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A NEW ROUTE TO THE SYNTHESIS OF 5-FLUOROURACIL

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Dedicated to Professor Hans Rudolph on the occasion of his 60th birthday.

SUMMARY

Starting from tetrafluoropyrimidine (1), selective fluorine/chlorine exchange reactions and selective hydrogenolysis of the chlorine substituents are described. Combination of these methods, together with a subsequent hydrolysis reaction, provides a new route to the synthesis of 5-fluorouracil via 4,6-dichloro-2,5-difluoropyrimidine and 4-chloro-2,5-difluoropyrimidine.

INTRODUCTION

Fluorine-containing pyrimidines are versatile intermediates for a variety of purposes [1].

Prominent among them is 5-fluorouracil, which is important as a carcinostatic and precursor for chemotherapeutic agents [2]. The more than 4,200 publications and patent applications concerning the

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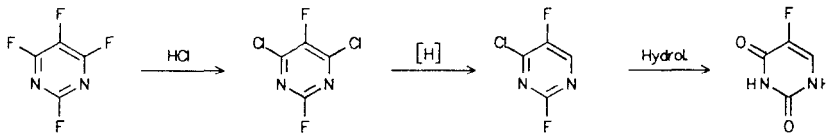
synthesis, chemistry, and use of this compound and its derivatives, that have appeared since C. Heidelberger and co-workers [3] described the first synthesis testify to the importance of this compound. The classical synthesis according to [3] proceeds by way of the ring closure reaction of a α-fluoro-ß-ketoester enolate with isothiourea. A second important synthesis consists of the direct fluorination of uracil with elemental fluorine, which was pioneered by I.L. Knunyants, L.S. German et al. [4] and by P.D. Schuman, P. Tarrant and co-workers [5]. A number of variations of this method have since become known [6]. Alternative syntheses according to various strategies [7,8,9,10] have also been described.

Through continuation of our work on perfluorinated pyrimidines [11], we have found a new route for the synthesis of 5-fluorouracil (10) - a route starting from tetrafluoropyrimidine (1), proceeding through a reaction sequence of rechlorination, selective hydrogenolysis, and subsequent hydrolysis [12]:

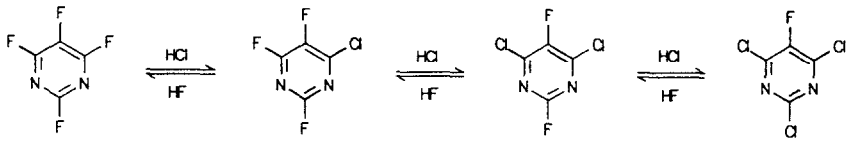


(1) (3) (6) (10)

RESULTS AND DISCUSSION

1. Selective chlorination of tetrafluoropyrimidine

The fluorination reaction of perchloro heterocyclic nitrogen compounds with anhydrous hydrogen fluoride is an equilibrium reaction [11]. This led to the investigation of the opposite reaction, namely the exchange of chlorine for fluorine with hydrogen chloride in perfluorinated pyrimidine derivatives. Using HCl it is indeed possible to substitute chlorine specifically for fluorine [13] in tetrafluoropyrimidine (1).



(1) (2) (3) (4)

The halogen substitution takes place stepwise in the order 4 > 6 >> 2. The fluorine atom bound in position 5 cannot be substituted under any reaction conditions. The reaction is performed by heating tetrafluoropyrimidine (1) with anhydrous hydrogen chloride under pressure in an autoclave. The ratio in which the products (2) to (4) are formed is based on the equilibria and is influenced by the chosen pressure, reaction time and reaction temperature. At 180°C, 30 bar and a reaction time of 4 hours (2), (3), and (4) are obtained in the ratio 2:6:1. The compounds are easily separated by distillation. Substitution patterns which are not accessible through chlorine/fluorine exchange reactions on perchlorinated primidines have thus became preparatively accessible. In particular, the order of reactivity for pyrimidines [14, 15] is such that fluorine cannot be substituted for chlorine bound selectively in position 5 unless chlorine atoms in other positions are substituted also. The fluorinated position 5 is particularly important in the pyrimidine series [2]. Indeed, it was formerly necessary to prepare 2,4,6-trichloro-5-fluoropyrimidine (4) by means of a sequence of reactions for which 5-fluorouracil, accessible according to [3] or [4], was used as the starting compound [16]. To the best of our knowledge, fluorine/chlorine exchange reactions of heterocyclic compounds with gaseous HCl have not been described previously. Only the substitution reaction of aqueous HCl with perfluorinated pyridine, pyrazine and quinoline, using, for example, sulpholane or ether as a solvent, has been reported [17].

