Acta Chemica Scandinavica B 33 (1979) 515—518

Regioselective *N*-Alkylation in 5-Fluorouracil

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5-Fluorouracil has been alkylated selectively on N-1 *via* its 4-methylthio derivative. Similarly N-3 alkylation is achieved *via* the 2-methylthio derivative of 5-fluorouracil.

5-Fluorouracil (5-FU) is an important drug in the treatment of neoplastic diseases.[1] Search is in progress, however, for analogues with improved drug characteristics.[2] We herein report syntheses of some *N*-substituted homologues of 5-FU. Direct alkylation of 5-FU may yield either the N-1 or the N-3 alkylated product, or a mixture thereof, or may result in dialkylation depending on reagents and solvents used.[3–7] Thus 5-FU reacted with chloroacetone to the dialkylated product *6* in low yield. In principle regioselective monoalkylation is attainable if the reactivities of the nitrogen atoms are made different by introduction of suitable substituents. For this purpose we have converted one of the oxo groups in 5-FU into a sulfide group. The electron releasing sulfide group has the added advantage that it activates the pyrimidine towards alkylation and is readily reconverted into an oxo group after the *N*-alkylation. Thus monoalkylation on N-1 in 5-FU was realized by way of the 4-thiolactam *2*; the latter is synthesized from 5-FU by treatment with phosphorus pentasulfide in pyridine.[8] The 4-thiolactam *2* was readily *S*-methylated to *3*.[9] The latter as potassium salt in dimethylformamide (DMF) was *N*-alkylated to *4* on treatment with an alkyl halide. The *N*-alkylated uracil *5* was generated from *4* by hydrolysis in a mixture of concentrated HCl and methanol. Regioselective N-1 alkylation in the case of the methyl derivative *5a* was verified by comparison with an authentic specimen.[10] The structures of the higher homologues are assigned by chemical analogy and by spectroscopic evidence. Thus the 1-methyl derivative *5a* has UV absorption maxima at 274 nm in 0.1 M HCl and at 271 nm in 0.1 M NaOH; the respective adsorption bands for the 3-methyl isomer *11* are at 266 and 292 nm. The UV absorption maxima for the other *N*-alkylated uracils in 0.1 M HCl were in the region 270–274 nm, and in 0.1 M NaOH in the region 269–272 nm. The weak shift to shorter wavelengths and a consistent and weak decrease in the molar absorptivity with increase in the pH (*cf.* Table 1) are consistent with alkylation on N-1 as in *5*. ^{1}H NMR gave little information about which isomer was obtained since the chemical shifts for H-6 in both isomers *5a* and *11* were very similar, δ 7.6–7.7, in agreement with a recent NMR study of uracil and derivatives.[11]

The 2-methylthio derivative *9* was the key intermediate for alkylation on N-3. *9* was synthesized by dithiation of 5-FU to *7*[12] which was *S*-methylated to *8*; selective removal of the 4-methylthio group in *8* could be effect by hydrolysis in 2 M NaOH. Attempts to carry out the selective hydrolysis of *8* under acidic conditions gave mainly 5-FU. The regioselective hydrolysis of *8* to *9* under alkaline conditions parallels the finding that 2,4-dimethoxy-5-fluoropyrimidine under alkaline conditions can be hydrolyzed selectively in the 4-position.[8] The ^{1}H NMR spectra of the *N*-methyl regioisomers *3* and *9* are closely similar but the isomers are distinguished by different UV spectra recorded in NaOH; *3* has λ_{max} at 314 nm and *9* at 281. Methylation of the potassium salt of *9* using methyl iodide gave the N-3 methyl derivative *10*. The assignment of structure to the latter follows from the product formed

