C-Alkylation of Pyrimidines by an Oxoalkyl Reactant

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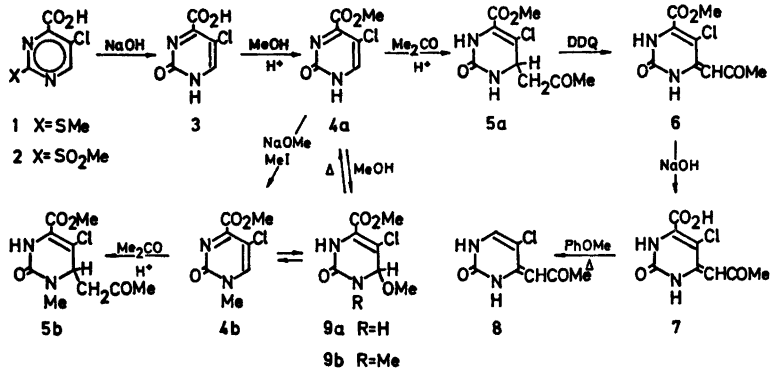
Certain 2-pyrimidinones are active metaphase inhibitors.[1] In this work we describe a route developed for the synthesis of some 4-acetonyl derivatives *6* – *8* of 2-pyrimidinones. An essential feature of the synthesis is the adduct formation between an electron deficient pyrimidine system and acetone. Such an addition was to be expected from the tendency of covalent hydration in nitrogen heterocycles.[2,3] For this to occur in monocyclic systems the ring should contain two doubly bonded nitrogen atoms and an electron withdrawing substituent.[4] Thus 5-nitropyrimidines are largely hydrated,[5] whereas hydration of 2-pyrimidinone is normally not seen but could be demonstrated by kinetic deuteriation experiments.[6] Activation by *N*-quaternization results in the analogous pseudo-base formation.[7] Addition of other nucleophiles have been less extensively studied.[7,8] We now have found 5-chloropyrimidin-2-one containing a carbonyl function in the 4-position to be readily covalently methanolated and acetonylated. When the latter adduct is dehydrogenated, the overall effect is a substitution of a hydrogen in the pyrimidine ring with a carbon substituent.

The starting pyrimidine *1* in the synthesis was prepared by condensation between *S*-methylisothiouronium iodide and mucochloric acid.[9] *1* was oxidised to the methyl sulfone *2* with peracetic acid.[10] Hydrolysis in aqueous alkali of the latter yielded the lactam *3* which was esterfied to *4a* in methanol with acid catalysis. *4a* was isolated as the covalently methanolated adduct *9a*, which, however, readily lost methanol on warming. A substituent such as a methyl group on N-1, *4b*, did not noticeably affect the tendency for methanol adduct formation; recrystallization of *4b* from methanol yielded *9b*. In ^{1}H NMR H-6 in the pyrimidines *4a* and *4b* resonates as a sharp singlet at δ 8.1 and 8.5, and in the respective methanol adducts as broad singlets at δ 5.3 and 5.4. Both *4a* and *4b* added acetone with acid catalysis; the *N*-methyl group in *4b* appeared to slightly decrease the reaction rate. Presumably it is the enol form of acetone which adds to a protonated pyrimidine molecule. ^{1}H NMR showed that H-6 in the adducts *5a* and *5b* resonates as a partly resolved quartet at δ 4.8 and 4.6. The mass spectra of the methanol adducts *9* show that these are thermally dissociated into the parent pyrimidines *4* and methanol in the mass spectrometer. The acetone adducts *5*, however, are volatilised intact since the molecular ion signal for the parent pyrimidines *4* was absent and a major fragment in the spectra at [M – 57] corresponds to electron impact induced expulsion of $^{\cdot}CH_2COCH_3$ from the molecular ion of *5*.

Dehydrogenation of *5a* to the pyrimidine was achieved using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). ^{1}H NMR in trifluoroacetic acid (TFA) showed that *6*, as well as *7* and *8*, exists predominantly as the acetonylidene tautomer (Scheme 1) rather than as the corresponding acetonyl tautomer. This preference is attributed to conjugation with the ketocarbonyl group. The ester hydrolysis of *6* to *7* was run in aqueous alkali and finally the acid *7* could be decarboxylated to *8* in good yield by heating a solution of *7* in anisole.

Experimental. 4-Carboxy-5-chloropyrimidin-2-one 3. 2-Methylsulfonyl-4-carboxy-5-chloropyrimidine [10] (32 mmol) was added in portions to 5 M NaOH (30 ml) with stirring; the reaction was slightly exothermic. The mixture was stirred without heating for 30 min and then acidified to pH *ca.* 1 with HCl. The precipitate collected was washed with water and dried *in*



Scheme 1.

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vacuo at 60 °C over NaOH pellets; yield 91 %, m.p. 145–147 °C (dec.). Anal. $C_5H_3ClN_2O_3$: C, H. ^1H NMR (DMSO-d_6): δ 8.60 (H-6).

4-Methoxycarbonyl-5-chloropyrimidin-2-one 4a. 4-Carboxy-5-chloropyrimidin-2-one (11 mmol) was dissolved in methanol which was saturated with HCl gas. The solution was left at room temperature for 17 h before evaporation. The residue was recrystallized from methanol and dried at 70 °C; yield 82 %, m.p. 160–161 °C. Anal. $C_6H_5ClN_2O_3$: C, H. ^1H NMR ($CDCl_3$): δ 4.00 (4-CO_2Me), 8,50 (H-6).

