THE SYNTHESIS AND SOME REACTIONS OF CHLOROPYRIMIDINES

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Abstract - Several chloro-hydroxy- and amino- chloropyrimidines have been prepared. The chloro groups have been replaced by hydrogen, mercapto, or hydroxyamino substituents to give useful synthetic intermediates.

The preparation of 2- or 4-chloropyrimidines is almost invariably achieved by reacting the corresponding 2- or 4-hydroxypyrimidine* with phosphorous oxychloride in the presence of a base such as N,N-diethyl or N,N-dimethylaniline.[1,2] However the reaction is often difficult when there are amino groups present, and there are comparatively few examples of the successful synthesis of chloropyrimidines having a 5-amino substituent and the yields are often very low.[1,2] There is only one recorded successful chlorination of a 5-hydroxypyrimidine to give a chloro-hydroxypyrimidine, namely 2,4-dichloro--5-hydroxypyrimidine.[3] We required some simple 5-amino, 5-hydroxy and some hydroxyaminopyrimidines and have prepared and further reacted some interesting chloropyrimidines.

4-Amino-5,6-dihydroxy-2-methylpyrimidine (1a) gave the corresponding 4-chloro compound (1b) (44%) by refluxing with phosphorus oxychloride alone. This product was readily dechlorinated by hydrogenation over palladium charcoal and magnesium oxide to give 4-amino-5-hydroxy-2-methylpyrimidine (1c).

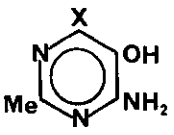
Chlorination of 2,5-dihydroxy-4,6-dimethylpyrimidine (2a) with phosphorus oxychloride and N,N-diethylaniline gave a syrup,which did not crystallise, of the 2-chloro compound (2b) from which crystalline 2-chloro-5-hydroxy-4,6-dimethylpyrimidine phosphate was obtained. The 2-chloro compound gave the corresponding 2-thiouronium chloride (2c) by refluxing with thiourea in ethanol and this product was subsequently converted to the 2-methylthiopyrimidine (2d).

5-Amino-2,4-dichloropyrimidine (3) (16%) was obtained by the direct chlorination of 5-amino-2, 4-

* In order to reduce complexities due to nomenclature and the drawing of structures, the pyrimidinones are referred to as "hydroxypyrimidines" irrespective of their true tautomeric forms.

dihydroxypyrimidine with phosphorus oxychloride in the presence of N,N-diethylaniline. This compound has previously been made by the reduction of 2,4-dichloro-5-nitropyrimidine [4,5] but this is also a low yielding route, and 5-amino-2,4-dichloropyrimidine is best synthesised by the direct chlorination method. Catalytic hydrogenation of this product over palladium charcoal in the presence of magnesium oxide gave 5-aminopyrimidine with some 5-amino-2-5-chloropyrimidine.

2-Chloro-5-nitropyrimidine (4a) has previously been obtained by the action of phosphorus oxychloride on the sodium salt of 2-hydroxy-5-nitropyrimidine.[6] However, the chloro-nitropyrimidine was obtained in 97% yield by the action of phosphorus oxychloride on the 2-hydroxy-5-nitropyrimidine-ethanol adduct (5) obtained by the nitration of 2-hydroxypyrimidine[7]. This route seems to be preferable for the synthesis of (4a).

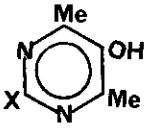


(1)

(a) X = OH

(b) X = Cl

(c) X = H



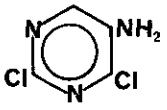
(2)

(a) X = OH

(b) X = Cl

(c) X = SC

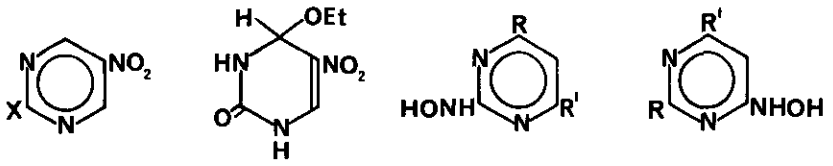
(d) X = MeS



(3)

