The Synthesis of Some 2-(Substituted) 5-Nitropyrimidines

Derek T. Hurst* and (in part) John Christophides

School of Chemical and Physical Sciences,
Kingston Polytechnic, Kingston upon Thames, KT1 2EE, U.K.

Summary

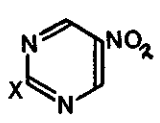
The synthesis of 2-(fur-2-yl)-, 2-(5-nitrofur-2-yl)-,2-(N-morpholinyl)-, and 2-methylsulphonyl-5-nitropyrimidine is described together with the synthesis of some other 2-(substituted) 5-nitropyrimidines.

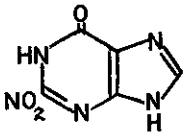
2-(N-Morpholinyl)- and 2-(fur-2-yl)-5-nitropyrimidine were reduced to the corresponding 5-amino derivatives.

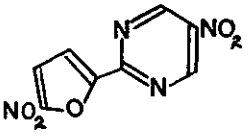
Although polysubstituted 5-nitropyrimidines are relatively easily obtained by nitration of suitably substituted pyrimidines[1], there are comparatively few known examples of simple substituted nitropyrimidines and 5-nitropyrimidine (Ia)[2,3] is the only known unsubstituted nitropyrimidine. There are no examples of 2- or 6-nitropyrimidines known although there is one such example in the purine series namely 2-nitrohypoxanthine (II) and its 9-β-D-ribonucleoside[4,5].

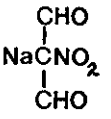
2-Trifluoroacetamido-5-nitropyrimidine (Ib) has been found[6] to be useful in treating infections caused by Trichomonas vaginalis and some compounds of type III have also been found to be active against this protozoan as well as having antibacterial activity[7]. Some other 2-(5-nitrofur-2-yl)pyrimidines have been shown to have bactericidal properties[8].

As part of our studies on pyrimidines and related compounds having potential pharmaceutical activity, and as part of our studies on nitro and nitrosopyrimidines, we have obtained a number of 5-nitropyrimidines having pharmaceutical potential.









Ia. X=H

b. X=CF_3CONH

c. X=MeS

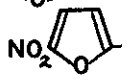
d. X= 

e. X= 

f. X=$MeSO_2$

g. X=NH_2NH

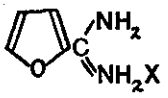
h. X= 

i. X= 

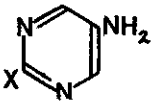
II

III

IV



V



VIa. X= 

b. X= 

Using the method of Boarland and McOmie[9], which involves the condensation of sodium nitromalondialdehyde (IV) with S-methylisothiourea in aqueous N-ethylpiperidine, we have obtained 2-methylthio-5-nitropyrimidine (Ic) in improved yield (35% relative to 26.4%[9]). Like the previous workers we have investigated various reaction conditions and basic catalysts including sodium hydroxide, sodium carbonate, triethylamine and "Triton B", but of these only aqueous N-ethylpiperidine gave moderate yields of the required product. In several reactions the only organic nitro-product isolated was 1,3,5-trinitrobenzene which is reported[10] to be the degradation product of sodium nitromalondialdehyde in aqueous solution.

When the reaction was carried out using morpholine as a basic catalyst a good yield of 2-(N-morpholinyl)-5-nitropyrimidine (Id) was obtained. An attempted condensation of sodium nitromalondialdehyde with thiourea in the presence of piperidine is reported[9] to give 5-nitro-2-(N-piperidinyl)pyrimidine (Ie). Thus it seems that 2-mercapto(or 2-methylthio)-5-nitropyrimidines readily undergo nucleophilic attack at sulphur which explains the low yield of the expected condensation products in aqueous

solution. Brown and Foster[11] have found that Ic is very susceptible to aminolysis.

The oxidation of an aqueous suspension of Ic using chlorine gave 2-methylsulphonyl-5-nitropyrimidine (If) in reasonable yield, and the reaction of Id with hydrazine in ethanol gave an excellent yield of the hydrazino derivative Ig. However, we have failed to oxidise this product to 5-nitropyrimidine using aqueous copper (II) sulphate.

The condensation of 2-furamidine (V) with sodium nitromalondialdehyde in aqueous piperidine gave 2-(fur-2-yl)-5-nitropyrimidine (Ih) in good yield. Attempted oxidations of this product using various oxidants have failed to give 5-nitropyrimidine-2-carboxylic acid but reaction with nitric acid gave 2-(5-nitrofur-2-yl)-5-nitropyrimidine (Ii), although in poor yield. Roberts and Shealy[12] failed to oxidise 2-styryl-5-nitropyrimidine (Ij) to 5-nitropyrimidine-2-carboxylic acid although they were able to oxidise 2-styryl-5-(substituted amino)pyrimidines to the corresponding 5-(substituted amino)pyrimidine-2-carboxylic acids.

The reduction of compounds Id and Ih using hydrazine in ethanol in the presence of palladium charcoal gave good yields of the 5-aminopyrimidines VIa and VIb respectively, but we have not yet further investigated these compounds.

Thus condensations using sodium nitromalondialdehyde and nucleophilic displacements using 2-(substituted thio)pyrimidines provide useful routes to pyrimidines having pharmaceutical potential. We hope to report the biological properties of such compounds at a later date.

