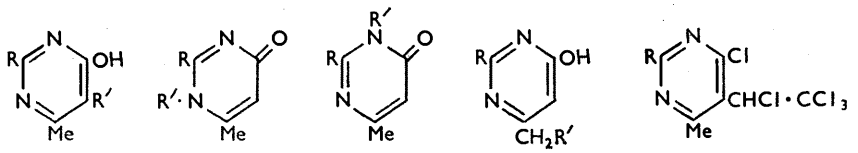
976. *Pyrimidines. Part II.* The Synthesis and Some Reactions of Pyrimidine-5-aldehydes.*

By R. Hull.

Some 4-hydroxypyrimidines react with chloral to give 4-hydroxy-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidines which can be hydrolysed to 4-hydroxypyrimidine-5-aldehydes. The Reimer–Tiemann aldehyde synthesis has also been applied to some 4-hydroxypyrimidines. Pyrimidines, containing electron-releasing groups, are described in which the above reactions either failed or gave other products. Some reactions of 2-amino-4-hydroxy-6-methylpyrimidine-5-aldehydes are also reported.

Pyrimidine-aldehydes have been previously suggested as a fruitful field for biological investigation, but possibly owing to the difficulty of synthesis no extensive work on them has been reported.

Pyrimidine-4-aldehydes have been prepared by Johnson and his co-workers [1] from aliphatic intermediates, and by Japanese workers [2] by ozonolysis of styrylpyrimidines. King and King [3] obtained a derivative of a pyrimidine-2-aldehyde after nitrosation of 4 : 6-dihydroxy-2-methylpyrimidine. Delépine [4] reported the formation of 4-amino-2-methylpyrimidine-5-aldehyde on reduction of the corresponding 5-cyanopyrimidine, and Price, May, and Pickel,[5] using McFadyen and Stevens's method,[6] converted the same cyano-compound into the 5-aldehyde. A derivative of 5-formylbarbituric acid has been



(I) (II) (III) (IV) (V)

synthesised by Ridi and Papini [7] from barbituric acid and diphenylformamidine. The present paper describes two methods [8] for the preparation of pyrimidine-5-aldehydes.

Method I.—Reaction of chloral with tertiary arylamines [9] and with phenols [10] yields addition products which decompose on alkaline hydrolysis to amino- and hydroxy-aldehydes respectively. It has now been found that a similar reaction takes place between chloral and some 4-hydroxypyrimidines. Reaction of chloral with 4-hydroxy-6-methyl-2-piperidinopyrimidine (I; R = piperidino, R′ = H) could yield, theoretically, four products [I—IV; R = piperidino, R′ = $CH(OH)\cdot CCl_3$] because chloral reacts with amides [11] and with activated methyl groups attached to heterocyclic rings.[12] The product

* Part I, *J.*, 1956, 2033.

[1] Johnson and Cretcher, *J. Amer. Chem. Soc.*, 1915, **37**, 2144; Johnson and Cretcher, *J. Biol. Chem.* 1916, **26**, 99; Johnson and Mikeska, *J. Amer. Chem. Soc.*, 1919, **41**, 810; Johnson, *ibid.*, 1929, **51**, 1274; Johnson and Schroeder, *ibid.*, 1931, **53**, 1989.

[2] Kondo and Yanai, *J. Pharm. Soc. Japan*, 1937, **57**, 747; Ochiai and Yanai, *ibid.*, 1938, **58**, 397.

[3] King and King, *J.*, 1947, 943.

[4] Delépine, *Compt. rend.*, 1938, **206**, 865; *Bull. Soc. chim. France*, 1938, **5**, 1539; Delépine and Jensen, *ibid.*, 1939, **6**, 1663.

[5] Price, May, and Pickel, *J. Amer. Chem. Soc.*, 1940, **62**, 2818.

[6] McFadyen and Stevens, *J.*, 1936, 584.

[7] Ridi and Papini, *Gazzetta*, 1946, **76**, 376.

[8] B.P. specifn. 741,667.

[9] Panly and Schanz, *Ber.*, 1923, **56**, 979; G.P. 475,918, 598,652; F.P. 791,818; Valvet and Mejuto, *Anales Fis. Quim.*, 1936, **34**, 641; Meldrum and Lonkar, *J. Univ. Bombay*, 1937, **6**, 116; Balfe and Webber, *J.*, 1942, 718.

[10] Boessneck, *Ber.*, 1885, **18**, 1516; 1886, **19**, 365; Knofler and Boessneck, *ibid.*, 1887, **20**, 3193; G.P. 61,551; Ettel and Weichet, *Coll. Czech. Chem. Comm.*, 1949, **14**, 747.

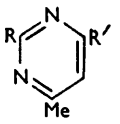
[11] Chattaway and James, *J.*, 1943, 109.

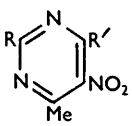
[12] Einhorn, *Ber.*, 1886, **19**, 904; *Annalen*, 1891, **265**, 208; Ettel, Weichet, and Chyba, *Coll. Czech. Chem. Comm.*, 1950, **15**, 528.

was soluble in alkali. The nitropyrimidine (I; R = piperidino, R′ = NO_2) did not react with chloral: formulæ (II—IV) may therefore be discounted. Subsequent alkaline hydrolysis of the product thus shown to have structure [I; R = piperidino, R′ = $CH(OH)\cdot CCl_3$] gave 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde in good yield. Reactions of the compound are described below; they are typical of aromatic aldehydes, and are in agreement with the structure proposed.

Chloral was caused to react with other pyrimidines (I; R = NH_2, NHMe, or NMe_2, R′ = H), and the addition products [R′ = $CH(OH)\cdot CCl_3$] were hydrolysed to the aldehydes (R′ = CHO). In most cases it was advantageous, in the addition reaction, to add pyridine as a solvent and possible catalyst. Attempted purification of the amino-compound [I; R = NH_2, R′ = $CH(OH)\cdot CCl_3$] by dissolution in cold aqueous alkali with subsequent reprecipitation by acid gave a substance $C_7H_9O_3N_3Cl_2$, indicating a formula [I; R = NH_2, R′ = $CH(OH)\cdot CCl_2\cdot OH$ or R′ = $CH{-}CCl_2,H_2O$]. 

(VI); R = N<[CH₂]₅
(VII); R′ = Cl
(VIII); R′ = SMe

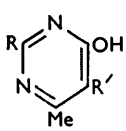




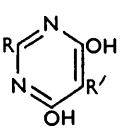
(IX)

Treatment of the piperidino-compound [I; R′ = $CH(OH)\cdot CCl_3$] with phosphoryl chloride gave the pentahalogenated derivative (V).

"Abnormal" Reactions of Chloral with Pyrimidines.—The aminopyrimidines (VI; R′ = NH_2; VII, VIII; R = NH_2) were recovered on alkaline hydrolysis from their chloral addition products, whose structures are tentatively given as [VI—VIII; R′ = R = $NH\cdot CH(OH)\cdot CCl_3$ respectively]. Chloral and the aminochloropyrimidine (IX; R = NH_2, R′ = Cl) were re-formed at the melting point of the addition product, probably [IX; R = $NH\cdot CH(OH)\cdot CCl_3$, R′ = Cl]. The corresponding aminohydroxypyrimidine (IX; R =



(X)



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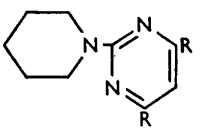

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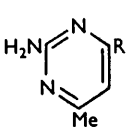

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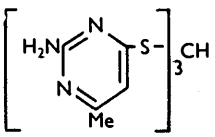
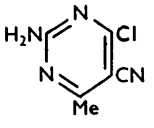


(XIV)

NH_2, R′ = OH) did not react with chloral. The addition products [X and XI; R = $CH_2\cdot CH(OH)\cdot CCl_3$, R′ = $CH(OH)\cdot CCl_3$] which resulted from the corresponding hydroxy-methylpyrimidines (X and XI; R = Me, R′ = H) with chloral gave, on hydrolysis, water-soluble products from which no pyrimidine-aldehydes could be isolated. The activity of the 2-methyl group was further exemplified by the addition product [XI; R = $CH_2\cdot CH(OH)\cdot CCl_3$, R′ = NO_2] which was obtained from the 2-methyl-5-nitro-pyrimidine (XI; R = Me, R′ = NO_2) and chloral.

The addition product [XI; R = Ph, R′ = $CH(OH)\cdot CCl_3$], obtained from the hydroxy-



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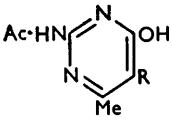

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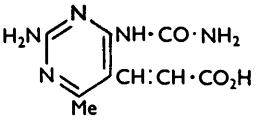

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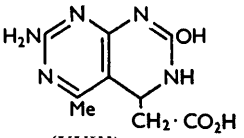


(XVIII)

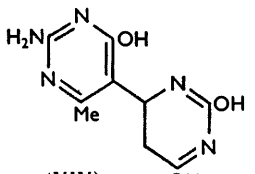
phenylpyrimidine (XI; R = Ph, R′ = H) and chloral, gave, on hydrolysis, an unidentified acid $C_{13}H_{10}O_4N_2$, which failed to react with dinitrophenylhydrazine.