Reaction of compound (4a) with thiourea in ethanol gave the thiouronium salt (4b) which was converted to the 2-methylthio derivative (4c). 5-Aminopyrimidine can also be obtained by reduction of the nitro compounds (4a) and (4c) but the ethanol adduct (5) resisted hydrogenation at atmospheric pressure over palladium-charcoal or platinum oxide at room temperature and was recovered unchanged. It is known that nitroalkenes are also difficult to hydrogenate under these conditions. Very few hydroxyaminopyrimidines have been reported and pyrimidines can undergo addition of hydroxylamine to the 5,6-bond to give reduced pyrimidines.[1,2] We have found that simple hydroxyaminopyrimidines are easily obtained by refluxing the corresponding chloropyrimidine with a solution of hydroxylamine (free base) in ethanol and we have obtained the hydroxyaminopyrimidines (6a-c) and (7a-c) by this method.

The reactions described in this note have produced some interesting and useful simple pyrimidines and we are developing further synthesis based on these reactions.



(4) (5) (6) (7)

(a) X = Cl (a) R=R'=H (a) R=R'=Me

(b) X = SC (b) R=R'=Me (b) R=H,R'=Cl

(c) X = MeS (c) R=H,R'=Me (c) R=NH_2,R'=Me

EXPERIMENTAL SECTION

All mp are uncorrected. ^{1}H nmr spectra are recorded with δ in ppm relative to Me_4Si in $(CD_3)_2SO$.

4-Amino-6-chloro-5-hydroxypyrimidine (1b)

4-Amino-5,6-dihydroxy-2-methylpyrimidine (2g) and phosphorus oxychloride (20 mℓ) were refluxed for 6 h. The reaction mixture was cooled, then carefully poured on to crushed ice (about 200g) with stirring. The reaction mixture was allowed to attain room temperature overnight, was adjusted to pH 5 to 6 with ammonia, and was continuously extracted with ether for 15 h. The ether extract was dried and then evaporated to yield a pale yellow crystalline product (1.0g, 44%) of the 6-chloropyrimidine (1b), mp 212-220°C (decomp.) (Found: C,38.1; H,3.99; N,26.3%. $C_5H_6ClN_3O$ requires C,37.5; H,3.75; N,26.3%). $M^{+\cdot}$ 159 (^{35}Cl molecular ion). Nmr 2.22(s,2-Me), 6.70 (broad s,NH_2).

4-Amino-5-hydroxy-2-methylpyrimidine (1c)

The above chloropyrimidine (0.5g) in ethanol (100 mℓ) was hydrogenated at room temperature and normal pressure over palladium charcoal (0.1g) and magnesium oxide (0.5g) for 2 h, during which the required amount of hydrogen was tekan up. The reaction mixture was filtered and then evaporated to leave a pale yellow crystalline product (0.4g, 83%) of 4-amino-5-hydroxy-2-methylpyrimidine (as the hydrochloride), mp 270-273°C. (Found: C,37.6; H,5.11; N,25.7%. $C_5H_7N_3OHCl$ requires C,37.2; H,4.95; N,26.0%). $M^{+\cdot}$ 125 (free base). Nmr 2.43(s,2-Me), 7.66(s,6-H), 8.47 (broad s,HN_2).

Reaction of 2,5-dihydroxy-4,6-dimethylpyrimidine[9] with phosphorus oxychloride

The dihydroxypyrimidine (2a) (5g) was refluxed with phosphorus oxychloride (50 mℓ) and N,N-diethylaniline (5 mℓ) for 3 h. The reaction mixture was cooled, poured on to crushed ice (about 250g), stirred for about ½ h, and when the reaction mixture had reached room temperature it was extracted with ether (3 x 80 mℓ). The ether layer was dried and was evaporated to leave a brown syrup (3.2g) which did not crystallise. Continuous ether extraction of the reaction mixture yielded a further

quantity (2.0g) of the syrupy 2-chloro-5-hydroxypyrimidine (2b). Cooling this product in the freezing compartment of the fridge gave some colourless, crystalline, product which was recrystallised from ethyl acetate-light petroleum to give 2-chloro-5-hydroxy-4,6-dimethylpyrimidine phosphate, mp 167-169°C (Found: C,26.3; H,4.12; N,9.94%. $C_6H_7ClN_2O.H_3PO_4.H_2O$ requires C,26.2; H,4.36; N,10.2%). $M^{+\cdot}$158 (for ^{35}Cl molecular ion of the free base). Nmr 2.37(s,4,6-Me), 7.70 (broad s,OH).

