

Some Derivatives of 5-Fluoropyrimidine

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An improved synthesis of 5-fluoropyrimid-2-one is reported. Selective nucleophilic displacements of the 4-substituent in 2,4-disubstituted-5-fluoropyrimidines have been studied.

The growth-inhibitory properties of 5-fluorouracil¹ and its use in cancer chemotherapy have resulted in extensive work on related compounds. This report describes work done around the synthesis of 5-fluoropyrimid-2-one since it was desirable to have this compound available for further enzymatic and biological studies.^{2,3} This substance was originally obtained in a very poor yield by sodium amalgam reduction of 5-fluorouracil in dilute acetic acid.² While our work was in progress Buděšinský *et al.*⁴ reported the synthesis of this derivative from 2-methylthio-5-fluoropyrimid-4-one. Their synthesis involved several steps including the synthesis of the starting material.⁵ The latter was chlorinated in the 4-position, reductively dechlorinated with zinc, the sulphur oxidized to a sulphone and the sulphone group removed by hydrolysis in aqueous alkali. We have used the commercially available 5-fluorouracil as our starting material and have worked out a very much simplified procedure.

In pyrimidines both the 2- and 4-carbons are about equally electrophilic. A substituent in the 5-position can change the relative electrophilicities. An electronegative substituent increases the relative electrophilicity of the C-4 carbon. Selective displacement of the 4-hydroxyl group in 5-fluorouracil should be possible. Thus Ueda⁶ has described the synthesis of the 4-thione (II) by treatment of 5-fluorouracil with phosphorus pentasulphide in pyridine. We used essentially his method for the synthesis of II. For biological reasons it was important not to have any 5-fluorouracil present. Therefore at least one mole equivalent of phosphorus pentasulphide was used. The product thus obtained was slightly contaminated by the dithione (V) as shown by chromatography. The Raney-Ni used in the desulphurisation was prepared according to Brown.⁷ The desulphurisation was carried out by heating in aqueous ammonia. In water another product was obtained, m.p. 250–55°, which had no aromatic UV absorption and whose NMR spectrum (TFA) had a quintet at 7.90 τ and a triplet at 6.46 τ , ratio 1:2. This compound there-

Treatment of the 4-thione (II) with thionyl chloride led to the 4-chloro derivative (IV). 5-Fluorouracil with phosphorus oxychloride yields the 2,4-dichloro compound.⁵ The highly activated chlorine was easily displaced by alcohols with formation of the corresponding ethers (VIII) and by ammonia with the formation of 5-fluorocytosine (IX). Reductive dehalogenation with zinc dust should yield III. 2,4-Dichloro-5-fluoropyrimidine⁵ with the sodium salt of ethanethiol gave the 4-ethio derivative (XIII). Attempted formation of XIV by selective acid hydrolysis of the 2-chlorine failed. Instead 5-fluorouracil was formed. Selective nucleophilic displacement of the 4-methoxy group in XI was also possible. This was achieved by heating the dimethoxy derivative⁹ (XI) in 2 N sodium hydroxide. That it was the 4-methoxy group which was replaced was evident by comparison of the UV-absorption. While the former had absorption bands at 269 (NaOH) and 263 m μ (HCl) the bands in the 4-methoxy derivative (VIIIa) were found at 290 and 280 m μ , respectively. In the NMR spectra in TFA the methoxy groups were found at 5.69 τ (VIIIa) and the aromatic protons at 1.84 τ and 1.90 τ , respectively. On this basis in the dimethoxy compound (XI) the signal found at the lower field (5.55 τ) has been assigned to the 4-methoxy group and the signal at the higher field (5.64 τ) to the 2-methoxy group.

Treatment of XII with phosphorus pentasulphide in pyridine rather surprisingly resulted in displacement of the 2-methoxy group besides the introduction of sulphur in the 4-position (II).

EXPERIMENTAL

Paper chromatography or TLC on silica gel in the systems BuOH:EtOH:NH₃:H₂O (4:1:2:1) and BuOH:HOAc:H₂O (100:22:50) have been used in this work.