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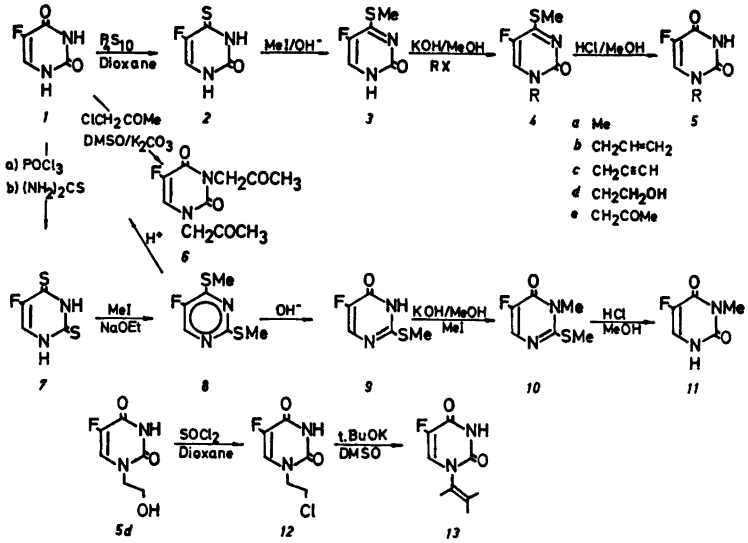

after acid hydrolysis which was identified as the N-3 methylated homologue of 5-FU *11*.

For N-1 vinylation of 5-FU the β-hydroxyethyl derivative *5d* was treated with thionyl chloride, and HCl eliminated from the chloro derivative *12* by the reaction with potassium *t*-butoxide in dimethylsulfoxide (DMSO) to *13*.

In order to differentiate between the monoalkylated derivatives of 5-FU, a table over spectroscopic data for the methyl derivatives has been assembled (Table 1). In ^{1}H NMR the chemical shifts for the *N*-methyl and *O*-methyl pairs are significantly different. The chemical shifts for the *O*-methyl isomers are similar and so are the shifts for the *N*-methyl isomers. The UV absorptions, however, are significantly different when measured both in acid and alkaline media pH 13; all isomers can thus be identified by spectroscopy.

EXPERIMENTAL

1-Alkyl-4-methylthio-5-fluoropyrimidin-2-one 4. 4-Methylthio-5-fluoropyrimidin-2-one [9] and KOH in equivalent amounts were dissolved in MeOH and the potassium salt isolated by evaporation of the solution. The salt (12 mmol) and the alkyl halide (16 mmol) in DMF (50 ml) were stirred together at room temperature. The progress of the reaction was monitored by TLC; silica gel F_{254} (Merck), EtOAc. When the reaction was complete, the solvent was removed under reduced pressure (1 Torr) and the residue extracted with chloroform (60 ml). The chloroform solution was washed with 0.1 M NaOH (2 × 10 ml), with water and then dried ($MgSO_4$) before evaporation. The residue was purified by crystallization as described below.

4a from methyl iodide in 76 % yield after 24 h; m.p. 154 °C (EtOAc/Ligroin). Anal. $C_5H_7FN_2OS$: C, H. ^{1}H NMR (TFA): δ 2.96 (*S*-Me), 3.83 (*N*-Me), 8.30 (H-6).

4b from allyl bromide in 72 % yield after 5 h;

Table 1. ^{1}H NMR and UV data for methyl derivatives of 5-FU.

	^{1}H NMR in TFA; δ-values					UV, 0.1 M HCl		UV, 0.1 M NaOH	
	H-6	N-1	N-3	O-2	O-4	λ_{max} nm	log ε	λ_{max} nm	log ε
1-Methyl-5-fluorouracil (*5a*)	7.70	3.56				274	3.92	271	3.80
3-Methyl-5-fluorouracil (*11*)	7.63		3.53			266	3.82	292	3.99
2-Methoxy-5-fluoropyrimidin-4-one [8]	8.16			4.31		263	3.67	269	3.82
4-Methoxy-5-fluoropyrimidin-2-one [8]	8.10				4.34	280	3.65	290	3.82

m.p. 117 °C (EtOAc). Anal. $C_8H_9FN_2OS$: C, H. ^1H NMR (TFA): δ 2.93 (*S*-Me), 4.73 (*N*-CH_2-), 8.25 (H-6).