It was not possible to isolate addition products from the pyrimidines (XII; R = H or Me) and chloral.

Method II.—The Reimer–Tiemann synthesis of phenolic aldehydes has now been successfully applied to a number of hydroxypyrimidines: the hydroxypyrimidines (I; R = NH_2, NHMe, or NMe_2, R′ = H), (X; R = OH, R′ = H), and (XI; R = piperidino or Ph, R′ = H) gave the corresponding pyrimidine-aldehydes (R′ = CHO).

The behaviour of pyrimidines having other electron-releasing groups was then investigated. The aminopyrimidines (XIII; R = NH_2 or SMe) did not yield aldehydes; the analogous mercapto-compound gave the trisubstituted methane (XIV); thiophenol and its *p*-chloro- and *p*-methyl derivative [13] undergo a similar type of reaction.

Some Reactions of 2-Amino-4-hydroxy-6-methylpyrimidine-5-aldehyde (I; R = NH_2, R′ = CHO).—This compound gave the usual ketonic derivatives and with permanganate yielded the 5-carboxylic acid. Attempts to prepare the 4-chloropyrimidine by treatment with phosphoryl chloride failed, as did experiments using the 2-acetamido-aldehyde.[14] However, the aldehyde oxime reacted normally with phosphoryl chloride and yielded the chloro-nitrile (XV). Dehydration of the oxime was also effected by acetic anhydride, which gave the nitrile (XVI; R = CN).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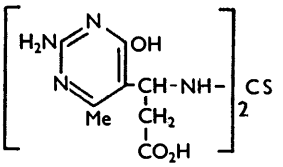
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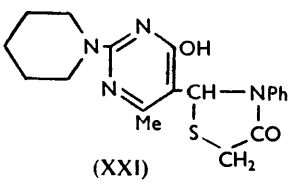
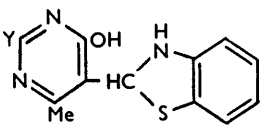

(XXI)

Possibly because of the insolubility of the aldehyde in common organic solvents, attempts to synthesise the pyrimidylacrylic acid by condensation with malonic acid were unsuccessful. Urea has been suggested as a versatile solvent.[15] With urea as " solvent," and under Knoevenagel conditions, a compound $C_9H_{11}O_3N_5$ was obtained. Potentiometric analysis indicated three acidic centres and absence of a true carboxylic group. If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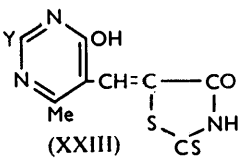
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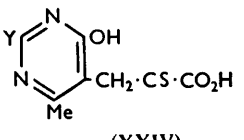
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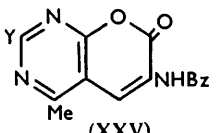
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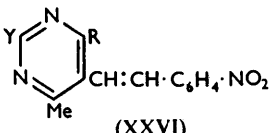
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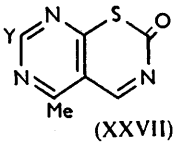
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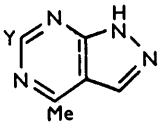
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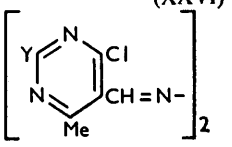
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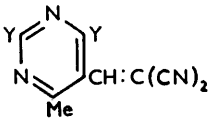
(XXX)

Y = piperidino

the acrylic acid had been formed as an intermediate, formulæ (XVII—XIX) are possible for the product of its reaction with urea. Since cinnamic acid with urea yields the 4 : 5-dihydro-2 : 6-hydroxy-4-phenylpyrimidine, the analogous structure (XIX) seems the most probable. The other two possibilities (XVII and XVIII) may be excluded since they

[13] Gabriel, *Ber.*, 1877, **10**, 185.
[14] Hull, Lovell, Openshaw, and Todd, *J.*, 1947, 41.
[15] Clark, *Nature*, 1951, **168**, 876.

both contain a carboxyl group, and, in a further experiment, 2-amino-4-hydroxy-6-methylpyrimidine (I; R = NH_2, R′ = H) was recovered unchanged under similar reaction conditions with urea.

Treatment of the aldehyde (I; R = NH_2, R′ = CHO) with malonic acid and thiourea gave an acid, believed to have structure (XX).

Some Reactions of 4-*Hydroxy*-6-*methyl*-2-*piperidinopyrimidine*-5-*aldehyde* (I; R = piperidino, R′ = CHO).—Treatment of this aldehyde with aniline, *NN*-dimethyl-*p*-phenylenediamine, hydroxylamine, (methylthio)thiocarbonylhydrazine,[17] and thiosemicarbazide readily yielded the expected products, and hydrazine gave the azine.

The Schiff base formed with aniline was converted by reaction with thioglycollic acid [18] into the thiazolidone (XXI), and with nitromethane (unlike benzylideneaniline which gave a bimolecular product [19]) it gave the 5-nitrovinylpyrimidine identical with the product obtained directly from the aldehyde and nitromethane.

The chloro-nitrile analogous to (XV) was obtained, either by treatment of the oxime with phosphoryl chloride, or by dehydration of the oxime with acetic anhydride to the hydroxy-nitrile (cf. XVI) followed by treatment with phosphoryl chloride. Hydrolysis of the hydroxy-nitrile with sulphuric acid at 100° gave the amide.

With acetophenone and malonic acid the aldehyde gave the chalcone and the pyrimid-5-ylacrylic acid respectively. Condensation with *o*-aminothiophenol was also smooth and gave the thiazoline (XXII). The product (XXIII), obtained by reaction with rhodanine, gave, on alkaline hydrolysis, the acid (XXIV). Hippuric acid yielded the expected azlactone, attempted hydrolysis of which with hot dilute sodium hydroxide solution gave, on acidification, an isomeric colourless compound believed to be the lactone (XXV). *p*-Nitrophenylacetic acid afforded the nitrostilbene (XXVI; R = OH) which was converted *via* the chloropyrimidine (XXVI; R = Cl) into the amine (XXVI; R = NH_2).

Conversion of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde into a compound containing a second reactive group was accomplished by conversion of the 4-hydroxyl group into a chloro-substituent by treatment with phosphoryl chloride in the cold. Treatment of this chloro-aldehyde with thiourea gave the thiazone (XXVII), with elimination of ammonia. Replacement of chlorine and condensation took place with hydrazine hydrate which gave the tetra-azaindene (XXVIII); hydrazine sulphate, however, yielded the chloro-azine (XXIX). The chloro-aldehyde with malononitrile under Knoevenagel conditions gave the dinitrile (XXX), replacement of the chlorine atom taking place with the catalyst (piperidine). Replacement of the chlorine atom, with retention of the aldehyde group, took place with piperidine alone, which yielded 4-methyl-2 : 6-dipiperidinopyrimidine-5-aldehyde; with potassium thiocyanate it gave the thiocyanato-, and with methanethiol the methylthio-pyrimidine subsequent treatment of which with hydrazine gave the azine.

Experimental

4-*Hydroxy*-6-*methyl*-2-*piperidino*-5-(2 : 2 : 2-*trichloro*-1-*hydroxyethyl*)*pyrimidine*.—(*a*) 4-Hydroxy-6-methyl-2-piperidinopyrimidine (116·5 g.), chloral (98·5 g.), and pyridine (91 ml.) were heated on a steam-bath during 2 hr. Next morning, the crude *product* [153 g.; m. p. 218° (decomp.)] obtained by the addition of water gave colourless needles, m. p. 230° (decomp.), from 2-ethoxyethanol (Found: C, 42·5; H, 4·55; N, 12·25. $C_{12}H_{16}O_2N_3Cl_3$ requires C, 42·3; H, 4·7; N, 12·3%). (*b*) 4-Hydroxy-6-methyl-2-piperidinopyrimidine (1·7 g.) and chloral (3 ml.) were heated with stirring on a steam-bath during 15 min. Water was added to the cooled mixture, and the crude product (2·6 g.) collected. The product, identical with the above, crystallised from 2-ethoxyethanol.

4-*Hydroxy*-6-*methyl*-2-*piperidinopyrimidine*-5-*aldehyde*.—Potassium hydroxide (154 g.) in

[16] Fisher and Roeder, *Ber.*, 1901, **34**, 3762; Evans and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 5001.
[17] Busch, *J. prakt. Chem.*, 1916, **93**, 60.
[18] Surrey, *J. Amer. Chem. Soc.*, 1947, **69**, 2911; 1948, **70**, 4262.
[19] Hurd and Strong, *J. Amer. Chem. Soc.*, 1950, **72**, 4813.

water (100 ml.) and alcohol (700 ml.) was added to a suspension of 4-hydroxy-6-methyl-2-piperidino-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidine (100 g.) in warm alcohol (1·1 l.). The mixture was heated on a steam-bath for 30 min. and the potassium derivative which had separated was collected and dissolved in water (4 l.). The solution was filtered from a small quantity of insoluble material, and the *aldehyde* (55 g.) was precipitated by acetic acid. It crystallised from alcohol in pale yellow plates, m. p. 235° (Found: C, 59·6; H, 6·9; N, 18·65. $C_{11}H_{15}O_2N_3$ requires C, 59·7; H, 6·8; N, 19·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from 2-ethoxyethanol in orange needles, m. p. >300° (Found: C, 50·95; H, 4·75; N, 23·8. $C_{17}H_{19}O_5N_7$ requires C, 50·9; H, 4·75; N, 24·4%).