1-Methyl-4-methoxycarbonyl-5-chloropyrimidin-2-one 4b. 4-Methoxycarbonyl-5-chloropyrimidin-2-one (20 mmol) was added to 0.34 M methanolic potassium methoxide (75 ml, 25 mmol) and the resultant solution evaporated to dryness under anhydrous conditions. The dried potassium salt thus obtained was suspended in anhydrous DMF (100 ml), methyl iodide (42 mmol) added, and the mixture stirred at room temperature for 20 h. The solvent was then distilled off at reduced pressure, the residue extracted with chloroform (100 ml) and the chloroform solution washed with 0.2 M NaOH (2 × 5 ml) and dried ($MgSO_4$) before evaporation. The residual product, after recrystallisation from methanol, was dried at 80 °C (0.1 Torr); yield 52 %, m.p. 135 °C. Anal. $C_7H_7ClN_2O_3$: C, H. ^1H NMR ($CDCl_3$): δ 3.67 (*N*-Me), 3.97 (4-CO_2Me), 8.14 (H-6).

4-Methoxycarbonyl-5-chloro-6-(2-oxopropyl)-1,6-dihydropyrimidin-2-one 5a. 4-Methoxycarbonyl-5-chloropyrimidin-2-one (18 mmol) in a solution of acetone (75 ml) and conc. HCl (0.2 ml) was heated under reflux for 90 min. After evaporation the residual material was crystallized from chloroform–isopropyl ether; yield 76 %, m.p. 127 °C. Anal. $C_9H_{11}ClN_2O_4$: C, H. ^1H NMR ($CDCl_3$): δ 2.22 (COMe), 2.99 (CH_2CO, m), 3.90 (4-CO_2Me), 4.75 (H-6, partly resolved q).

1-Methyl-4-methoxycarbonyl-5-chloro-6-(2-oxopropyl)-1,6-dihydropyrimidin-2-one 5b was obtained by heating 1-methyl-4-methoxycarbonyl-5-pyrimidin-2-one under reflux in acetone and conc. HCl as above for 210 min; yield 90 %, m.p. 132 °C ($CHCl_3$–iPr_2O). Anal. $C_{10}H_{13}ClN_2O_4$: C, H. ^1H NMR ($CDCl_3$): δ 2.22 (COMe), 2.90 (CH_2CO, m), 2.94 (*N*-Me), 3.90 (4-CO_2Me), 4.55 (H-6, q).

4-Methoxycarbonyl-5-chloro-6-(2-oxopropyl)-pyrimidin-2-one 6. 4-Methoxycarbonyl-5-chloro-6-(2-oxopropyl)-1,6-dihydropyrimidin-2-one (12 mmol) was dissolved in dioxane (50 ml) together with DDQ (14 mmol). The reaction mixture was stirred at room temperature for 3 days and then filtered. The residual material was crystallized from chloroform–isopropyl ether; yield 50 %, m.p. 225–226 °C. Anal. $C_9H_9ClN_2O_4$: C, H. ^1H NMR (TFA): δ 2.43 (CO_2Me), 6.33 (–CH=); (the acetonylidene tautomer).

4-Carboxy-5-chloro-6-(2-oxopropyl)pyrimidin-2-one 7. 4-Methoxycarbonyl-5-chloro-6-(2-oxopropyl)pyrimidin-2-one (26 mmol) was added to 1 M NaOH (5 ml) and the mixture stirred at room temperature for 1 h. The reaction mixture was then acidified to pH *ca.* 1 and the precipitated material recrystallized from aq. methanol; yield 67 %, m.p. 192 °C (dec). Anal. $C_8H_7ClN_2O_4$: C, H. ^1H NMR (TFA): δ 2.45 (COMe), 6.35 (CH=); (the acetonylidene tautomer).

4-(2-Oxopropyl)-5-chloropyrimidin-2-one 8. 4-Carboxy-5-chloro-6-(2-oxopropyl)pyrimidin-2-one (1.3 mmol) was added to anisole (2 ml) and the resultant solution heated under reflux for 45 min. After evaporation at reduced pressure the residue was crystallized from chloroform–diisopropyl ether; yield 85 %, m.p. 197 °C. Anal. $C_7H_7ClN_2O_2$: C, H. ^1H NMR (TFA): δ 2.50 (COMe), 6.06 (CH=), 7.85 (H-6); (the acetonylidene tautomer).

4-Methoxycarbonyl-5-chloro-6-methoxy-1,6-dihydropyrimidin-2-one 9a. When 4-methoxycarbonyl-5-chloropyrimidin-2-one *4a* after recrystallization from methanol is dried *in vacuo* at room temperature instead of heating as when *4a* is desired, the covalently bound methanol adduct is obtained. Anal. $C_7H_9ClN_2O_4$: C, H. ^1H NMR ($CDCl_3$): δ 3.33 (6-OMe), 3.93 (4-CO_2Me), 5.30 (H-6).

1-Methyl-4-methoxycarbonyl-5-chloro-6-methoxy-1,6-dihydropyrimidin-2-one 9b was similarly obtained on recrystallization of *4b* from methanol and drying at room temperature. Anal. $C_8H_{11}ClN_2O_4$: C, H. ^1H NMR ($CDCl_3$): δ 3.08 (*N*-Me), 3.20 (6-OMe), 3.97 (4-CO_2Me), 5.38 (H-6).

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