4c from propargyl bromide in 71 % yield after 40 h; m.p. 141–142 °C (EtOAc). Anal. $C_8H_7FN_2OS$: C, H. ^1H NMR (TFA): δ 2.88 (CH), 3.00 (*S*-Me), 4.95 (CH_2), 8.58 (H-6).

4d from ethylene bromohydrin in 77 % yield after 24 h; m.p. 161–162 °C (Acetone). Anal. $C_7H_9FN_2O_2S$: C, H. ^1H NMR (TFA): δ 2.96 (*S*-Me), 4.31 and 4.35 (*N*-CH_2CH_2-*O*), 8.36 (H-6).

4e from chloroacetone in DMSO 85 % yield after 2 h; m.p. 195–196 °C (EtOH). Anal. $C_8H_9FN_2O_2S$: C, H. ^1H NMR (TFA): δ 2.45 (Ac), 2.96 (*S*-Me), 5.16 (CH_2), 8.18 (H-6).

1-Alkyl-5-fluorouracil 5. A solution of *4* (10 mmol) in methanol (100 ml) and conc. HCl (40 ml) was heated at 60 °C. The progress of the reaction was monitored by TLC; silica gel F_{254} (Merck), EtOAc or dioxane. After the reaction was completed the mixture was evaporated and the desired compound purified by crystallization of the residue.

5a[10] 80 % yield after 12 h; m.p. 263–264 °C (EtOH/H_2O). Anal. $C_5H_5FN_2O_2$: C, H. ^1H NMR (TFA): δ 3.56 (*N*-Me), 7.70 (H-6).

5b[3] 72 % yield after 12 h; m.p. 126–127 °C (EtOAc). Anal. $C_7H_7FN_2O_2$: C, H. ^1H NMR (TFA): δ 4.53 (*N*-CH_2), 7.68 (H-6). UV (0.1 M HCl; log ε): 273 (3.92) nm; (0.1 M NaOH): 271 (3.80) nm.

5 43 % yield after 8 days at room temperature. Before recrystallization the crude product was filtered through a silica gel column in dioxane solution. M.p. 150–151 °C (EtOAc). Anal. $C_7H_5FN_2O_2$: C, H. ^1H NMR (TFA): δ 2.63 (CH), 4.68 (CH_2), 7.96 (H-6). UV (0.1 M HCl, log ε): 270 (3.96) nm; (0.1 M NaOH): 269 (3.78) nm.

5d 78 % yield after 24 h; m.p. 159–160 °C (iPrOH). Anal. $C_6H_7FN_2O_3$: C, H. ^1H NMR (TFA): δ 4.19 and 4.20 (*N*-CH_2-CH_2-*O*), 7.81 (H-6). UV (0.1 M HCl, log ε): 274 (3.94) nm; (0.1 M NaOH): 272 (3.80) nm.

5e 64 % after 12 h, m.p. 220 °C (iPrOH). Anal. $C_7H_7FN_2O_3$): C, H. ^1H NMR (TFA): δ 2.41 (Ac), 4.88 (*N*-CH_2), 7.58 (H-6). UV (0.1 M HCl, log ε): 270 (3.90) nm; (0.1 M NaOH): 269 (3.80) nm.

1,3-Diacetonyl-5-fluorouracil 6. A mixture of 5-fluorouracil (16 mmol), chloroacetone (16 mmol) and anhydrous K_2CO_3 (16 mmol) in DMSO (50 ml) was stirred at room temperature for 40 h. Evaporation at reduced pressure and crystallization of the residue from iPrOH yielded the title compound in 15 % yield, m.p. 132 °C. Anal. $C_{10}H_{11}FN_2O_4$: C, H. ^1H NMR (TFA): δ 2.38 and 2.43 (Me), 4.91 and 5.10 (CH_2), 7.60 (H-6).