2-*Dimethylamino*-4-*hydroxy*-6-*methyl*-5-(2 : 2 : 2-*trichloro*-1-*hydroxyethyl*)*pyrimidine*.—A mixture of 2-dimethylamino-4-hydroxy-6-methylpyrimidine (2·9 g.), chloral (3·1 g.), and pyridine (3 ml.) was heated on a steam-bath during 2 hr. and worked up in the usual manner. Recrystallisation of the crude material (6·0 g.) from 2-ethoxyethanol gave the *product* as colourless needles, m. p. 221—222° (decomp.) (Found: C, 36·0; H, 4·1; N, 14·15. $C_9H_{12}O_2N_3Cl_3$ requires C, 35·95; H, 4·0; N, 14·0%).

2-*Dimethylamino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Potassium hydroxide (3·85 g.) in water (2·5 ml.) and alcohol (18 ml.) was added to a suspension of 2-dimethylamino-4-hydroxy-6-methyl-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidine (2·1 g.) in warm alcohol (28 ml.). Working up by the usual procedure gave the *aldehyde* (1·2 g.) which crystallised from 2-ethoxyethanol as colourless needles, m. p. >300° (Found: C, 53·55; H, 6·25; N, 23·2. $C_8H_{11}O_2N_3$ requires C, 53·05; H, 6·1; N, 23·2%).

4-*Hydroxy*-6-*methyl*-2-*methylamino*-5-(2 : 2 : 2-*trichloro*-1-*hydroxyethyl*)*pyrimidine*.—Prepared from 4-hydroxy-6-methyl-2-methylaminopyrimidine (2·78 g.), chloral (3·25 g.) and pyridine (3·0 ml.), the *compound* (4·4 g.) crystallised from aqueous 2-ethoxyethanol in colourless plates, m. p. 202° (decomp.) (Found: C, 33·9; H, 3·5; N, 14·4. $C_8H_{10}O_2N_3Cl_3$ requires C, 33·5; H, 3·5; N, 14·6%).

4-*Hydroxy*-6-*methyl*-2-*methylaminopyrimidine*-5-*aldehyde*.—4-Hydroxy-6-methyl-2-methylamino-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidine (2·86 g.) in warm alcohol (20 ml.) was added to potassium hydroxide (2·8 g.) in water (10 ml.) and alcohol (15 ml.), and heated on a steam-bath for 2 hr. Excess of reagent was removed under diminished pressure, the residue dissolved in water (20 ml.) and filtered from insoluble material, and the *aldehyde* (0·95 g.) precipitated by acetic acid. It crystallised from 2-ethoxyethanol in colourless needles, m. p. 290° (decomp.) (Found: C, 50·6; H, 5·6; N, 25·5. $C_7H_9O_2N_3$ requires C, 50·3; H, 5·4; N, 25·2%).

2-*Amino*-4-*hydroxy*-6-*methyl*-5-(2 : 2 : 2-*trichloro*-1-*hydroxyethyl*)*pyrimidine*.—Prepared from 2-amino-4-hydroxy-6-methylpyrimidine (5·0 g.), chloral (6·5 g.), and pyridine (8·0 ml.), the *compound* [8·2 g.; m. p. 185—190° (decomp.)] crystallised from aqueous 2-ethoxyethanol in colourless prismatic needles, m. p. 192—194° (decomp.) (Found: N, 15·2; Cl, 39·3. $C_7H_8O_2N_3Cl_3$ requires N, 15·4; Cl, 39·1%). The crude product was dissolved in alkali and extracted with ether. Addition of acetic acid precipitated a *substance* which dried as an amorphous powder, m. p. >300° (Found: N, 16·95; Cl, 28·55. $C_7H_9O_3N_3Cl_2$ requires N, 16·6; Cl, 28·05%).

2-*Amino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Potassium hydroxide (38·5 g.) in water (25 ml.) was diluted with alcohol (180 ml.) and added to a slurry of 2-amino-4-hydroxy-6-methyl-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidine (20 g.) in warm alcohol (280 ml.) and heated on a steam-bath for 2 hr. The solid was collected and combined with the residue left after evaporation of the solvent from the filtrate. The combined solids were treated with warm water (150 ml.), filtered from insoluble material, and acidified to pH 6 with hydrochloric acid. The *compound* (12 g.; m. p. 263°) was collected and purified from a small quantity of water. It dried as a pale yellow amorphous powder, m. p. 269—270° (decomp.) (Found: C, 44·65; H, 5·5; N, 25·65. $C_6H_7O_2N_3,0{\cdot}5H_2O$ requires C, 44·4; H, 5·0; N, 25·9%).

The semicarbazone hydrochloride (see below) had m. p. 242° (decomp.), undepressed on admixture with the semicarbazone hydrochloride prepared from the aldehyde obtained by the Reimer–Tiemann method.

4-*Chloro*-6-*methyl*-2-*piperidino*-5-(1 : 2 : 2 : 2-*tetrachloroethyl*)*pyrimidine*.—4-Hydroxy-6-methyl-2-piperidino-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)pyrimidine (4·4 g.) was heated at 100° with phosphoryl chloride (20 ml.) during 10 min. and next morning added to ice. The precipitate (2·75 g.) was collected and washed with water. Crystallisation from alcohol gave

the *product* as colourless prismatic needles, m. p. 115° (Found: C, 38·35; H, 3·85; Cl, 48·0. $C_{12}H_{14}N_3Cl_5$ requires C, 38·15; H, 3·7; Cl, 47·05%).

4-Amino-6-methyl-2-piperidinopyrimidine.—4-Chloro-6-methyl-2-piperidinopyrimidine [20] (50 g.) was heated in an autoclave with alcoholic ammonia (1 l., saturated at 10°) at 150° during 14 hr. After evaporation the resulting mixture was treated with sodium hydroxide and ether-extracted, and the extract evaporated. The residue (20 g.; m. p. 129°), after being washed with light petroleum, crystallised from benzene–light petroleum (b. p. 60—80°) and gave the *aminopyrimidine* as colourless prisms, m. p. 137—138° (Found: C, 62·8; H, 8·75; N, 28·65. $C_{10}H_{16}N_4$ requires C, 62·5; H, 8·35; N, 29·15%).

6-Methyl-2-piperidino-4-(2 : 2 : 2-trichloro-1-hydroxyethylamino)pyrimidine.—Prepared from the above aminopyrimidine (0·85 g.), chloral (0·78 g.), and pyridine (1·0 ml.) the *compound* (1·25 g.) crystallised from benzene in colourless prisms, m. p. 147—148° (Found: N, 16·05; Cl, 31·8. $C_{12}H_{17}ON_4Cl_3$ requires N, 16·5; Cl, 31·4%).

Potassium hydroxide (0·92 g.) in water (0·6 ml.) and alcohol (5 ml.) was added to a hot solution of this product (0·6 g.) in alcohol (4·2 ml.) and the whole heated on a steam-bath for 10 min. The mixture was evaporated under diminished pressure and the residue extracted with hot benzene, then evaporated to a small volume, and light petroleum was added. The compound was collected and was crystallised from aqueous alcohol, to give 4-amino-6-methyl-2-piperidinopyrimidine, m. p. 132° (Found: C, 62·5; H, 8·2; N, 28·5. Calc. for $C_{10}H_{16}N_4$: C, 62·5; H, 8·35; N, 29·15%).

4-Chloro-6-methyl-2-(2 : 2 : 2-trichloro-1-hydroxyethylamino)pyrimidine.—2-Amino-4-chloro-6-methylpyrimidine (2·0 g.) and chloral (6·0 ml.) were heated together on a steam-bath during 2 hr., then cooled; water was added and the solid (3·9 g.) collected and washed with water. Recrystallisation from alcohol gave the *product* as colourless prismatic needles, m. p. 160—161° (Found: C, 29·1; H, 3·0; Cl, 49·1. $C_7H_7ON_3Cl_4$ requires C, 28·9; H, 2·4; Cl, 48·8%).

Potassium hydroxide (0·385 g.) in water (0·5 ml.) and alcohol (5 ml.) was added to a suspension of this product (1·0 g.) in alcohol (20 ml.). A solution was formed from which colourless needles (0·65 g.) of 2-amino-4-chloro-6-methylpyrimidine were precipitated (m. p. and mixed m. p. 182°).