5-Hydroxy-4,6-dimethylpyrimidine-2-thiouronium hydrochloride (2c).

The above syrupy chloro compound (3g) was refluxed with thiourea (3g) in ethanol (200 mℓ) for 10 h. After cooling the reaction mixture pale yellow crystals (0.25g) formed and a further crop (0.4g) was obtained by reducing the volume of the solution and further cooling. The product was recrystallised from ethanol as pale yellow crystals (mp 198-205°C) of the pyrimidine thiouronium hydrochloride (2c) (Found: C,33.2; H,5.13; N,22.1%. $C_7H_{11}ClN_4OSH_2O$ requires C,33.0; H,5.27; N,21.5%.) Mass spectrum: m/e 156 for the 2-mercapto compound, m/e 76 for thiourea. Nmr 2.41(s,4,6-Me).

5-Hydroxy-4,6-dimethyl-2-methylthiopyrimidine (2d)

The above product (0.4g)in 2M sodium hydroxide (5 mℓ) was stirred and methyl iodide (0.5g) was added. After 1 h at room temperature the solution was neutralised with 2M hydrochloric acid and the cream solid (0.3g,87%) was collected. It was recrystallised from ethanol to give 5-hydroxy-4,6-dimethyl-2-methylthiopyrimidine, mp 225-229°C (Found: C,49.2; H,5.90; N,16.6%. $C_7H_{10}N_2OS$ requires C,49.4; H,5.88; N,16.5%). $M^{+\cdot}$170. Nmr 2.33(s,4,6-Me), 2.37(s,SMe).

2-Hydroxy-5-nitropyrimidine-ethanol adduct (5)[7], mp 205-208°C (lit.203-203.5°C), was obtained in 39.5% yield by the method of Wempen et al.[7] with the additional procedure of treating the ethanolic solution of product with solid sodium bicarbonate before filtering and then evaporating to dryness.

2-Chloro-5-nitropyrimidine (4a)

The above product (1g) was refluxed with phosphorus oxychloride (10 mℓ) for ½ h when a clear yellow solution was obtained. This solution was cooled, cautiously poured on to crushed ice (about 100g) and the reaction mixture was stirred and allowed to attain room temperature. Extraction of the aqueous solution with dichloromethane (3 x 30 mℓ) followed by drying and evaporation of the organic layer gave 2-chloro-5-nitropyrimidine (1.0g, 97%), mp 106-109°C (lit.[6] 110-111°C), by purification by sublimation (Found: C,30.5; H,1.23; N,25.8%. $C_4H_2ClNO_2$; requires C,30.0; H,1.25; N,26.2%). $M^{+\cdot}$ 129 (for ^{35}Cl molecular ion).

5-Nitropyrimidine-2-thiouronium hydrochloride (4b)

The above product (0.7g) and thiourea (0.5g) were mixed together and dissolved in ethanol (10 mℓ). The reaction mixture was gently warmed, when a crystalline precipitate forms, and was refluxed for 20 min. The mixture was cooled and the crystalline product (0.75g, 73%) was collected. The

product was recrystallised from ethanol as colourless crystals of the thiouronium hydrochloride(4b), mp darkens >150°C(decomp.) >180°C (Found: C,25.5; H,2.29; N,29.4%. $C_5H_6ClN_5O_2S$ requires C,25.4; H,2.54; N,29.7%). Mass spectrum shows m/e 157 as base peak (molecular ion for 2-mercapto-5-nitropyrimidine).