2. Selective hydrogenolysis

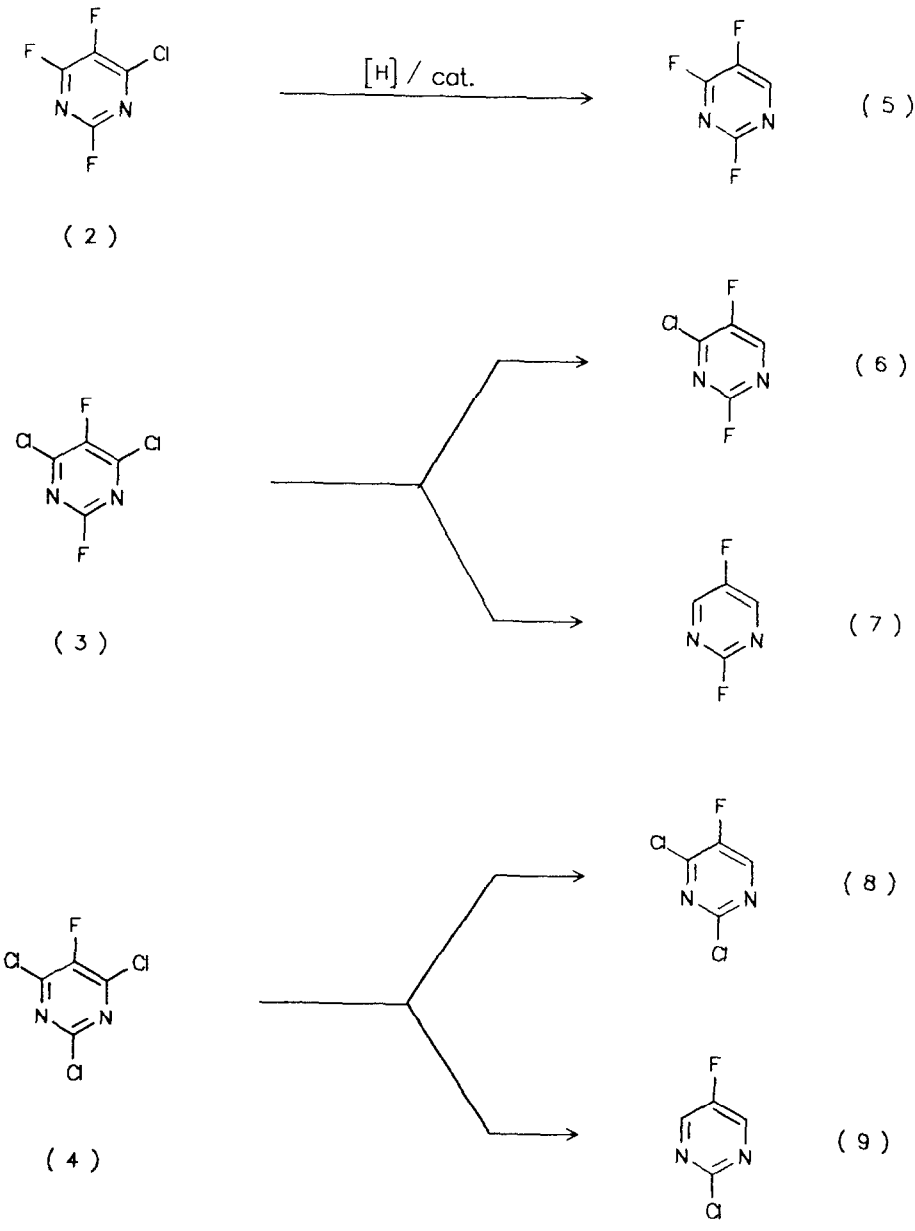
Studies of the chemical behaviour of the fluoro/chloropyrimidines not only included nucleophilic substitution reactions [18] but

also catalytic hydrogenolysis [19]. It was found that under mild conditions hydrogen can be substituted for chlorine exclusively and regioselectively. The reactions performed are summarized in Scheme 1. Thus trifluoropyrimidine (5) is obtained from chlorotrifluoropyrimidine (2), the derivative (6) or (7) is obtained from chlorotrifluoropyrimidine (3); and finally, compound (8) or (9) is obtained from trichlorofluoropyrimidine (4).