4-Methyl-6-methylthio-2-(2 : 2 : 2-trichloro-1-hydroxyethylamino)pyrimidine.—Prepared from 2-amino-4-methyl-6-methylthiopyrimidine [21] (1·0 g.) and chloral (2·0 ml.), the *compound* (1·9 g.) crystallised from aqueous methanol as colourless prisms, m. p. 150—152° (Found: C, 32·3; H, 3·2; N, 13·8; Cl, 36·2. $C_8H_{10}ON_3Cl_3S$ requires C, 31·75; H, 3·3; N, 13·9; Cl, 35·2%).

This product (1·75 g.) was heated with potassium hydroxide (0·65 g.) in water (0·5 ml.) and alcohol (15 ml.) on a steam-bath for 20 min. After evaporation to dryness and washing with water the solid (0·7 g.) gave, on crystallisation from methanol, 2-amino-4-methyl-6-methylthiopyrimidine as light brown hexagonal prisms, m. p. 155° (Found: C, 46·3; H, 5·6; N, 27·6. Calc. for $C_6H_9N_3S$: C, 46·45; H, 5·8; N, 27·1%).

Reaction of Chloral with 2-Amino-4-chloro-6-methyl-5-nitropyrimidine.—A mixture of chloral (11 ml.) and 2-amino-4-chloro-6-methyl-5-nitropyrimidine (5·6 g.) was heated on a steam-bath during 2 hr., cooled, and treated with water. After 2 days the solid was collected. Crystallisation from aqueous alcohol (carbon) gave the product (4·2 g.) as colourless prismatic needles (Found: Cl, 41·5. $C_7H_6O_3N_4Cl_4$ requires Cl, 42·25%). The substance, which was probably *4-chloro-6-methyl-5-nitro-2-(2 : 2 : 2-trichloro-1-hydroxyethylamino)pyrimidine*, melted and resolidified at 130°, giving off chloral, finally melting at 219° alone or mixed with 2-amino-4-chloro-6-methyl-5-nitropyrimidine.

4-Hydroxy-6-methyl-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)-2-(3 : 3 : 3-trichloro-2-hydroxypropyl)-pyrimidine.—4-Hydroxy-2 : 6-dimethylpyrimidine [22] (10·0 g.), chloral (15·0 g.), and pyridine (10 ml.) were caused to react and worked up in the usual way. The *product* (6·6 g.) was purified for analysis by dissolution in 2-ethoxyethanol, filtration, and addition of water to incipient precipitation, which gave a colourless amorphous powder, m. p. 177° (decomp.) (Found: C, 28·6; H, 2·55; N, 6·85; Cl, 50·8. $C_{10}H_{10}O_3N_2Cl_6$ requires C, 28·65; H, 2·4; N, 6·7; Cl, 50·8%).

4 : 6-Dihydroxy-5-(2 : 2 : 2-trichloro-1-hydroxyethyl)-2-(3 : 3 : 3-trichloro-2-hydroxypropyl)pyrimidine.—Pyridine (8·0 ml.) was added slowly to 4 : 6-dihydroxy-2-methylpyrimidine (2·5 g.)

[20] Hull, Lovell, Openshaw, Payman, and Todd, *J.*, 1946, 357.
[21] Backer and Grevenstuk, *Rec. Trav. chim.*, 1942, **61**, 291.
[22] Pinner, *Ber.*, 1889, **22**, 1616.

and chloral (6·5 g.), and the mixture was heated on a water-bath for 3 hr. Water was added to the cooled mixture. After 7 days, the solid (4·1 g.) was collected. Purification by extraction with hot alcohol and addition of water to incipient precipitation gave the *product*, which dried as a light brown amorphous powder, m. p. >300° (Found: N, 7·1; Cl, 48·8. $C_8H_8O_4N_2Cl_6$ requires N, 6·7; Cl, 50·6%).

4 : 6-*Dihydroxy*-5-*nitro*-2-(3 : 3 : 3-*trichloro*-2-*hydroxypropyl*)*pyrimidine*.—4 : 6-Dihydroxy-2-methyl-5-nitropyrimidine [23] (1·7 g.), chloral (1·77 g.), and pyridine (3·0 ml.) were heated on a steam-bath during 2 hr., then cooled. Water was added and the solution was decanted from a little unchanged starting material. 5N-Sodium hydroxide (4 ml.) was added, and the solution was extracted with ether. The aqueous layer was acidified with hydrochloric acid (cooling), and, after 2 days, the solid (1·8 g.) was collected. The *pyrimidine* [m. p. 205—210° (decomp.) (inserted at 200°)] was obtained as light brown prismatic needles by adding boiling water to an alcoholic extract of the crude product (Found: C, 25·5; H, 2·45; N, 12·35. $C_7H_6O_5N_3Cl_3,H_2O$ requires C, 25·0; H, 2·4; N, 12·5%).

4 : 6-*Dihydroxy*-2-*phenyl*-5-(2 : 2 : 2-*trichloro*-1-*hydroxyethyl*)*pyrimidine*.—Prepared from 4 : 6-dihydroxy-2-phenylpyrimidine [24] (12·25 g.), chloral (10·65 g.), and pyridine (15 ml.), the *compound* (3·4 g.) separated from 2-ethoxyethanol and water, and dried as a light cream amorphous powder, m. p. >300° (Found: C, 43·4; H, 2·85; N, 8·3. $C_{12}H_9O_3N_2Cl_3$ requires C, 42·95; H, 2·7; N, 8·35%).

2-*Amino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Potassium hydroxide (80·5 g.) was dissolved in water (960 ml.), and one-fifth of this solution was added to a suspension of 2-amino-4-hydroxy-6-methylpyrimidine (300 g.) in alcohol (1·2 l.) in a bath at 80° with good stirring. The remainder of the potassium hydroxide solution and chloroform (286 ml.) were then added simultaneously during 4 hr. The bath was lowered during this addition, the heat of reaction being sufficient to maintain gentle reflux. After overnight stirring and cooling, the solid was collected, washed with alcohol, and dissolved in warm water (2·5 l.). The solution was filtered from a little insoluble material, and 5N-hydrochloric acid added to pH 10, followed by acetic acid to pH 6. The crude product (140 g.) crystallised from water as pale yellow prismatic needles, m. p. >300° (Found: C, 41·8; H, 5·0; N, 24·7. Calc. for $C_6H_7O_2N_3,H_2O$: C, 42·1; H, 5·25; N, 24·55%. Loss *in vacuo* at 130°; 11·1%. Calc. for the monohydrate, 10·5%). The *hydrochloride* (m. p. >300°) was obtained by dissolving the base in the minimum quantity of warm 5N-hydrochloric acid, then quickly cooling and scratching the mixture. The solid was collected and washed with acetone (Found: Cl, 17·3. $C_6H_7O_2N_3,HCl,H_2O$ requires Cl, 17·1%).

2-*Dimethylamino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Chloroform (3·82 g.) was added slowly to a stirred mixture of potassium hydroxide (8·4 g.) and 2-dimethylamino-4-hydroxy-6-methylpyrimidine (3·06 g.) in alcohol (10 ml.) and water (10 ml.) at 80°. The mixture was then refluxed during 1 hr. and cooled. Next morning the solid (mainly inorganic material) was collected and the filtrate evaporated to dryness. The residue was dissolved in water (25 ml.) and filtered, and the product (1·0 g.) was precipitated with acetic acid. It crystallised from 2-ethoxyethanol as colourless needles, m. p. >300° (Found: C, 53·4; H, 6·1; N, 23·9. Calc. for $C_8H_{11}O_2N_3$: C, 53·05; H, 6·1; N, 23·2%).

4-*Hydroxy*-6-*methyl*-2-*piperidinopyrimidine*-5-*aldehyde*.—Chloroform (2·55 ml.) was added to a stirred mixture of sodium hydroxide (5·6 g.) and 4-hydroxy-6-methyl-2-piperidinopyrimidine (3·86 g.) in 2-ethoxyethanol (15 ml.) and water (15 ml.) at 80°. Working up by the usual procedure gave the aldehyde (0·8 g.) which crystallised from aqueous ethanol as pale yellow needles, m. p. 230—232°, undepressed on admixture with the aldehyde obtained by the chloral reaction (Found: C, 60·0; H, 6·6; N, 18·9. Calc. for $C_{11}H_{15}O_2N_3$: C, 59·7; H, 6·8; N, 19·0%).