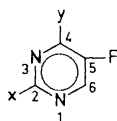
5-Fluoropyrimid-2-one (III). 5-Fluoropyrimid-2-one-4-thione⁶ (1.46 g, 0.01 mole) was dissolved in 6.6 M aqueous ammonia (120 ml) and Raney-Ni⁷ (about 5 g) added. The reaction mixture was heated under reflux with stirring for 3 h, the catalyst removed by filtration through a bed of Celite and the aqueous washings and filtrate evaporated at reduced pressure. The residue was dissolved in water (50 ml) and applied on a column of Amberlite IRC-50 (36 g). The column was washed with water (300 ml) and the pyrimidine eluted with 0.1 % NH₃ aq. Evaporation of the eluate left a white solid (1.0 g) which after recrystallisation from ethyl acetate yielded 0.68 g (60 %) of the title compound, m.p. 170–171°. (lit.⁴ 172–173°). (Found: C 42.28; H 2.86; N 24.56. Calc. for C₄H₃FN₂O: C 42.18; H 2.65; N 24.58).

When the desulphurisation was attempted in water the crude product obtained melted at 237–240°. Sublimation at 160°/20 mm Hg gave m.p. 250–255°. This compound has been identified as trimethyleneurea (lit.⁸ m.p. 258–259°).

4-Chloro-5-fluoro-pyrimid-2-one (IV). 5-Fluoropyrimid-2-one-4-thione (2.92 g, 0.02 mole) was added with stirring to cold thionyl chloride (60 ml). The resultant solution was left at room temperature for 12 h, evaporated at reduced pressure, benzene (100 ml) added and the solution again evaporated. The residue was treated with ice-cold water, neutralized with 2 N sodium bicarbonate and freeze dried. The remaining, dried solid was extracted with boiling ethyl acetate. The title compound crystallized out on cooling; yield 1.33 g (45 %), m.p. 173–176° (decomp.). (Found: C 32.62; H 1.36; N 19.00. Calc. for C₄H₂ClFN₂O: C 32.34; H 1.35; N 18.87).

5-Fluoro-4-methoxypyrimid-2-one (VIIIa). 4-Chloro-5-fluoropyrimid-2-one (1.11 g, 0.0075 mole) was dissolved in 0.005 N methanolic HCl, the solution left at room temperature for 5 h and evaporated. Chromatography showed the product to be contaminated by 5-fluorouracil. Part of this material (140 mg) dissolved in pyridine (2 ml) was applied to a Whatman No. 3 paper which was developed in BuOH:EtOH:NH₃:H₂O (4:1:2:1).

Table 1. NMR data of 5-fluoropyrimidine derivatives.



Comp.	Substituents		Chemical shifts in τ values			Coupling constants in cps
	x	y	2	4	6	
III	OH ^a	H	—	0.88	0.88	1.8
I	OH ^b	OH	—	—	2.41	5.0
VIIIb	OH	OC ₂ H ₅	—	5.20 8.45	1.87	3.5
VIIIa	OH ^a	OCH ₃	—	5.66	1.90	3.8
XI	OCH ₃ ^a	OCH ₃	5.64	5.55	1.70	4.0
XII	OCH ₃ ^a	OH	5.69	—	1.84	3.5
II	OH ^b	SH	—	—	2.35	2.5
IX	OH ^a	NH ₂	—	—	2.01	4.5
IV	OH ^b	Cl	—	—	1.85	1.5
X	Cl ^c	Cl	—	—	3.36	0

^a Measured in TFA, ^b measured in NaOD, ^c measured in CCl₄.

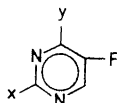
Pyridine elution of the band containing the desired substance, evaporation, and crystallisation from aqueous methanol furnished the title compound in 65 % yield, m.p. 189–190°. (Found: C 41.46; H 3.69; N 19.11. Calc. for C₅H₅FN₂O₂: C 41.67; H 3.50; N 19.44).

