2 hr. During this period the mixture was kept warm by directing the rays from an infrared lamp on the reaction bottle. At the conclusion of the shaking period, a theoretical quantity of hydrogen had been absorbed. The hydrogenation mixture was heated to an incipient boil and the catalyst removed by filtration from the hot solution. Evaporation of the clear, colorless filtrate with the aid of a hot air fan yielded 2.4 g. of crude material. This was recrystallized from 25 ml. of heptane to yield 1.9 g. (76%) of thick, off-white, needle-like crystals, m.p. 95–96° (accompanied by sublimation). The product had a pronounced odor resembling that of licorice. A small amount of material was sublimed for analysis.

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.4; H, 5.85; N, 27.1. Found: C, 46.6; H, 6.03; N, 27.0.

Product(s) of the Reaction of Methylhydrazine with 4,6-Dimethoxy-5-nitropyrimidine.—A hot solution of 4,6-dimethoxy-5-nitropyrimidine (1 g., 0.0054 mole) in 65 ml. of 1-butanol was added, with stirring, to a solution of 1.1 ml. (0.021 mole) of methylhydrazine in 5 ml. of 1-butanol. The mixture was then refluxed with stirring for 3 hr., during which time it turned to a bright yellow color. Toward the end of the reflux period, a fine, solid material began to precipitate. After a night in the deep-freeze, crude XIV (150 mg.) was removed by filtration from the cold reaction mixture and recrystallized from water. The product consists of very tiny, yellow-tan, needle-like crystals, m.p. 240–260° dec.

Anal. Calcd. for $C_{10}H_{16}N_{10}O_3$: C, 37.1; H, 4.95; N, 43.3. Found: C, 37.0; H, 4.95; N, 43.4.

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(19) F. L. Rose and D. J. Brown, *J. Chem. Soc.*, 1953 (1956).