2 : 4-*Dihydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Chloroform (8·95 g.), and potassium hydroxide (14 g.) in water (15 ml.) were added simultaneously to a stirred suspension of 2 : 4-dihydroxy-6-methylpyrimidine (6·3 g.) in potassium hydroxide (2·8 g.) and water (25 ml.) and alcohol (20 ml.) at 80° during 15 min. After 1 hour's stirring under reflux the mixture was cooled and filtered and the filtrate evaporated to dryness. The residue was dissolved in water and acidified to litmus with 5N-hydrochloric acid, no solid being precipitated. The aldehyde could be isolated as the *phenylhydrazone*, which was purified from dimethylformamide as a pale cream powder, m. p. >300° (Found: C, 58·6; H, 5·3; N, 23·2. $C_{12}H_{12}O_2N_4$ requires C, 59·0; H, 4·9; N, 22·95%), as the 2 : 4-*dinitrophenylhydrazone*, which was purified by dissolution in

[23] Huber and Holscher, *Ber.*, 1938, **71**, 94.
[24] Pinner, *Ber.*, 1908, **41**, 3517.

hot dimethylformamide and addition of water to incipient precipitation and obtained as an orange-red powder, m. p. >300° (Found: C, 42·7; H, 2·9; N, 24·3. $C_{12}H_{10}O_6N_6$ requires C, 43·1; H, 3·0; N, 25·1%), or as the *semicarbazone*, which was purified by solution in dilute alkali and reprecipitation with hydrochloric acid and obtained as a pale cream powder, m. p. 289° (decomp.) (Found: C, 38·1; H, 4·6. $C_7H_9O_3N_5,0·5H_2O$ requires C, 38·2; H, 4·55%).

4 : 6-*Dihydroxy*-2-*piperidinopyrimidine*-5-*aldehyde*.—Chloroform (16·8 g.), and potassium hydroxide (26·5 g.) in water (28 ml.) were added simultaneously to 4 : 6-dihydroxy-2-piperidinopyrimidine (20 g.) and potassium hydroxide (5·3 g.) in alcohol (40 ml.) and water (8 ml.) at 80° during 30 min., then allowed to reflux for a further hour, cooled, and filtered, and the filtrate was evaporated to dryness. The combined solids were dissolved in water (320 ml.) and filtered, and the *product* (8·1 g.) precipitated by the addition of 5N-hydrochloric acid to pH 6. From 7 : 3 propan-2-ol–water it formed orange crystals, m. p. >300° (sintering at 290°) (Found: N, 19·4. $C_{10}H_{13}O_3N_3$ requires N, 18·85%). The 2 : 4-*dinitrophenylhydrazone* was obtained as an orange amorphous powder, m. p. 294° (decomp.) (Found: N, 24·7. $C_{16}H_{17}O_6N_7$ requires N, 24·3%).

4 : 6-*Dihydroxy*-2-*phenylpyrimidine*-5-*aldehyde*.—Prepared from 4 : 6-dihydroxy-2-phenylpyrimidine (3·76 g.), the crude *product* [2·5 g.; m. p. 286—287° (decomp.)] was obtained as a pale cream powder (Found: C, 60·1; H, 4·3; N, 13·0. $C_{11}H_8O_3N_2,0·25H_2O$ requires C, 59·85; H, 3·85; N, 12·7%).

Tri-(2-*amino*-4-*methyl*-6-*pyrimidylthio*)*methane*.—Chloroform (5·75 g.) was added slowly to a stirred solution of 2-amino-4-mercapto-6-methylpyrimidine [25] (4·2 g.) and potassium hydroxide (6·35 g.) in alcohol (10 ml.) and water (10 ml.) at 80°. After a further 1 hr. the precipitate was collected and washed with water, then dissolved in alcohol; addition of water to incipient precipitation gave the crude product, which after a second similar purification gave *tri*-(2-*amino*-4-*methyl*-6-*pyrimidylthio*)*methane* (2·85 g.) as a cream amorphous powder, m. p. 217—218° (Found: C, 44·1; H, 4·6; S, 22·3. $C_{16}H_{19}N_9S_3$ requires C, 44·3; H, 4·4; S, 22·2%).

Tri-p-*tolyl Trithio-orthoformate*.—Chloroform (11·5 g.) was added slowly to *p*-tolylthiophenol (6·2 g.) and potassium hydroxide (12·7 g.) in alcohol (19 ml.) and water (19 ml.) at 80°. After a further 1 hr., the mixture was cooled, water (100 ml.) was added, and the oil was extracted with ether (3 × 100 ml.). The combined extracts were washed with water and dried, and the ether was removed. The residual *thio-orthoformate* (7·4 g.) crystallised from light petroleum as needles, m. p. 111° (Found: C, 69·0; H, 6·1; S, 25·2. $C_{22}H_{22}S_3$ requires C, 69·1; H, 5·8; S, 25·1%).

Tri-p-*chlorophenyl Trithio-orthoformate*.—This was prepared as described above, but with *p*-chlorothiophenol (7·25 g.). The *thio-orthoformate* (8·7 g.) crystallised from light petroleum in prismatic needles, m. p. 111—112° (Found: S, 21·5; Cl, 24·25. $C_{19}H_{13}S_3Cl_3$ requires S, 21·65; Cl, 24·0%).

Compounds from 2-*Amino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—Semicarbazide hydrochloride (3·35 g.) in water (22·5 ml.) was added to the aldehyde (4·25 g.) in warm 5N-hydrochloric acid (27·5 ml.). The *semicarbazone hydrochloride* (6·25 g. crude) crystallised from aqueous alcohol containing a few drops of 5N-hydrochloric acid as needles, m. p. 240° (decomp.) (Found: C, 34·0; H, 4·8; N, 34·3; Cl, 14·0. $C_7H_{10}O_2N_6,HCl$ requires C, 34·1; H, 4·45; N, 34·1; Cl, 14·4%). Acetic acid precipitated the *semicarbazone* from alkaline solution which dried as an amorphous powder, m. p. 280—283° (decomp.) (Found: C, 36·8; H, 5·5. $C_7H_{10}O_2N_6,H_2O$ requires C, 36·8; H, 5·3%).

The *thiosemicarbazone dihydrochloride* [6·3 g. from 4·25 g.; m. p. 235° (decomp.)] (Found: Cl, 23·8. $C_7H_{10}ON_6S,2HCl$ requires Cl, 23·9%) dissociated on attempted recrystallisation from water. Addition of ammonium chloride to a solution of the solid in N-sodium hydroxide gave the *thiosemicarbazone*, m. p. 255—256° (decomp.) (Found: C, 33·1; H, 5·1; N, 32·5. $C_7H_{10}ON_6S,1·5H_2O$ requires C, 33·2; H, 5·15; N, 33·2%).

The aldehyde (3·4 g.) in 5N-sulphuric acid (8 ml.) was added to hydrazine sulphate (8·1 g.) in water (100 ml.). The yellow *azine sulphate* (3·6 g.) was collected and after being washed with hot water and alcohol had m. p. 273—274° (decomp.) (Found: C, 33·6; H, 4·3; N, 25·7. $C_{12}H_{14}O_2N_8,H_2SO_4,2H_2O$ requires C, 33·05; H, 4·6; N, 25·7%). The *azine hydrochloride* (3·1 g.), prepared similarly from the aldehyde (3·06 g.) and hydrazine hydrochloride, had m. p. 270° (decomp.) (Found: C, 38·0; H, 5·0; N, 29·3. $C_{12}H_{14}O_2N_8,2HCl$ requires C, 38·4; H, 4·25; N, 29·85%).

The aldehyde (50 g.) in warm 5N-hydrochloric acid (300 ml.) and hydroxylamine

[25] Gabriel and Cohen, *Ber.*, 1899, **32**, 2926.

hydrochloride (41·25 g.) in warm water (90 ml.) were mixed. The following morning the *oxime hydrochloride* (34·7 g.) was crystallised from water, giving needles, m. p. 225° (decomp.) (Found: C, 34·7; H, 4·3; Cl, 16·8. $C_6H_8O_2N_4$,HCl requires C, 35·2; H, 4·4; Cl, 17·35%). Repeated recrystallisation of the hydrochloride from water gave the *oxime* as prisms, m. p. >300° (Found: C, 41·8; H, 5·0; N, 31·8. $C_6H_8O_2N_4$,0·25H_2O requires C, 41·7; H, 4·9; N, 32·4%).

The aldehyde (6·4 g.) in 5N-hydrochloric acid (21 ml.) with *o*-hydroxybenzhydrazide [26] (5·7 g.) in 5N-hydrochloric acid (38 ml.) gave the yellow N′-*o*-*hydroxybenzoylhydrazone dihydrochloride* (8·0 g.) which, washed with water and alcohol, had m. p. >300° (Found: C, 42·9; H, 5·0; N, 19·6. $C_{13}H_{13}O_3N_5$,2HCl requires C, 43·35; H, 4·2; N, 19·45%).

4-(2-*Acetamido*-4-*hydroxy*-6-*methyl*-5-*pyrimidylmethylidene*)-5-*oxo*-2-*phenyloxazoline*.—The aldehyde (1·7 g.), hippuric acid (1·8 g.) and fused sodium acetate (0·8 g.) were heated under reflux in acetic acid (5·0 ml.) and acetic anhydride (4·0 ml.) during 5 min. After storage, the yellow solid (0·95 g.) was collected. It crystallised from 2-ethoxyethanol, to give the *azlactone* as pale yellow needles, m. p. 281—283° (Found: C, 59·8; H, 4·3; N, 15·9. $C_{17}H_{14}O_4N_4$ requires C, 60·35; H, 4·15; N, 16·55%).