The hydrogenolysis can be carried out in various organic solvents. Normally, ethyl acetate is used, but comparably high yields are obtainable in methanol or dioxane. Palladium on carbon (5%) has proved to be the most suitable catalyst. An equimolar amount of a hydrogen chloride acceptor must also be added. Triethyl amine produces the best results; slightly inferior yields result from the use of pyridine, inorganic carbonates, or hydrogen carbonates. The reaction temperature ranges from 30° to 50°C and the hydrogen pressure is 2 to 5 bar. If these hydrogenolysis conditions are maintained, only the amount of hydrogen theoretically needed for reduction of a single chlorine atom is taken up. If the pyrimidine derivative contains two chlorine atoms, only one is selectively hydrogenolysed at first. The second chlorine atom is not split off until a second equivalent of the HCl acceptor has been added. In no case were mixtures obtained. The hydrogenolysis of fluorine atoms was not observed either. The product is separated from the amine hydrochloride and catalyst by filtration. After the solvent has been removed from the filtrate by distillation the crude product is either distilled at atomspheric pressure or under vacuum or recrystallized.

Compared with other methods, this reduction process for obtaining partly halogenated pyrimidines is highly advantageous. For example, the reduction of tetrafluoropyrimidine (1) with lithium aluminium hydride is non-selective and incomplete - 2,4,5-trifluoropyrimidine (5) and 2,5-difluoropyrimidine (7) are obtained together as a mixture [20].

Reduction of chlorine substituents with zinc powder in benzene in the presence of aqueous ammonia [21], a method applicable to perchlorinated pyrimidines, results in only a low degree of conversion and complex mixtures in the case of systems containing fluorine. Other reductive methods [22, 23] have also failed to give usable results.



Scheme 1. Selective hydrogenolysis of the chloro/fluoropyrimidines (2), (3) and (4).

TABLE

Physical data of the pyrimidines

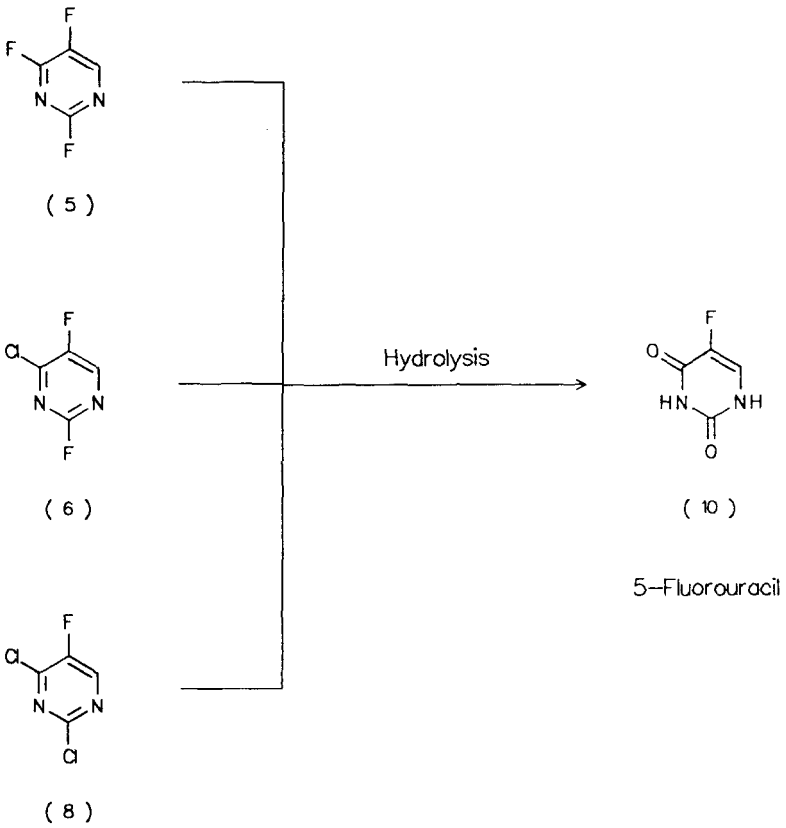
Comp. No.	Substitution 2-	4-	5-	6-	b.p./m.p. [°C]	^{19}F δ (ppm) 2-	4-	5-	6-	Ref.
1	F	F	F	F	b.p.: 83	+ 33.4	+ 6.8	- 95.0	+ 6.8	14
2	F	Cl	F	F	b.p.: 121	+ 32.6		- 73.5	+ 5.4	13
3	F	Cl	F	Cl	b.p.: 162	+ 32.5		- 52.8		13
4	Cl	Cl	F	Cl	b.p.: 198			- 50.3		16
5	F	F	F	H	b.p.: 92-3	+ 30.8	+ 4.5	- 79.2		14,20
6	F	Cl	F	H	b.p.: 145-6	+ 30.4		- 58,2		19
7	F	H	F	H	b.p.: 116-7	+ 28.3		- 65.2		20,25
8	Cl	Cl	F	H	b.p.: 89-91/30 mbar			- 56.1		16,24
9	Cl	H	F	H	b.p.: 92-4/100 mbar			- 62.8		25,26
10	OH	OH	F	H	m.p.: 280-2°C			- 92.8		3

