A SIMPLE SYNTHESIS OF 5-FLUORO-2-PYRIMIDINONE AND ITS N^1-SUBSTITUTED DERIVATIVES*

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Fluorination of 2-pyrimidinone (*Ia*) and its N^1-substituted derivatives *Ib*—*Ig* with elemental fluorine in acetic acid or in anhydrous hydrogen fluoride yielded 5-fluoro-2-pyrimidinone (*IIa*) and its N^1-methyl (*IIb*), N^1-benzyl (*IIc*), 1-(tri-O-benzoyl-β-D-ribofuranosyl) (*IId*), 1-(2,3,5-tri-O-benzoyl-β-D-xylofuranosyl) (*IIe*), 1-(2,3,4-tri-O-benzoyl-β-D-ribopyranosyl) (*IIf*), and 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl) (*IIg*) derivatives. 1-(β-D-Ribofuranosyl)-5-fluoro-2-pyrimidinone (*IIh*) was prepared by methanolysis of the tribenzoate *IId*.

In the series of 5-fluoro substituted pyrimidine derivatives such as 5-fluorouracil and derivatives, a high biological activity is *inter alia* exhibited by 5-fluoro-2-pyrimidinone (*IIa*) (*cf.*[1]). Compound *IIa* has been several times reported in the literature. The earlier procedures start from toxic or hardly accessible monofluoroacetic acid derivatives, the condensation of which with urea affords compound *IIa* in unsatisfactory yields[2-4]. Another synthetic approach consists in the Raney nickel desulfurisation of 4-thio-5-fluorouracil[5]; the quality of the thus-obtained product is questionable[4,6]. In this Laboratory, a process was developed leading to 5-fluoro-2-pyrimidinone by cleavage of 5-fluoro-4-hydrazino-2-pyrimidinone in the presence of silver oxide[6]. An analogous reaction may be performed with the appropriate N^1-substituted derivatives which are accessible from the corresponding compounds of the 5-fluorouracil series. The biologically attractive 1-(β-D-ribofuranosyl)- and 1-(2-deoxy-β-D-ribofuranosyl)-5-fluoro-2-pyrimidinone were prepared similarly[7-9]. Even this method requires a multistep process and isolation of the particular intermediates; the preparative value of the method is thus somewhat lowered by these requirements.

The direct halogenation of 2-pyrimidinone (*Ia*) and its N^1-substituted derivatives with elemental chlorine or bromine affords smoothly the corresponding 5-halo derivatives[10,11]. It was therefore of interest to attempt the preparation of 5-fluoro-

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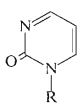
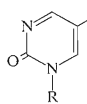
-2-pyrimidinone and derivatives by a direct fluorination of 2-pyrimidinone and derivatives with elemental fluorine. This procedure was developed in this Laboratory and successfully employed in the preparation of compounds of the 5-fluorouracil series from uracil derivatives[12,13]. By introduction of fluorine in a stream of nitrogen



I



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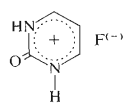

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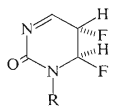

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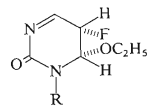

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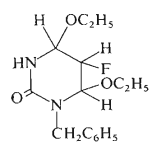

VI

In formulae *I*, *II*, *III*, *V*

a: R = H
b: R = CH_3
c: R = $CH_2C_6H_5$
d: R = 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl
e: R = 2,3,5-tri-O-benzoyl-β-D-xylofuranosyl
f: R = 2,3,4-tri-O-benzoyl-β-D-ribopyranosyl
g: R = 2,3,5-tri-O-acetyl-β-D-ribofuranosyl
h: R = β-D-ribofuranosyl

into a solution of compound *Ia* in acetic acid[12] or by addition of an equimolar amount of fluorine in acetic acid[13], 5-fluoro-2-pyrimidinone (*IIa*) is obtained in 5–10% yield. A precipitate is simultaneously formed, the analysis of which corresponds to the hydrofluoride of compound *Ia*. The formation of this salt *III*, insoluble in acetic acid, could be responsible for the low yield of compound *IIa*. The salt *III* is formed by reaction of compound *Ia* with hydrogen fluoride which is always present in elemental fluorine or which arises by reaction of compound *Ia* with elemental fluorine.