(2-*Amino*-4-*hydroxy*-6-*methyl*-5-*pyrimidylmethylidene*)*rhodanine*.—A mixture of the aldehyde (1·53 g.), rhodanine (1·33 g.), fused sodium acetate (2·4 g.), and acetic acid (25 ml.) was heated under reflux for 1 hr. The *rhodanine derivative* (2·15 g.) was collected and washed with water and alcohol; it crystallised from aqueous dimethylformamide as yellow prismatic needles, m. p. >300° (Found: C, 40·8; H, 3·5; N, 21·1. $C_9H_8O_2N_4S_2$ requires C, 40·3; H, 3·0; N, 20·9%).

2-*Amino*-4-*hydroxy*-6-*methylpyrimidine*-5-*carboxylic Acid*.—Potassium permanganate (1·05 g.) in water (15 ml.) was added with shaking to a warm solution of the aldehyde (1·71 g.) in 5N-sodium hydroxide (2·0 ml.) and water (10 ml.). After 5 min. the mixture was filtered and the filtrates were adjusted to pH 5 with 5N-hydrochloric acid. The *acid* (1·0 g.) was collected; it crystallised from water as colourless prismatic needles, m. p. 245—246° (decomp.) (Found: C, 42·7; H, 4·2; N, 24·5. $C_6H_7O_3N_3$ requires C, 42·6; H, 4·15; N, 24·85%).

2-*Amino*-4-*chloro*-5-*cyano*-6-*methylpyrimidine*.—Dimethylaniline (3·9 ml.) was added slowly to 2-amino-4-hydroxy-6-methylpyrimidine-5-aldoxime hydrochloride (6·5 g.) and phosphoryl chloride (39 ml.) and the whole heated under reflux for 20 mins. The cooled mixture was added to ice-water, and aqueous ammonia added to alkalinity to Brilliant Yellow. The *chlorocyanopyrimidine* (3·6 g.) was collected. It crystallised from alcohol as colourless prisms, m. p. 258—259° (decomp.) (inserted at 240°) (Found: N, 33·5; Cl, 21·05. $C_6H_5N_4Cl$ requires N, 33·25; Cl, 21·05%).

2-*Acetamido*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde*.—2-Amino-4-hydroxy-6-methylpyrimidine-5-aldehyde (1·5 g.) and acetic anhydride (40 ml.) were heated under reflux for 2 hr. After 2 days the solid (7·2 g.) was collected and washed with ethyl acetate. Recrystallisation from aqueous alcohol gave the *acetyl derivative* as light brown prisms, m. p. 240° (decomp.) (Found: C, 49·2; H, 4·8; N, 21·3. $C_8H_9O_3N_3$ requires C, 49·2; H, 4·6; N, 21·55%).

2-*Acetamido*-5-*cyano*-4-*hydroxy*-6-*methylpyrimidine*.—2-Amino-4-hydroxy-6-methylpyrimidine-5-aldoxime hydrochloride (6·8 g.) and acetic anhydride (40 ml.) were heated under reflux for 1 hr. The *cyanopyrimidine* was collected and washed with alcohol. It crystallised from aqueous 2-ethoxyethanol as light brown needles (2·35 g.), m. p. 285—286° (Found: C, 49·6; H, 3·8; N, 28·6. $C_8H_8O_2N_4$ requires C, 50·0; H, 4·15; N, 29·15%).

2-*Amino*-5-(5 : 6-*dihydro*-2 : 4-*dihydroxy*-6-*pyrimidyl*)-4-*hydroxy*-6-*methylpyrimidine*.—A mixture of the aldehyde (1·7 g.), malonic acid (1·15 g.), urea (3 g.), and γ-picoline (1·0 ml.) was heated with stirring at 130—135° during 30 min., then cooled. Water was added to the resin and the mixture was set aside. The solid (1·25 g.) was later collected. Purification from water gave the *product* as yellow crystals, m. p. >300° (Found: C, 45·6; H, 5·2; N, 29·5. $C_9H_{11}O_3N_5$ requires C, 45·6; H, 4·65; N, 29·5%). It dissolved in aqueous sodium carbonate or hydrochloric acid. It was insoluble in cold aqueous sodium hydrogen carbonate. It did not form a derivative with 2 : 4-dinitrophenylhydrazine.

Reaction of 2-*Amino*-4-*hydroxy*-6-*methylpyrimidine*-5-*aldehyde with Malonic Acid and Thiourea*.—A mixture of the aldehyde (1·7 g.), malonic acid (1·15 g.), thiourea (3·0 g.), and γ-picoline (1·0 ml.) was heated with stirring at 150° during 20 min., then cooled and treated with water. After standing overnight the solid was collected. It was purified from water as a light yellow amorphous powder. The product, believed to be NN′-*di*-[1-(2-*amino*-4-*hydroxy*-6-*methyl*-5-*pyrimidyl*)-2-*carboxyethyl*]*thiourea*, had m. p. >300° (Found: C, 44·3; H, 5·2; N,

[26] Struve and Radenhausen, *J. prakt. Chem.*, 1895, **52**, 239.

25·3; S, 5·7. $C_{17}H_{22}O_6N_8S$ requires C, 43·8; H, 4·7; N, 24·1; S, 6·85%). It dissolved in excess of aqueous sodium hydrogen carbonate. It did not form a 2 : 4-dinitrophenylhydrazone.

4-Hydroxy-6-methyl-5-phenyliminomethyl-2-piperidinopyrimidine.—4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (22 g.) and freshly distilled aniline (10·2 g.) were heated together at 100° for 15 min. Crystallisation of the melt from aqueous alcohol gave the *anil* as feathery yellow needles (27·9 g.), m. p. 110—112° (Found: C, 65·25; H, 7·1; N, 17·6. $C_{17}H_{20}ON_4,H_2O$ requires C, 65·0; H, 7·0; N, 17·8%).

5-p-Dimethylaminophenylimino-4-hydroxy-6-methyl-2-piperidinopyrimidine.—4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (1·1 g.) and *NN*-dimethyl-*p*-phenylenediamine (0·68 g.) were ground together and heated at 180° during 5 min. The mixture was extracted with alcohol, and water added to incipient precipitation. Crystallisation of the solid from ethyl acetate gave the *anil* as red prisms, m. p. 171—172° (Found: C, 68·05; H, 7·9; N, 20·85. $C_{19}H_{25}ON_5$ requires C, 67·3; H, 7·4; N, 20·65%).

4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldoxime.—A solution of hydroxylamine hydrochloride (14 g.) and sodium acetate (28 g.) in water (45 ml.) was added to a suspension of the aldehyde (22 g.) in alcohol (300 ml.), and the mixture was heated under reflux during 5 hr. The solid (26 g.) was collected. Recrystallisation from 2-ethoxyethanol gave the *oxime* as colourless needles, m. p. 240° (decomp.) (Found: C, 55·4; H, 6·75; N, 23·85. $C_{11}H_{16}O_2N_4$ requires C, 55·9; H, 6·8; N, 23·75%).

N'-(4-Hydroxy-6-methyl-2-piperidino-5-pyrimidylmethylidene)-N'-[(methylthio)carbonylthio]-hydrazine.—(Methylthio)thiocarbonylhydrazine [17] (1·3 g.) in methanol (7 ml.) was added to a hot solution of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.) in dioxan (60 ml.). Next morning the *product* (2·25 g.) was collected. It crystallised from methanol as yellow prisms, m. p. 216—217° (decomp.) (Found: C, 48·45; H, 5·5; N, 20·8. $C_{13}H_{19}ON_5S_2$ requires C, 48·0; H, 5·8; N, 21·5%).

4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde Thiosemicarbazone.—Thiosemicarbazide (0·55 g.) was added to a hot solution of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (1·1 g.) in 2-ethoxyethanol and quickly heated to the b. p. to effect dissolution, then cooled to 100° and kept at this temperature for 30 min. The *product* (1·2 g.) crystallised on cooling. It recrystallised from acetic acid as light buff prismatic needles, m. p. >300° (Found: C, 49·3; H, 6·15; S, 10·4. $C_{12}H_{18}ON_6S$ requires C, 49·0; H, 6·1; S, 10·9%).

4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldazine.—Hydrazine hydrate (65% w/v, 5 g.) in 2-ethoxyethanol (50 ml.) was added to a solution of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (11 g.) in 2-ethoxyethanol (100 ml.), and the mixture was kept at 100° for 2 hr. The *azine* (8·0 g.) was precipitated on cooling. It was purified from dimethylformamide as a yellow amorphous powder, m. p. 307° (decomp.) (Found: C, 60·0; H, 6·95; N, 25·7. $C_{22}H_{30}O_2N_8$ requires C, 60·25; H, 6·85; N, 25·6%).