Of the partly halogenated pyrimidines, 2,4-dichloro-5-fluoropyrimidine (8) [24] and 2-chloro-5-fluoropyrimidine (9) [25, 26] are known compounds, previously obtained from the starting product 5-fluorouracil.

The physical data of the pyrimidines are summarized in the table.

3. Hydrolysis

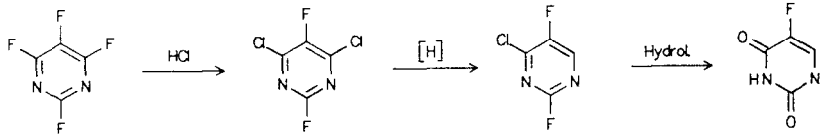
The pyrimidines (5), (6) and (8) can be converted into the 5-fluorouracil (10) by hydrolysis of the reactive halogens in positions 2 and 4 (Scheme 2).



Scheme 2. Hydrolysis of the pyrimidines (5), (6) and (8) to yield 5-fluorouracil.

There are two methods available for this transformation using either basic or acidic media [27]. In the first case, the pyrimidine derivative is reacted in a two phase system with aqueous alkaline solution at an elevated temperature. In the second case, the reaction can be performed with comparable yield in aqueous mineral acids [28].

All three compounds (5), (6) and (8) can be converted into 5-fluorouracil (10) equally well. In the rechlorination of tetrafluoropyrimidine (1) 4,6-dichloro-2,5-difluoropyrimidine (3) is the most suitable precursor with regard to reaction condition and yield. It may therefore be said in summary that a new and convenient route to 5-fluorouracil has been found - a route starting from (1), proceeding through the reaction sequence of rechlorination to (3), the selective hydrogenolysis to (6), and subsequent hydrolysis:



(1) (3) (6) (10)

Analogous reaction sequences can also be performed successfully with 2-trichloromethyl-4,5,6-trifluoropyrimidine and 6-trifluoromethyl-2,4,5-trifluoropyrimidine [13,19,27].

EXPERIMENTAL

^{19}F NMR spectra were recorded on a Bruker WP 80 FT nuclear magnetic resonance spectrometer with a ^{1}H, ^{19}F dual sample holder at a frequency of 75.39 MHZ. All measurements were carried out in $CDCl_3$ (compound (10) in DMSO-d_6) using CF_3COOH as an external standard. Chemical shifts were determined in ppm (δ_{CF_3COOH} = 0 ppm), positive values refer to downfield absorptions.

Tetrafluoropyrimidine (1) was prepared as reported previously [14].

Chlorination of tetrafluoropyrimidine (1)

Tetrafluoropyrimidine (1) (304 g, 2 mol) was introduced into a stainless steel autoclave, 30 bar of gaseous hydrogen chloride were injected and the autoclave was heated to 160°C. The amount of hydrogen chloride consumed in the reaction was continously replaced by injection until the pressure remained constant. After 4 hours the autoclave was cooled, the excess pressure of hydrogen chloride was released and the product was worked up by distillation. The crude distillate (354 g) was analyzed by gas chromatography and found to have the following composition: 4% starting material, 16% 4-chloro-2,5,6-trifluoropyrimidine, 64% 4,6-dichloro-2,5-difluoropyrimidine, and 14,5% 2,4,6-trichloro-5-fluoropyrimidine. The various pyrimidines were isolated by fractional distillation:

I. 4-Chloro-2,5,6-trifluoropyrimidine (2), b.p.: 120-121°C, n^{20}: 1.4465; yield: 49 g (14.5%, calculated on the basis of tetrafluoropyrimidine)

II. 4,6-Dichloro-2,5-difluoropyrimidine (3), b.p.: 162°C, n^{20}: 1.5021; yield: 225 g (60.8%, calculated on the basis of tetrafluoropyrimidine)

