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The Synthesis of Some Halogenopyrimidines and Some Routes to Cyanopyrimidines

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Summary

The syntheses of a number of new halogenopyrimidines related to commercially available agricultural chemicals are described. Some further reactions of these compounds are recorded and routes to some new cyanopyrimidines are outlined. The synthesis of 2-chloro-4,6-dicyanopyrimidine, the second recorded dicyanopyrimidine, is reported.

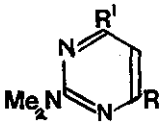
Pyrimidine derivatives provide a wide range of compounds which have useful biological activity[1], and of these, halogeno and alkylaminopyrimidines have found particular use as agricultural chemicals. For example, compounds of type I show fungicidal activity[1] and a number of compounds such as "Dimethirimol" (II) (I.C.I., Plant Protection Ltd.) are widely used as agricultural fungicides. The compound III is a well-known rodenticide[2] and some thiocyanato nucleosides have been reported to have useful antiviral activity[3].

We are interested in the synthesis of pyrimidines and related heterocycles having potential biological activity, and are interested in the synthesis and properties of pyrimidines having electron-attracting substituents, e.g. halogeno, cyano, nitro, and nitroso groups. We are also interested in the charge-transfer complexing ability of such compounds[4], this effect being suggested to be implicated in drug-receptor interactions.

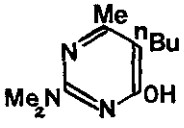
The cyano group is a "pseudo-halogen" and thus cyanopyrimidines may also have useful biological activity. However, cyanopyrimidines seem to have attracted little attention, and polycyanopyrimidines seem to be

unknown except for 4,5-dicyano-2-methylpyrimidine (IV)[5].

This communication reports our syntheses of some halogenopyrimidines having interesting biologically active potential and our approaches to some polycyanopyrimidines.



I



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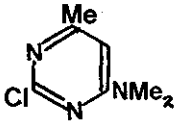

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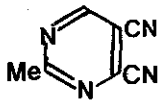

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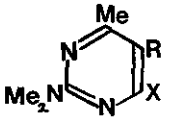
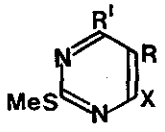


V (a) R=H, X=OH (e) R=Me, X=OH
(b) R=Br, X=OH (f) R=Me, X=Cl
(c) R=Br, X=Cl (g) R=Me, X=I

(d) R=Br, X=



VI (a) R=Br, R'=H, X=I
(b) R=R'=H, X=I

(c) R=R'=H, X=

(d) R=R'=H, X=Cl
(e) R=R'=H, X=CN
(f) R=H, R'=Me, X=CN

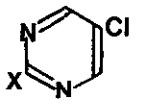
The bromination of 2-dimethylamino-4-hydroxy-6-methylpyrimidine (Va) in glacial acetic acid gave the 5-bromo derivative Vb in good yield, this product being readily converted by phosphorus oxychloride to 5-bromo-4-chloro-2-dimethylamino-6-methylpyrimidine (Vc). We attempted to convert the 4-chloro derivative Vc to the 4-mercapto derivative by refluxing it with thiourea in ethanol, a method frequently used[6] for such conversions. However, we obtained the bipyrimidinyldisulphide Vd as the only isolable pyrimidine product. Polonovski and Schmitt[7] found that they could only isolate the bipyrimidinyldisulphide when they attempted a similar reaction using 2-amino-4-chloro-6-methylpyrimidine.

By a similar method to that mentioned above we have converted 4-hydroxy-2-dimethylamino-5,6-dimethylpyrimidine (Ve) to the corresponding 4-chloro derivative Vf, and by reacting the chloro derivative with

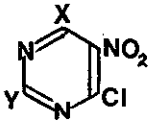
hydrogen iodide have also obtained the 4-iodo derivative Vg. In a similar way we have obtained the iodo compounds VIa and VIb. Refluxing VIb with copper bronze in N,N-dimethylformamide gave a poor yield of the bipyrimidine VIc, this compound having been now synthesised by an alternative route[8].