Experimental

2-Methylthio-5-nitropyrimidine, Ic[9]; Sodium nitromalondialdehyde hydrate (21.0 g) and S-methylisothiouronium sulphate (19.0 g) were dissolved in water (200 ml) and N-ethylpiperidine (15.0 g) was added. The mixture was warmed on a water-bath for 5 min, then allowed to stand at room temperature

for 2 days. The dark precipitate was collected and recrystallised from ether (charcoal) as yellow crystals, mp 80-81° (lit.[9] 82-83°) of the methylthiopyrimidine (5.6 g, 35%).

2-Methylsulphonyl-5-nitropyrimidine, If; The above product (3.0 g) was suspended in water and cooled to 0-5° by immersion in an ice bath. Chlorine was passed through the suspension for 1 hr during which the yellow crystalline compound reacted to give a colourless product. The mixture was allowed to stand in ice for 1 hr after which the solid was collected and recrystallised from ethanol to give 2-methylsulphonyl-5-nitropyrimidine (1.7 g, 48%) as colourless needles mp 157.5-158°. Found C, 29.7; H, 2.5; N, 20.8%. $C_5H_5N_3O_4S$ requires C, 29.6; H, 2.5; N, 20.7%.

2-Hydrazino-5-nitropyrimidine, Ig; 2-Methylsulphonyl-5-nitropyrimidine (1.0 g) was dissolved in boiling ethanol (50 ml) and hydrazine hydrate (0.5 ml) was added. The mixture was refluxed for 1 hr, filtered, and the filtrate cooled in ice. The solid which formed was recrystallised from ethanol (charcoal) as colourless needles, (0.8 g, 100%) mp 173-175° (lit.[13] 168-169°), which became bright yellow when left in the air. Found C, 30.9; H, 3.4; N, 45.3%. Calc. for $C_4H_5N_5O_2$: C, 31.0; H, 3.2; N, 45.1%.

2-(N-Morpholinyl)-5-nitropyrimidine, Id; Sodium nitromalondialdehyde hydrate (10.0 g) and S-methylisothiouronium sulphate (10.0 g) were dissolved in water (100 ml) and morpholine (10.0 g) was added. The reaction mixture was warmed on a water bath for 5 min then allowed to stand at room temperature overnight. The solid which formed was recrystallised from ethanol-light petroleum (bp 40-60°) (charcoal) as pale yellow crystals, mp 165-168°, of the N-morpholinylpyrimidine (5.3 g, 50%). Found C, 45.6; H, 4.9; N, 26.6%. $C_8H_{10}N_4O_3$ requires C, 45.6; H, 4.8; N, 26.7%. M^+ 210.

$\tau(CDCl_3)$ 0.93 (s,4,6-H) 6.0 (m,$(CH_2)_2N$) 6.24 (m, $O(CH_2)_2$) (1:2:2).

2-(Fur-2-yl)-5-nitropyrimidine, Ih; Furamidine hydrochloride (50 g) was dissolved in water (250 ml) and to this was added sodium nitromalondialdehyde hydrate (36 g) in water (250 ml). Fine colourless needles separated almost immediately but on the addition of piperidine (10 ml) these dissolved and a yellow precipitate formed. The reaction mixture was allowed to stand at room temperature overnight and the product (36 g, 82%) was collected. A portion was recrystallised from glacial acetic acid as yellow needles, mp 226-228°, which darken on exposure to light and air, of the furylpyrimidine. Found C, 50.3; H, 2.8; N, 22.1%. $C_8H_5N_3O_3$ requires C, 50.2; H, 2.6; N, 22.0%. M^+ 191. $\tau(d_6DMSO)$ 1.4 (s,4,6-H) 2.81 (d,furan-5-H?) 3.30 (d,furan-3-H?) 6.10 (m, furan-4-H) (2:1:1:1).

2-(5-Nitrofur-2-yl)-5-nitropyrimidine, Ii; The above product (2.0 g) was warmed with concentrated nitric acid (10 ml) for 1-2 min. An exothermic reaction occurred which kept the solution boiling for a few minutes. On cooling the reaction mixture in ice, crystals were obtained. The nitrofurylpyrimidine (0.4 g, 16%) was recrystallised from ethanol as colourless plates mp 186-188°. Found C, 40.7; H, 1.7; N, 23.5%. $C_8H_4N_4O_5$ requires C, 40.6; H, 1.7; N, 23.7%. M^+ 236. $\tau(d_6DMSO)$ 0.35 (s,4,6-H) 2.15 (m,furan-3,4-H) (1:1).

5-Amino-2-(N-morpholinyl)pyrimidine, VIa; Compound Id (5.0 g) was dissolved in ethanol (200 ml) then hydrazine hydrate (16 ml) and 10% palladium on charcoal (0.5 g) were added. The mixture was refluxed for 4 hr after which the catalyst was filtered off and the reaction mixture was concentrated to about 15 ml when a yellow crystalline product was obtained. Recrystallisation of this product from ethanol-light petroleum (bp 40-60°) gave off-white crystals, mp 99°, of the aminomorpholinylpyrimidine (1.8 g, 42%). Found C, 53.1; H, 6.7; N, 30.8%. $C_8H_{12}N_4O$ requires C, 53.3;

H, 6.7; N, 31.1%.

5-Amino-2(fur-2-yl)pyrimidine, VIb (81%) was obtained in a similar way as pale yellow crystals (from ethanol) mp 182-184°. Found C, 59.4; H, 4.4; N, 26.4%. $C_8H_7N_3O$ requires C, 59.6; H, 4.4; N, 26.1%.

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