2-Methylthio-5-nitropyrimidine (4c)

The above product (0.7g) was warmed with 0.5M sodium hydroxide (10 mℓ) for a few minutes, the solution was filtered, and then methyl iodide (1 mℓ) was added. The reaction micture was stirred for ½ h and the colourless crystalline precipitate which formed was collected. This was recrystallised from ether to give the methylthiopyrimidine (4c) (0.2g, 46%), mp 82-83°C (lit.[8] 82-83°C). $M^{+\cdot}$ 171.

Free hydroxylamine in ethanol

Hydroxylamine hydrochloride (12g) was dissolved in ethanol (200 mℓ) with warming and a warm solution of potassium hydroxide (11.2g) in ethanol (40 mℓ) was added slowly with stirring. The mixture was cooled to room temperature and the solution filtered. The filter cake was washed with ethanol and the filtrate and washings were combined to give an 0.7M solution of hydroxylamine.

2-Hydroxyamino-4,6-dimethylpyrimidine (6b)

A solution of 2-chloro-4,6-dimethylpyrimidine (2.4g) in ethanol (5 mℓ) was added to the above solution of hydroxylamine in ethanol (240 mℓ) and the mixture was refluxed for 4 h. The reaction mixture was evaporated to dryness and then the residue was recrystallised from ethanol to give the hydroxyaminopyrimidine (6b). (1.3g,63%), mp 207-210°C (lit.[10] 210-211°C) (Found: C,51.6; H,6.30; N,30.5%. $C_6H_9N_3O$ requires C,51.8; H,6.47; N,30.2%). $M^{+\cdot}$ 139. Nmr 2.25(s,4,6-Me), 6.51(s, 5-H), 8.9 (broad s,NH,OH). The above method was used to obtain the following compounds:

2-Hydroxyaminopyrimidine (as hydrochloride) (6a) (42%), mp 180°C. M^{+} 111 (free base) Nmr 6.99(t, 5-H), 8.63(d,4,6-H), 9.0 (broad s,NH,OH).

2-Hydroxyamino-4-methylpyrimidine (6c) (83%), mp 105°C. $M^{+\cdot}$ 125. Nmr 2.31(s,4-Me),4.05 (broad s, NH,OH), 6.66(d,5-H), 8.26(d,6-H).

4-Hydroxyamino-2,6-dimethylpyrimidine (7a) (80%). mp 198-200°C. (Found: C,52.2; H,7.00; N,30.6% $C_6H_9N_3O$ requires C,51.8; H,6.47; N,30.2%). $M^{+\cdot}$ 139. Nmr 2.21(s,4-Me), 2.27(s,2-Me),6.38(s,5-H), 8.5(broad s, NH,OH).

4-Chloro-6-hydroxyaminopyrimidine (7b) (50%), mp 165°C (Found: C,33.2; H,3.00; N,28.3%. $C_4H_4ClN_3O$ requires C,33.0; H,2.74; N,28.8%). $M^{+\cdot}$ 145 (for ^{35}Cl molecular ion).

2-Amino-4-hydroxyamino-6-methylpyrimidine (as hydrate) (7c) (45%), mp range 200°C (Found: C,37.9; H,5.60; N,34.7%. $C_5H_8N_4O.H_2O$ requires C,38.0; H,6.33; N,35.4%). $M^{+\cdot}$ 140.

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REFERENCES

1. D.J. Brown, "The Pyrimidines", Wiley-Interscience, New York and London, 1962.
2. D.J. Brown, "The Pyrimidines, Supplement I", Wiley-Interscience, New York and London, 1970.
3. D.T.Hurst, J.F.W.McOmie and J.B. Searle, J.Chem.Soc., 1965, 7116.
4. N. Whittaker, J.Chem.Soc., 1951, 1565.
5. S. Inoue, Chem.Pharm.Bull., 1958, 6,343.
6. R.O. Roblin, P.S. Winnek and J.P. English, J.Amer.Chem.Soc., 1942,64,567.
7. I. Wempen, H.U. Blank and J.J. Fox, J.Heterocyclic Chem., 1969, 6,593.
8. D.T. Hurst and J.C. Christophides, Heterocycles, 1977,6, 1999.
9. R. Hull, J.Chem.Soc., 1956, 2033.
10. K. Shirakawa, J.Pharm.Soc.Japan, 1959, 9, 1477.

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