The conversion of 4-chloro-2-methylthiopyrimidine (VId) to the 4-cyanopyrimidine by reaction with trimethylamine in benzene followed by heating the trimethyl(4-pyrimidinyl) ammonium chloride so formed with potassium cyanide in acetamide has been reported[9]. In a similar way we have obtained 4-cyano-6-methyl-2-methylthiopyrimidine (VIf) and 5-chloro-2-cyanopyrimidine (VIIa).

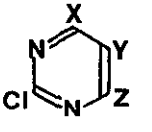
The alternative synthesis of VII(a) published[10] whilst this work was being carried out seems to be preferable as we obtained a very poor yield of product. However, our synthesis of 2,5-dichloropyrimidine (VIIb) from 2-amino-5-chloropyrimidine by a reverse addition diazotisation seems preferable to the previously reported[11] synthesis of this compound.



VII (a) X=CN
(b) X=Cl

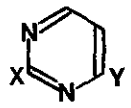


VIII (a) X=H, Y=Cl
(b) X=Cl, Y=H
(c) X=NH_2, Y=H

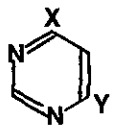


IX (a) X=Z=H, Y=NO_2
(b) X=Y=H, Z=CN
(c) Y=H, X=Z=CN

The method of Klötzer[12] for the synthesis of cyanopyrimidines using potassium cyanide in acetamide at 100° seems to give good yields when electron-releasing substituents, e.g. Me or MeO, are present on the pyrimidine ring but we have found it to be very unsatisfactory in the case of pyrimidine carrying electron-attracting substituents. We have failed to obtain cyanopyrimidines satisfactorily by this method from the compounds VIIIa-c and IXa-c.



X (a) X=Y=Cl
(b) X=NMe_2, Y=CN
(c) X=CN, Y=NMe_2
(d) X=Y=NMe_2



XI (a) X=Y=Cl
(b) X=CN, Y=NMe_2
(c) X=Y=NMe_2

In our attempts to obtain some simple dicyanopyrimidines we reacted the dichloropyrimidines Xa and XIa with trimethylamine in benzene and then reacted the crude trimethylammonium salts with potassium cyanide in acetamide according to the method of Klötzer[12].

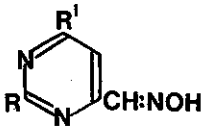
The crude product of the reaction of Xa was shown by n.m.r. spectroscopy to consist of three components Xb, c and d. One product was obtained pure by crystallisation which was shown by elemental analysis to be either Xb or Xc. However, we have not yet unambiguously synthesised these compounds to confirm its identity, nor have we effected a completely satisfactory separation of the product mixture.

In the case of the crude reaction product of XI(a) we obtained two crystalline products 4-cyano-6-dimethylaminopyrimidine (XIb) and 4,6-bisdimethylaminopyrimidine (XIc). In neither case have we observed a dicyanopyrimidine.

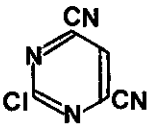
Thus under the conditions used in these reactions it seems that methyl elimination from the trimethylaminopyrimidine salt occurs in preference to nucleophilic displacement of trimethylamine by cyanide. The loss of methyl chloride from trimethylpyrimidinylammonium chloride salts has been reported by Klötzer[12] who observed this effect when the preparation of trimethyl(4,6-dimethylpyrimidin-2-yl)ammonium chloride was carried out at 100° rather than room temperature and also when the salt was heated to 100°.

In our attempts to synthesise polycyanopyrimidines we have also used an alternative method of synthesis, namely the dehydration of hydroxyiminomethylpyrimidines[13,14,15]. These hydroxyiminomethylpyrimidines may be obtained by the action of sodium nitrite, or ethyl or amyl nitrite, in acid solution on 2- or 4-methylpyrimidines[14-17].