III. 2,4,6-Trichloro-5-fluoropyrimidine (4), b.p.: 82°C/14 mbar (b.p.: 198°C/1013 mbar) m.p.: 37-38°C; yield: 53 g (13.1%, calculated on the basis of tetrafluoropyrimidine)

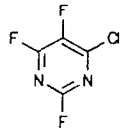
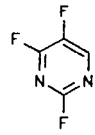
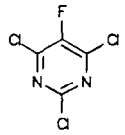
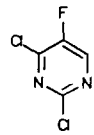
Chlorination of 4,6-dichloro-2,5-difluoropyrimidine (3)

4,6-Dichloro-2,5-difluoropyrimidine (3) (444 g, 2.4 mol) was introduced into an autoclave, and than treated with 100 bar of HCl at 200°C for 3 h. After cooling and releasing the pressure, 473 g of a mixture of liquid and crystals were obtained, that had the following composition (GC): 38% 4,6-dichloro-2,5-difluoropyrimidine (3) and 60% 2,4,6-trichloro-5-fluoropyrimidine (4). The products were separated by distillation as described above.

Synthesis of 4-chloro-2,5-difluoropyrimidine (6)

4,6-Dichloro-2,5-difluoropyrimidine (3) (185 g, 1 mol) was dissolved in 1800 ml of ethyl acetate to which 110 g of triethyl amine and 15 g of palladium on carbon (5% by weight) had been added. Hydrogenation proceeded with stirring in a stainless steel autoclave for 95 minutes at 30°C under a hydrogen pressure of 3.5 bar. Thereafter, the solid components of the reaction mixture were filtered off, the residue was washed with ethyl acetate, and the wash liquid together with the filtrate was distilled at atmospheric pressure over a 30 cm packed column. After the solvent was distilled off, 4-chloro-2,5-difluoropyrimidine (6), b.p.: 145-146°C, was obtained in 70.5% yield (106 g). According to analysis by gas chromotography, the reaction product isolated was 94.7% pure.

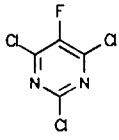
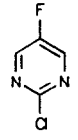
The following were obtained analogously:

Starting product	Reaction product	b.p. [°C] / mbar	Yield (%)	Purity (%)
 (2)	 (5)	88–91 / 30	68	94.1
 (4)	 (8)	92–93 / 1013	87	98.4

Synthesis of 2,5-difluoropyrimidine (7)

4,6-Dichloro-2,5-difluoropyrimidine (3) (50 g, 0.27 mol) was added to 500 ml of ethyl acetate to which 60 g of triethyl amine and 7 g of palladium on carbon (5% of weight) had been added. This mixture was hydrogenated in a glass apparatus for 3.5 hours at 50°C under a hydrogen pressure of 4 bar. Thereafter, the solid components of the reaction mixture were filtered off, the residue was washed with ethyl acetate, and the wash liquid together with the filtrate was distilled at atmospheric pressure over a 30 cm packed column. After the solvent was removed 25.7 g of 2,5-difluoropyrimidine (7) (b.p.: 116-117°C; yield 82.2%) were obtained. According to GC analysis the product isolated was 98.3% pure.

The following was obtained analogously:

Starting product	Reaction product	b.p. [°C] / mbar	Yield (%)	Purity (%)
 (4)	 (9)	92–94 / 100	78	96.9

Synthesis of 5-Fluorouracil (10)

(a) Basic hydrolysis

4-Chloro-2,5-difluoropyrimidine (6) (150.5 g, 1 mol) was dissolved in 1.5 l of water, and the stirred solution was heated to 80°C. The dropwise addition of 200 g of 45% (by weight) aqueous sodium hydroxide solution was also begun. When this addition was complete, stirring was continued for 4 hours at 80°C. After the

mixture was cooled, it was neutralised with concentrated HCl, and the precipitate was filtered off under suction. This solid was stirred with 500 ml of water, once again filtered off under suction, and dried at 50°C in vacuo. 5-Fluoro-2,4-(1H, 3H)-pyrimidinedione (= 5-fluorouracil) (10) was obtained in 93% yield (121 g), m.p.: 280-282°C (decomposition).

(b) Acidic hydrolysis

Aqueous sulphuric acid (300 ml, 70% by weight) was added to 150.5 g (1 mol) of 4-chloro-2,5-difluoropyrimidine (6) and the mixture was heated for 5 hours at 140°C. The reaction mixture was then poured into ice water and the precipitate was filtered off under suction. After recrystallizing from ethyl acetate, 110 g (85%) of 5-fluorouracil (10), m.p.: 280-281°C (decomposition) was obtained.

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