The formation of the salt *III* can be somewhat suppressed by the addition of trifluoroacetic acid into the solution of compound *Ia* in acetic acid but the yields of compound *IIa* never exceed 25%. The salts of compound *Ia* are soluble in water but when the fluorination of *Ia* is performed in an aqueous medium, a complete destruction

of the molecule takes place. It appears as the most advantageous method to introduce excess fluorine in a stream of nitrogen into a solution of compound *Ia* in anhydrous liquid hydrogen fluoride at −20°C to −30°C. The hydrogen fluoride is then evaporated, the residual hydrofluoride of compound *IIa* neutralised, and chromatographed on a column of cellulose to afford 5-fluoro-2-pyrimidinone (*IIa*) identical with a specimen prepared by another route[6].

Contrary to the protonable 2-pyrimidinone (*Ia*), its N^1-substituted derivatives are fluorinated without difficulty. The reaction of compounds *Ib*–*Ig* in acetic acid with a solution of an equimolar amount of fluorine in the same solvent affords the corresponding derivatives of 5-fluoro-2-pyrimidinone *IIb*–*IIg* as the main products. The solvent is evaporated and the residual reaction mixture is advantageously processed with triethylamine (analogously to the uracil series[13]) to eliminate the primarily formed 4,5-dihydrouracil derivatives *IV*. The remaining fluoride ions are preferably removed by washing the chloroform solutions of crude compounds *II* with aqueous sodium hydrogen carbonate. The application of Dowex 1X2 (OH^- or HCO_3^- form) ion exchange resin is much less efficient. Purification by chromatography on silica gel afforded compounds *IIb*–*IIg* in high preparative yields. The thus-obtained 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) derivative *IId* was identical with material obtained by an independent route[7]; similarly, the 1-methyl derivative *IIb* was identical with a compound obtained from 5-fluoro-2-pyrimidinone (*IIa*) by reaction with methyl iodide in the presence of an equimolar amount of methanolic sodium methoxide. Compound *IIb* exhibits a characteristic UV absorption with a maximum at 320 nm which does not change in acidic or alkaline media.

From the side reactions accompanying the direct fluorination of compounds *I*, the formation of about 5% 5-fluorouracil derivatives is worth of mentioning. The separation of these by-products from the fully benzoylated nucleoside derivatives *IId*–*IIg* is rather difficult but after the removal of benzoyl groups by alcoholysis, the derivatives of 5-fluorouracil are acidic enough to be separated on a column of a weakly basic anion exchange resin (DEAE-cellulose), *cf.*[7].

The mechanism of the direct fluorination of 2-pyrimidinone derivatives *I* is obviously similar to that of uracil and its derivatives[13,14]. Thus, a direct attack of fluorine on the double bond at position 5,6 affords the 5,6-difluoro-5,6-dihydro-2-pyrimidinone derivatives *IV* from which hydrogen fluoride can be eliminated with the formation of compounds *II*. Owing to the instability of such compounds, the primary adducts of the type *IV* were not isolated but their existence is suggested by an indirect evidence. When the reaction mixture after the fluorination of compounds *Ib* and *Ic* was processed with ethanol, compounds *Vb* and *Vc* were isolated. The latter compounds can be formed by an exchange reaction from compounds *IVb* and *IVc* but not by addition of ethanol to the final compounds *II*. The structure of compounds of the type *V* was confirmed by mass spectra (*Vb*, *m/e* 174; *Vc*, *m/e* 295). The stability of dihydro derivatives *V* is obviously affected by the −I effect of the substituent

at position 1; it is enhanced in the case of the benzyl derivative *Ic* to such an extent that compound *VI* (formed by exchange and addition) represents the principal fluorination product after processing with ethanol. The products of the type *V* and *VI* have been earlier observed in the bromination of 2-pyrimidinone and its derivatives[11,15] and in halogenations of uracil derivatives[14,16].

In conclusion, the direct fluorination of 2-pyrimidinone and its derivatives represents a simple preparation of pure compounds of the 5-fluoro-2-pyrimidinone series and appears more advantageous than the earlier methods because of the accessibility of the starting compounds and a sufficient selectivity[17–19].