We have obtained the three 4-hydroxyiminomethylpyrimidines XIIa-c from the corresponding 4-methylpyrimidines using amyl nitrite in absolute ethanol containing hydrogen chloride. Bredereck[17] has reported that 4,6-dimethylpyrimidine gives the bishydroxyiminomethyl product, but we have only obtained the monosubstituted product.



XII (a) R=R'=H
(b) R=H, R'=Me
(c) R=R'=Me
(d) R=OH, R'=CH:NOH



XIII

We have affected the dehydration of these hydroxyiminomethylpyrimidines to the corresponding cyanopyrimidines using phosphorus oxychloride but so far we have had varying yields of product of differing purity. However, we have converted the bishydroxyiminomethyl derivative XIId[16] to the chlorodicyanopyrimidine (XIII) by a similar reaction.

Thus we have synthesised a number of compounds which themselves show potential for biological activity or which may be useful intermediates for the synthesis of compounds of greater interest. However, we have been so far disappointed in our approaches to polycyanopyrimidines and to some products of particular interest to us. We intend to report our studies on the charge-transfer complexing abilities and on other properties of some interesting examples of the above types of compound at a later date.

Experimental

5-Bromo-2-dimethylamino-4-hydroxy-6-methylpyrimidine, Vb; Bromine (5.0 g) was added dropwise with stirring during 20 min to a solution of 2-dimethylamino-4-hydroxy-6-methylpyrimidine (5.0 g) in glacial acetic acid (15 ml). The mixture was cooled then neutralised with sodium carbonate when the product precipitated. The product was washed with sodium thiosulphate solution then water and recrystallised from ethanol to give the bromopyrimidine (5.7 g, 75%) mp 229° (decomp). Found C, 36.3; H, 4.5; N, 18.3%. $C_7H_{10}BrN_3O$ requires C, 36.2; H, 4.3; N, 18.1%. τ ($CDCl_3$) 6.70 (s, NCH_3) 7.50 (s, 6-CH_3) (2:1).

5-Bromo-4-chloro-2-dimethylamino-6-methylpyrimidine, Vc; The above product (5.0 g) and phosphorus oxychloride (10 ml) were refluxed together for 1 hr. The cooled mixture was then carefully poured onto crushed ice (250 g). The product precipitated and was collected, dried, and sublimed under vacuum to give colourless needles, mp 79-80°, of the bromochloropyrimidine (2.2 g, 40%). Found C, 33.7; H, 3.6; N, 16.4%. $C_7H_9BrClN_3$ requires C, 33.5; H, 3.6; N, 16.7%. τ ($CDCl_3$) 6.80 (s, N-CH_3) 7.45 (s, 6-CH_3) (2:1).

4-Chloro-2-dimethylamino-5,6-dimethylpyrimidine, Vf; was obtained similarly from 2-dimethylamino-5,6-dimethyl-4-hydroxypyrimidine as colourless needles mp 40-41° (60%). Found C, 52.1; H, 6.9; N, 23.0%. $C_8H_{12}ClN_3$ requires C, 51.8; H, 6.5; N, 22.6%. $M^{\dagger}$ (^{35}Cl) 186. τ ($CDCl_3$) 6.84 (s, N-CH_3) 7.74 (s, 6-CH_3) 7.90 (s, 5-CH_3) (2:1:1).

Bis-(5-bromo-2-dimethylamino-6-methylpyrimidin-4-yl)disulphide, Vd; Compound Vc (0.3 g) and thiourea (0.2 g) were dissolved in ethanol (10 ml) and the solution was refluxed for 6 hr. The volume of the mixture was reduced to about 5 ml and subsequent ice-cooling caused the deposition

of a solid which was collected and recrystallised from ethanol to give colourless crystals mp 219-222° of the bipyrimidinyl disulphide (35%). Found C, 33.7; H, 3.7; N, 17.1%. $C_{14}H_{18}Br_2N_6S_2$ requires C, 34.0; H, 3.6; N, 17.1%. M^+ (^{81}Br) 494. τ (CF_3CO_2H) 7.04 (s, N-CH_3) 7.64 (s, 6-CH_3) (2:1).