2-(4-Hydroxy-6-methyl-2-piperidino-5-pyrimidyl)-4-oxo-3-phenylthiazolidine.—4-Hydroxy-6-methyl-5-phenylimino-2-piperidinopyrimidine (2·97 g.) and 90% mercaptoacetic acid (1·02 g.) in benzene (40 ml.) were heated under a Dean and Stark receiver during 30 min. Excess of reagent was removed under diminished pressure. The residue, washed with aqueous sodium hydrogen carbonate and twice recrystallised from alcohol, gave the *product* (1·5 g.) as orange-yellow prisms, m. p. 272—274° (inserted at 250°) (Found: C, 57·35; H, 6·3; N, 14·85. $C_{19}H_{22}O_2N_4S,1·5H_2O$ requires C, 57·4; H, 6·3; N, 14·1%).

4-Hydroxy-6-methyl-5-2'-nitrovinyl-2-piperidinopyrimidine.—(*a*) 4-Hydroxy-6-methyl-5-phenylimino-2-piperidinopyrimidine (1·6 g.) and nitromethane (0·54 ml.) in alcohol (5 ml.) were heated under reflux during 2 hr. After cooling, the solid (1·15 g.) was collected and washed with alcohol. The filtrates gave a positive test for a primary arylamine. Recrystallisation from 2-ethoxyethanol gave the *product* as orange-yellow prismatic needles, m. p. 282° (decomp.) (Found: C, 54·95; H, 6·25; N, 21·05. $C_{12}H_{16}O_3N_4$ requires C, 54·55; H, 6·05; N, 21·2%). (*b*) Nitromethane (0·8 ml.) was added to a warm solution of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.) in 2-ethoxyethanol (15 ml.) and piperidine (0·1 ml.). Next morning the precipitate (2·2 g.) was collected. Recrystallisation from 2-ethoxyethanol gave the nitrovinylpyrimidine, m. p. 279—280° (decomp.), identical with the above (Found: C, 54·85; H, 6·35%).

5-Cyano-4-hydroxy-6-methyl-2-piperidinopyrimidine.—4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldoxime (1·2 g.) and acetic anhydride (10 ml.) were heated under reflux during 2 hr., cooled and poured on ice. Next morning the solid (0·8 g.) was collected. Crystallisation

from 2-ethoxyethanol gave the *cyanopyrimidine* as colourless needles, m. p. 292—294° (Found: C, 60·6; H, 6·5; N, 25·85. $C_{11}H_{14}ON_4$ requires C, 60·55; H, 6·4; N, 25·7%).

4-Chloro-5-cyano-6-methyl-2-piperidinopyrimidine.—(*a*) 4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldoxime (2·9 g.) was heated under reflux with phosphoryl chloride (12 ml.) during 1 hr. The mixture was cooled and decomposed with ice. The solid (2·75 g.; m. p. 126—127°) was collected. Crystallisation from alcohol gave the *chlorocyanopyrimidine* as colourless plates, m. p. 133—134° (Found: C, 55·75; H, 5·6; N, 23·35. $C_{11}H_{13}N_4Cl$ requires C, 55·8; H, 5·5; N, 23·65%). (*b*) 5-Cyano-4-hydroxy-6-methyl-2-piperidinopyrimidine (2·2 g.) was heated under reflux with phosphoryl chloride (10 ml.) during 15 min. and worked up as above, giving the chlorocyanopyrimidine as colourless prisms, m. p. 131·5—132·5°, identical with the above.

5-Carbamoyl-4-hydroxy-6-methyl-2-piperidinopyrimidine.—5-Cyano-4-hydroxy-6-methyl-2-piperidinopyrimidine (0·22 g.) and concentrated sulphuric acid (2·5 ml.) were heated together at 100° during 1½ hr., then kept for 2 days. Excess of acid was reduced with 5N-sodium hydroxide and finally removed with sodium acetate, and the solid (0·3 g.) collected. Recrystallisation from 2-ethoxyethanol gave the *amide* as colourless prismatic needles, m. p. 290° (decomp.) (Found: C, 56·15; H, 6·85; N, 23·3. $C_{11}H_{16}O_2N_4$ requires C, 55·95; H, 6·8; N, 23·7%).

5-(2-Benzoylvinyl)-4-hydroxy-6-methyl-2-piperidinopyrimidine.—A mixture of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.), acetophenone (1·2 g.), and sodium hydroxide (0·8 g.) in water (40 ml.) and alcohol (1 ml.) was set aside, with occasional shaking, during 7 days. The orange-red solid (1·1 g.) was collected, suspended in water, and acidified with acetic acid. Crystallisation of the resulting solid (1·0 g.) from 2-ethoxyethanol gave the *chalcone* as pale yellow needles, m. p. 256° (Found: C, 70·8; H, 6·65; N, 13·5. $C_{19}H_{21}O_2N_3$ requires C, 70·6; H, 6·5; N, 13·0%).

5-2′-Carboxyvinyl-4-hydroxy-6-methyl-2-piperidinopyrimidine.—A mixture of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.), malonic acid (1·05 g.), and piperidine (5·0 ml.) was warmed, with stirring, to a homogeneous melt, then set aside overnight, diluted with water (15 ml.), and acidified, and the precipitate collected. Purification, by dissolution of the crude product in dilute aqueous ammonia followed by acidification, gave the *pyrimidylacrylic acid* (1·3 g.) as a yellow amorphous powder, m. p. 231° (decomp.) (Found: C, 58·95; H, 6·75; N, 15·7. $C_{13}H_{17}O_3N_3$ requires C, 59·3; H, 6·45; N, 15·95%).

2-(4-Hydroxy-6-methyl-2-piperidino-5-pyrimidyl)benzothiazoline.—Dimethylaniline (1·2 g.) was added to a stirred mixture of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.) and *o*-aminothiophenol hydrochloride (1·6 g.) in alcohol (50 ml.), and the whole was heated under reflux for 30 min. Water (100 ml.) was added to the solution. Dissolution of the precipitate (4 g.) in 5N-hydrochloric acid and then basification with ammonia gave a solid. Extraction with hot butanol gave the *product* as an orange-red amorphous powder, m. p. 212—213° (decomp.) (inserted at 200°) (Found: C, 62·15; H, 6·1; N, 17·0. $C_{17}H_{20}ON_4S$ requires C, 62·2; H, 6·1; N, 17·05%).

(4-Hydroxy-6-methyl-2-piperidino-5-pyrimidylmethylidene)rhodanine.—Fused sodium acetate (2·4 g.) was added to a hot solution of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.) and rhodanine (1·3 g.) in acetic acid (15 ml.) and the whole was heated, with stirring, on a steam-bath during 30 min. After cooling, the orange-yellow solid (2·0 g.) was collected and washed with water. Crystallisation from 2-ethoxyethanol–propan-2-ol gave the *rhodanine derivative acetate* as dark orange prismatic needles, m. p. 315—316° (decomp.) (Found: C, 48·15; H, 5·2; N, 14·5; S, 16·7. $C_{14}H_{16}O_2N_4S_2,C_2H_4O_2$ requires C, 48·5; H, 5·05; N, 14·15; S, 16·2%).

5-(2-Carboxy-2-thionoethyl)-4-hydroxy-6-methyl-2-piperidinopyrimidine.—A mixture of 11N-sodium hydroxide (11·75 ml.), water (15 ml.), and the foregoing acetate (10 g.) was heated on a steam-bath during 30 min., then diluted with water (80 ml.), filtered, cooled, and acidified quickly with 5N-acetic acid. The yellow solid (7·8 g.) was collected and washed with water. Purification from hot methanol with addition of water to incipient precipitation gave the *acid* as an amorphous yellow powder, m. p. 182—183° (decomp.) (Found: C, 53·5; H, 6·0; N, 14·8. $C_{13}H_{17}O_3N_3S$ requires C, 52·9; H, 5·75; N, 14·25%).

4-[4-Hydroxy-6-methyl-2-piperidino-5-pyrimidylmethylidene]-5-oxo-2-phenyloxazoline.—A mixture of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.), hippuric acid (1·8 g.), fused sodium acetate (0·8 g.), acetic anhydride (4·0 ml.), and acetic acid (5·0 ml.) was heated under reflux during 5 min., then kept for 2 days. The yellow precipitate (1·8 g.) was collected

and washed with alcohol. Recrystallisation from 2-ethoxyethanol gave the *product* as yellow needles, m. p. 215—217° (Found: C, 65·85; H, 5·4; N, 14·8. $C_{20}H_{20}O_3N_4$ requires C, 65·95; H, 5·5; N, 15·4%).

α-Benzamido-β-(4-hydroxy-6-methyl-2-piperidino-5-pyrimidyl)acrylic Lactone.—A mixture of the above oxazoline (1·2 g.), 0·5N-sodium hydroxide (13·2 ml.), and alcohol (20 ml.) was heated under reflux during 20 min. Excess of reagent was removed under diminished pressure at 40°. The volume was adjusted to 50 ml. with water and the whole acidified with acetic acid. The precipitate (1·2 g.) was collected and washed with water. Crystallisation from 2-ethoxyethanol gave the *lactone* as colourless needles, m. p. 205° (Found: C, 65·95; H, 5·7; N, 15·75. $C_{20}H_{20}O_3N_4$ requires C, 65·95; H, 5·5; N, 15·4%).