2,4-Dimethylthio-5-fluoropyrimidine 8. Methyl iodide (50 mmol) was added over 30 min to a solution of 2,4-dithio-5-fluorouracil[12] (23 mmol) in 0.48 M ethanolic sodium ethoxide (100 ml) at room temperature. The mixture was then heated under reflux for 40 min and evaporated. The residue was extracted with ether (150 ml), the ethereal extracts washed with 1 M NaOH, water, and dried ($MgSO_4$) before evaporation. The residue was the title compound, yield 73 %, which was further purified by sublimation before elemental analysis; m.p. 39 °C. Anal. $C_6H_7FN_2S_2$: δ C, H. ^1H NMR (TFA): δ 2.88 (*S*-Me), 8.10 (H-6).

2-Methylthio-5-fluoropyrimidin-4-one 9.[13] 2,4-Dimethylthio-5-fluoropyrimidine (4 mmol) was suspended in 2 M NaOH (15 ml) and the mixture heated at 80 °C for 3 days. Ether extraction of the cold reaction mixture removed any unchanged *8*. The title compound was precipitated on neutralization and was purified by crystallization from H_2O, m.p. 240 °C. Anal. $C_6H_5FN_2OS$: C, H. ^1H NMR (TFA): δ 2.95 (*S*-Me), 8.11 (H-6).

2-Methylthio-3-methyl-5-fluoropyrimidin-4-one 10. The potassium salt of 2-methylthio-5-fluoropyrimidin-4-one was prepared and methylated with methyl iodide as described for *4a* above. The reaction mixture was evaporated at reduced pressure (1 Torr) and the residue extracted with ether. Evaporation of the ether solution and recrystallization of the residue from EtOAc–Ligroin gave the title compound in 30 % yield, m.p. 126–128 °C. Anal. $C_6H_7FN_2OS$: C, H. ^1H NMR (TFA): δ 3.05 (*S*-Me), 3.83 (N-Me), 8.05 (H-6).

3-Methyl-5-fluorouracil 11.[11] 2-Methylthio-3-methyl-5-fluoropyrimidin-4-one was hydrolyzed in acid solution as described for the synthesis of *5a* above; yield 87 %, m.p. 190–191 °C (iPrOH). Anal. $C_5H_5FN_2O_2$: C, H. ^1H NMR (TFA): δ 3.53 (*N*-Me), 7.63 (H-6).

1-2'-Chloroethyl-5-fluorouracil 12. Thionyl chloride (34 mmol) dissolved in dioxane (80 ml) was added dropwise to a solution of 1-2'-hydroxyethyl-5-fluorouracil (12 mmol) dissolved in dioxane (60 ml) containing a few drops of pyridine. The mixture was next refluxed for 50 min and then evaporated to dryness. The residue on trituration with ice-water gave the crystalline title compound in 80 % yield. The analytical specimen was recrystallized from iPrOH, m.p. 199–201 °C. Anal. $C_6H_6ClFN_2O_2$: C, H. ^1H NMR (TFA): δ 3.86 and 4.25 ($-CH_2-CH_2-$), 7.76 (H-6).

1-Vinyl-5-fluorouracil 13. A solution of 1-2'-chloroethyl-5-fluorouracil (6.6 mmol) in DMSO (11 ml) was added dropwise with stirring to a suspension of *t*-BuOK (25 mmol) in DMSO (11 ml). The mixture was stirred for another 2 h and was then diluted with water (40 ml) and stirred in the presence of a strong cation exchanger (Dowex 50 in H^+ form). The filtrate was evaporated at reduced pressure (0.1 torr) and the residue triturated with ether to leave the title compound. The analytical specimen was purified by preparative chromatography on Whatman No. 3 paper BuOH–EtOH–

NH_3-H_2O (4:1:2:1); yield 40 %, m.p. 197–199 °C (iPrOH). Anal. $C_6H_5FN_2O_2$: C, H. ^1H NMR (DMSO-d_6): δ 4.86, 5.33, 7.08 ($CH=CH_2$), 8.36 (H-6).

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Received April 2, 1979.