4-Iodo-2-dimethylamino-5,6-dimethylpyrimidine, Vg; Compound Vf (1.0 g) was shaken overnight with 48% hydriodic acid (5 ml). The product was isolated by pouring the reaction mixture into sodium bicarbonate solution and collecting the precipitate. The iodopyrimidine (50%) was recrystallised from ethanol as colourless crystals mp 45°. Found C, 34.6; H, 4.5; N, 15.4%. $C_8H_{12}IN_3$ requires C, 34.6; H, 4.3; N, 15.2%. τ (CCl_4) 6.94 (s, N-CH_3) 7.72 (s, 6-CH_3) 7.85 (s, 5-CH_3) (2:1:1).

5-Bromo-4-iodo-2-methylthiopyrimidine, VIa (51%) was obtained similarly as colourless needles mp 130-131° (from light petroleum). Found C, 18.0; H, 1.2; N, 8.9%. $C_5H_4BrIN_2S$ requires C, 18.2; H, 1.2; N, 8.4%.

4-Iodo-2-methylthiopyrimidine, VIb (40%) was obtained similarly as colourless crystals mp 45-46° (lit.[9] 45-47°). Found C, 23.9; H, 2.1; N, 10.9%. Calc. for $C_5H_5IN_2S$: C, 23.8; H, 2.0; N, 11.1%.

2,2'-Bismethylthio-4,4'-bipyrimidine, VIc; The above product (2.5 g) was refluxed with copper bronze (2.5 g) in N,N-dimethylformamide (20 ml) for 2 hr. The solution was filtered hot and the filtrate was saturated with hydrogen sulphide. Copper sulphide was removed by filtration and the filtrate was diluted with water (200 ml). The resulting precipitate was recrystallised from ethanol giving the bipyrimidine (15%) as fine needles mp 178-180° (lit.[8] 184°). Found C, 48.0; H, 4.1; N, 22.3%. Calc. for $C_{10}H_{10}N_4S_2$: C, 48.0; H, 4.0; N, 22.4%.

4-Cyano-6-methyl-2-methylthiopyrimidine, VI,f; 4-Chloro-6-methyl-2-methylthiopyrimidine (5.0 g) was dissolved in a solution of trimethylamine in benzene (30 ml of a 15% solution) and allowed to stand at room temperature for 3 days. The trimethylammonium salt (3.5 g) was collected and added to a melt of potassium cyanide (3.5 g) in acetamide (7.0 g). The mixture was heated on a water-bath for 1 hr then dissolved in water (200 ml). Ether extraction of the aqueous solution gave an oil which was crystallised from light petroleum (bp 40-60°) (charcoal) as colourless needles mp 65-66° of the cyanopyrimidine (0.8 g, 17%). Found C, 50.9; H, 4.4; N, 25.3%. $C_7H_7N_3S$ requires C, 51.0, H, 4.3, N, 25.4%.

4-Cyano-2-methylthiopyrimidine, VIe, (15%) was obtained similarly as colourless needles (light petroleum) mp 76-77° (lit.[9] 82-84). Found C, 47.6; H, 3.4; N, 27.7%. Calc. for $C_6H_5N_3S$: C, 47.7; H, 3.3; N, 27.8%.

5-Chloro-2-cyanopyrimidine, VIIa, was obtained similarly but in only 4% yield as pale yellow crystals mp 78° (lit.[10] 85-86°). Found C, 42.7; H, 1.7; N, 30.0%. Calc. for $C_5H_2ClN_3$: C, 43.0; H, 1.4; N, 30.1%.

Attempted conversion of 2,4-dichloropyrimidine to 2,4-dicyanopyrimidine.