4-Hydroxy-6-methyl-5-4′-nitrostyryl-2-piperidinopyrimidine.—A mixture of 4-hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·2 g.), *p*-nitrophenylacetic acid (1·85 g.), and piperidine (7·5 ml.) was heated with stirring at 150—160° during 3 hr. After cooling, the mixture was acidified with dilute acetic acid, and the solid (2·05 g.) was collected, and washed with water, sodium hydrogen carbonate solution, and alcohol. Crystallisation from 2-ethoxyethanol gave the *styrylpyrimidine* as red needles, m. p. 310° (Found: C, 62·3; H, 6·0; N, 15·9. $C_{18}H_{20}O_3N_4,0·5H_2O$ requires C, 61·9; H, 6·0; N, 16·05%).

4-Chloro-6-methyl-5-4′-nitrostyryl-2-piperidinopyrimidine.—4-Hydroxy-6-methyl-5-4′-nitrostyryl-2-piperidinopyrimidine (17 g.) was heated under reflux with phosphoryl chloride (100 ml.) during 20 min. The whole was cooled and decomposed by ice. The yellow precipitate was collected and washed with water. Crystallisation from 2-ethoxyethanol gave the *chloropyrimidine* (13·1 g.) as yellow needles, m. p. 164—165° (Found: C, 59·9; H, 5·6; N, 16·15. $C_{18}H_{19}O_2N_4Cl$ requires C, 60·25; H, 5·3; N, 15·65%).

4-Amino-6-methyl-5-4′-nitrostyryl-2-piperidinopyrimidine.—4-Chloro-6-methyl-5-4′-nitrostyryl-2-piperidinopyrimidine (27 g.) was heated in an autoclave with alcoholic ammonia (1 l. saturated at 0°) at 125° during 10 hr. The *aminopyrimidine* (22·3 g.) was collected. After recrystallisation from alcohol it had m. p. 217—218° (Found: C, 63·5; H, 6·2; N, 20·65. $C_{18}H_{21}O_2N_5$ requires C, 63·7; H, 6·2; N, 20·65%).

4-Chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde.—4-Hydroxy-6-methyl-2-piperidinopyrimidine-5-aldehyde (10 g.) was added slowly to phosphoryl chloride (50 ml.) with shaking and cooling. The following morning the mixture was poured on ice and extracted with ether, and the extract washed with sodium hydrogen carbonate solution, dried, and evaporated. The oil (11·3 g.) gradually crystallised. Recrystallisation from aqueous alcohol gave the *chloropyrimidine* as colourless needles, m. p. 91—92° (Found: C, 55·8; H, 5·45; N, 17·4. $C_{11}H_{14}ON_3Cl$ requires C, 55·1; H, 5·85; N, 17·55%). The 2 : 4-*dinitrophenylhydrazone* crystallised from 2-ethoxyethanol in crimson red prismatic needles, m. p. 259—260° (decomp.) (Found: C, 48·25; H, 4·4; N, 23·0. $C_{17}H_{18}O_4N_7Cl$ requires C, 48·6; H, 4·3; N, 23·35%).

5-Methyl-2-oxo-7-piperidino-2H-1-thia-3 : 6 : 8-triazanaphthalene.—4-Chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (6·5 g.), thiourea (2·26 g.), alcohol (30 ml.), and water (25 ml.) were heated under reflux during 45 min., then kept for 2 days, diluted with water, and neutralised with sodium hydrogen carbonate solution. The *product* (6·7 g.) was collected. When purified from aqueous alcohol it was obtained as an amorphous yellow powder, m. p. 228—230° (decomp.) (inserted 220°) (Found: C, 54·3; H, 6·1; N, 21·0; S, 13·0. $C_{12}H_{14}ON_4S$ requires C, 54·95; H, 5·35; N, 21·4; S, 12·2%).

4-Methyl-6-piperidino-1 : 2 : 5 : 7-tetra-azaindene.—A solution of 4-chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (1·2 g.) in warm alcohol (10 ml.) was added to hydrazine hydrate (75% w/v; 3·8 g.) in alcohol (5 ml.) and kept for 2 days. The solid (0·95 g.) was collected. Recrystallisation from alcohol gave the *product* as prismatic needles, m. p. 209—210° (Found: C, 60·3; H, 6·6; N, 32·3. $C_{11}H_{15}N_5$ requires C, 60·8; H, 6·9; N, 32·25%).

4-Chloro-6-methyl-2-piperidinopyrimidine-5-aldazine.—Hydrazine sulphate (0·09 g.) in water (1 ml.) was added to a hot solution of 4-chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (0·24 g.) in alcohol (7 ml.). Immediate precipitation took place. After 30 minutes' heating on the steam-bath the product (0·24 g.) was collected and washed with alcohol. Recrystallisation from 2-ethoxyethanol gave the *azine* as pale yellow needles, m. p. 256° (decomp.) (Found: C, 55·9; H, 6·4; N, 23·55. $C_{22}H_{28}N_8Cl_2$ requires C, 55·6; H, 5·9; N, 23·55%).

5-(2 : 2-Dicyanovinyl)-4-methyl-2 : 6-dipiperidinopyrimidine.—Piperidine (4·0 ml.) was added to a solution of malononitrile (1·06 g.) and 4-chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (4·8 g) in hot alcohol (12 ml.) and the mixture was heated under reflux during 30 min. After

cooling, the solid was collected. Recrystallisation from alcohol gave the *product* (3·1 g.) as yellow prismatic needles, m. p. 196° (Found: C, 67·85; H, 7·2; N, 25·2. $C_{19}H_{24}N_6$ requires C, 67·85; H, 7·15; N, 25·0%).

4-*Methyl*-2 : 6-*dipiperidinopyrimidine*-5-*aldehyde*.—Piperidine (0·2 ml.), 4-chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (0·24 g.), and alcohol (7 ml.) were heated under reflux during 30 min., then cooled, and the solid (0·15 g.) collected. Recrystallisation from aqueous alcohol gave 4-*methyl*-2 : 6-*dipiperidinopyrimidine*-5-*aldehyde* as pale yellow prisms, m. p. 117° (Found: C, 66·1; H, 7·8; N, 19·5. $C_{16}H_{24}ON_4$ requires C, 66·65; H, 8·3; N, 19·45%).

4-*Methyl*-2-*piperidino*-6-*thiocyanatopyrimidine*-5-*aldehyde*.—4-Chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·4 g.), potassium thiocyanate (1·49 g.), water (25 ml.), and alcohol (25 ml.) were heated under reflux during 3 hr. After cooling, the product with a little unchanged starting material was collected. Two recrystallisations from aqueous alcohol gave the *thiocyanatopyrimidine* as needles, m. p. 172° (Found: C, 54·7; H, 5·4; N, 21·7. $C_{12}H_{14}ON_4S$ requires C, 54·95; H, 5·3; N, 21·4%).

4-*Methyl*-6-*methylthio*-2-*piperidinopyrimidine*-5-*aldehyde*.—11N-Sodium hydroxide (6·0 ml.) was added with rapid stirring to mixed solutions of 4-chloro-6-methyl-2-piperidinopyrimidine-5-aldehyde (2·4 g.) in hot alcohol (20 ml.) and *S*-methyl*iso*thiuronium sulphate (2·61 g.) in hot water (9 ml.), and the whole was kept at 50—60° during 30 min. The mixture was cooled and the *methylthiopyrimidine* (2·6 g.) collected. Recrystallisation from alcohol gave pale yellow needles, m. p. 126—127° (Found: C, 57·4; H, 6·3; N, 16·25. $C_{12}H_{17}ON_3S$ requires C, 57·35; H, 6·8; N, 16·75%). The 2 : 4-*dinitrophenylhydrazone* crystallised from 2-ethoxyethanol as red needles, m. p. 284—285° (decomp.) (Found: C, 50·25; H, 4·8; N, 22·7. $C_{18}H_{21}O_4N_7S$ requires C, 50·1; H, 4·85; N, 22·75%).

4-*Methyl*-6-*methylthio*-2-*piperidinopyrimidine*-5-*aldazine*.—5N-Hydrochloric acid (2·0 ml.) was added to a warm solution of 4-methyl-6-methylthio-2-piperidinopyrimidine-5-aldehyde (0·25 g.) and hydrazine hydrate (75% w/v; 0·7 g.) in alcohol (4 ml.). After 1 hr. the solid (0·29 g.) was collected, then extracted with dilute sodium hydroxide and refiltered. Recrystallisation from 2-ethoxyethanol gave the *azine* as fine yellow needles, m. p. 275—276° (Found: C, 57·8; H, 6·6; N, 22·4. $C_{24}H_{34}N_8S_2$ requires C, 57·8; H, 6·85; N, 22·5%).

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