4-Ethoxy-5-fluoropyrimid-2-one (VIIIb). Prepared as above in 46 % yield, m.p. 165–167° (ethyl acetate). (Found: C 45.25; H 4.49; N 17.87. Calc. for C₆H₇FN₂O₂: C 45.57; H 4.46; N 17.72).

5-Fluoro-2-methoxypyrimid-4-one (XII). 2,4-Dimethoxy-5-fluoropyrimidine⁹ (0.79 g, 0.005 mole) in 2 N KOH (20 ml) was refluxed for 20 h, the cold solution extracted with ether and the aqueous solution acidified to pH 2. The white solid precipitated (0.55 g, 72 %) was recrystallised from dilute ethanol; white flakes, m.p. 195–197°. (Found: C 41.87; H 3.53. Calc. for C₅H₅FN₂O₂: C 41.67; H 3.50).

5-Fluorocytosine (IX). 4-Chloro-5-fluoropyrimid-2-one (0.83 g, 0.0056 mole) was added to methanol (35 ml) saturated with ammonia at 0°. The solution was refluxed for 3 h, evaporated, the residue dissolved in water (3 ml) and aqueous 0.88 M ammonia (0.9 ml) added. The solid precipitate (0.58 g, 80 %) thus obtained had the properties of 5-fluorocytosine as described in the literature.⁵

Table 2. UV absorption of 5-fluoropyrimidine derivatives.



Comp.	Substituents		0.1 N NaOH aq.		0.1 N HCl aq.	
	x	y	λ	$\log \epsilon$	λ	$\log \epsilon$
III	OH	H	312	3.65	322	3.61
VIIIb	OH	OC ₂ H ₅	289	3.68	273	3.68
VIIIa	OH	OCH ₃	290	3.82	280	3.65
XI	OCH ₃	OCH ₃	268 ^a	3.95		
XII	OCH ₃	OH	269	3.83	263	3.67
IV	OH	Cl	311	3.83	317	3.65

^a Measured in ethanol.

5-Fluoropyrimid-2-one-4-thione (II). 5-Fluoro-2-methoxypyrimid-4-one (0.29 g, 0.002 mole) was dissolved in pyridine and phosphorus pentasulphide (0.44 g, 0.002 mole) and a drop of water added. The resultant solution was heated under reflux for 2 h, evaporated at reduced pressure, the residue dissolved in water (5 ml) and the solution left in the cold. The yellowish brown solid which was precipitated (0.21 g) was purified by recrystallisation from water with charcoal treatment; yellow crystalline material, m.p. 275°, (lit.⁶ 277–280°).

2-Chloro-4-ethio-5-fluoropyrimidine (XIII). Sodium (0.23 g, 0.01 mole) was added to ethylthiol (6 ml), the reaction mixture stood at room temperature until all the metal had reacted and dissolved, and the solution was evaporated at reduced pressure. The residue was suspended in dioxane (40 ml) and 2,4-dichloro-5-fluoropyrimidine (1.7 g, 0.01 mole) added and the reaction mixture heated under reflux overnight. The solid was then filtered off and the filtrate evaporated *in vacuo* leaving a white semisolid which could not be crystallized but was distilled, b.p. 90°/0.5 mm Hg, colourless liquid (1.5 g, 79 %) which set to a white solid. (Found: S 16.85. Calc. for C₆H₆ClFN₂S: S 16.66).

Acid hydrolysis of 2-chloro-4-ethio-5-fluoropyrimidine (XIII); formation of 5-fluorouracil (I). 2-Chloro-5-fluoro-4-ethylthiopyrimidine (100 mg) in 6 N hydrochloric acid (10 ml) was refluxed for 4 h and the solution evaporated to dryness at reduced pressure. The white solid residue was triturated with ethanol and the insoluble material filtered off (50 mg, 74 %), m.p. 285–287° (decomp.). Mixed m.p. with 5-fluorouracil gave no depression, the IR and the chromatographic data were identical.

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