2,4-Dichloropyrimidine (5.0 g) was dissolved in benzene (40 ml) and a solution of trimethylamine in benzene (40 ml of a 15% solution) was added. The crude trimethylammonium salt was collected after 12 hr, washed with light petroleum (bp 40-60°) and dried. This product was added with stirring during 1 hr to a melt of potassium cyanide (10 g) in acetamide (20 g) heated on a water-bath. The reaction mixture was then cooled, dissolved in water (200 ml), and ether extracted (3 x 20 ml). The extract gave a yellow solid (0.6 g) which gave τ ($CDCl_3$) 1.62, 1.90, 2.12 (ds, 6-Hs) 3.34, 3.54, 4.28 (ds, 5-Hs) 6.9-7.0 (3 overlapping s, 2,4-N-CH_3s), showing it to be a mixture of the three compounds Xb, c

and d. Recrystallisation of the solid residue from light petroleum (bp 40-60°) gave pale yellow crystals, mp 116-118°, of a cyano-dimethylaminopyrimidine (20 mg). Found C, 56.7; H, 5.8; N, 37.9%. $C_7H_8N_4$ requires C, 56.7; H, 5.4; N, 37.8%.

A similar reaction using 4,6-dichloropyrimidine (6.6 g) gave 4-cyano-6-dimethylaminopyrimidine (15 mg) recrystallised from light petroleum (bp 40-60°) as pale yellow crystals, mp 88-90°. Found C, 56.7; H, 5.9; N, 37.1%. $C_7H_8N_4$ requires C, 56.7; H, 5.4; N, 37.8%) and 4,6-bisdimethylaminopyrimidine (66 mg) mp 105-107° (lit.[18] 108°). Found C, 58.1; H, 8.3; N, 33.5%. Calc. for $C_8H_{14}N_4$: C, 57.8; H, 8.2; N, 33.7%. τ ($CDCl_3$) 1.82 (s, 2-H) 4.73 (s, 5-H) 6.95 (s, 4,6-N-CH_3) (1:1:12).

4-Hydroxyiminomethyl-6-methylpyrimidine, XIIb; To ethanolic hydrogen chloride (11.5 ml containing 4.7 g HCl) cooled to 0° was added 4,6-dimethylpyrimidine (5.4 g) when the hydrochloride of the pyrimidine precipitated. Amyl nitrite (11.7 g) in absolute ethanol (60 ml) was then added to the cold, stirred suspension. The mixture was stirred below 5° for 5 hr then brought to room temperature and the colourless crystalline product was collected. The oxime hydrochloride was dissolved in water and neutralised with potassium bicarbonate to give colourless crystals mp 180° (decomp.) of the hydroxyiminomethyl product (5.0 g, 78%). Found C, 52.1; H, 5.0; N, 30.5%. $C_6H_7N_3O$ requires C, 52.6; H, 5.1; N, 30.7%. τ (CF_3CO_2H) 0.58 (s, 2-H) 1.60 (s, CH:NOH) 1.79 (s, 5-H) 7.0 (s, 6-CH_3) (1:1:1:3).

4-Hydroxyiminomethyl-2,6-dimethylpyrimidine, XIIc, was obtained similarly as the monohydrate (51%) mp 195°. Found C, 49.1; H, 6.0; N, 24.2%. $C_7H_9N_3O.H_2O$ requires C, 49.6; H, 6.5; N, 24.8%. τ (CF_3CO_2H) 1.63 (s, CH:NOH) 2.02 (s, 5-H) 6.88 (s, 2-CH_3) 7.0 (s, 6-CH_3) (1:1:1:3).

2-Chloro-4,6-dicyanopyrimidine, XIII; 2-Hydroxy-4,6-bishydroxyiminomethyl-pyrimidine[16] (10 g) was added to phosphorus oxychloride (100 ml) and the mixture was refluxed for 0.5 hr. Excess phosphorus oxychloride was removed by distillation under reduced pressure and the mixture was cooled then carefully poured onto crushed ice. Ether extract gave a solid (3.0 g) which was vacuum sublimed to give colourless crystals mp 93-95° of 2-chloro-4,6-dicyanopyrimidine (2.5 g, 27.5%). Found C, 43.7; H, 0.7; N, 34.0%. C_6HClN_4 requires C, 43.6; H, 0.6; N, 33.9%.

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