EXPERIMENTAL

Melting points (uncorrected) were taken on a heated microscope stage (Boetius apparatus). Unless stated otherwise, solutions were taken down on a rotatory evaporator at 40°C/15 Torr and substances dried over phosphorus pentoxide at 0·1 Torr. Thin-layer chromatography was performed on ready-for-use Silufol UV_{235} (Kavalier Glassworks, Votice, Czechoslovakia) silica gel sheets; preparative runs were carried out on loose layers (40 × 15 × 0·3 cm) of silica gel containing a fluorescent indicator (produced by Service Laboratories of this Institute) and of the Kieselgel silica gel (Merck, Darmstadt, Federal Republic Germany). Solvent systems: S_1, 2-propanol–water (7 : 3); S_2, chloroform–ethanol (4 : 1); S_3, chloroform–ethanol (9 : 1); S_4, chloroform–ethanol (95 : 5); and S_5, chloroform–ethanol (98 : 2). The column (80 × 3 cm) chromatography was performed on microcrystalline cellulose (Macherey & Nagel) in the solvent system S_1 with rate of 20 ml per h; the course of the elution was checked by the Uvicord apparatus (LKB, Uppsala, Sweden). The UV absorption spectra were taken in aqueous or methanolic solutions on a Specord apparatus (Carl Zeiss, Jena). Mass spectra were recorded on a Varian CH-6 apparatus. Acetic acid was dried over phosphorus pentoxide and distilled. The solution of fluorine in acetic acid was prepared according to ref.[7] and the content of fluorine was determined iodometrically.

1-Benzyl-2-pyrimidinone (*Ic*)

Benzyl chloride (0·7 ml; 0·77 g; 6·1 mmol) was added to a solution of compound[17] *Ia* (0·48 g; 5 mmol) in 7·5 ml of methanol containing 5·5 mmol of sodium methoxide. The mixture was stirred at room temperature overnight and then chromatographed on a layer of loose silica gel in the solvent system S_3. The product-containing band was eluted with methanol, the eluate evaporated, and the residue crystallised from a mixture of ethanol and cyclohexane. Yield, 0·40 g (43%) of compound *Ic*, m.p. 134–135°C. R_F value: 0·70 in S_2 (*Ia*, R_F 0·22 in S_2). For $C_{11}H_{10}.N_2O$ (186·2) calculated: 70·95% C, 5·41% H, 15·05% N; found: 70·54% C, 5·36% H, 14·82% N.

5-Fluoro-2-pyrimidinone (*IIa*)

At 0°C, fluorine was introduced in a stream of nitrogen into a solution of 2-pyrimidinone[17] (*Ia*; 1·43 g; 15 mmol) in anhydrous hydrogen fluoride (50 ml) placed in a polyethylene vessel. When the reaction was complete (as determined by evaporation of an aliquot, neutralisation, and chromatography in the solvent system S_2), the hydrogen fluoride was allowed to evaporate and the residue was washed by repeated decantations with ether, dissolved in water (10 ml), the aqueous solution neutralised with aqueous ammonia, and applied to a column of cellulose.

After elution (S_1), the product-containing fractions were pooled and evaporated under diminished pressure. The residue was crystallised from ethyl acetate and light petroleum which was added until the solution was turbid. Yield, 0·65 g (38%) of compound *IIa*, m.p. 170°C, identical on chromatography in S_1 and S_2 with a specimen obtained according to ref.[6]. For $C_4H_3FN_2O$ (114·1) calculated: 42·11% C, 2·65% H, 16·65% F, 24·56% N; found: 41·91% C, 2·98% H, 16·13% F, 24·31% N. R_F value: 0·37 in S_2. UV spectrum, pH 2: λ_{max} 320 nm (ε_{max} 4000); pH 7; λ_{max} 318 nm (ε_{max} 4000); pH 12: λ_{max} 311 nm.

5-Fluoro-1-methyl-2-pyrimidinone (*IIb*)

A. *Fluorination of compound* Ib. A solution of fluorine (136 mg; 3·6 mmol) in acetic acid[13] was added to a solution of compound[20] *Ib* (0·35 g; 3·2 mmol) in acetic acid (100 ml). The mixture was kept at room temperature for 1 h, evaporated under diminished pressure, and the residue coevaporated with two portions of acetic acid and two portions of ethyl acetate (25 ml each). The final residue was dissolved in dichloromethane (30 ml) and triethylamine (1 ml) was added. The mixture was kept at room temperature for 1 h and evaporated under diminished pressure. The residue was chromatographed on cellulose in S_1 and then rechromatographed on a layer of loose silica gel in the solvent system S_4. The product was eluted with methanol and the eluate evaporated under diminished pressure. Yield, 0·25 g (61%) of the amorphous compound *IIb*, R_F 0·25 in S_3 (*Ib*, 0·17 in S_3). For $C_5H_5FN_2O$ (128·1) calculated: 46·87% C, 3·93% H, 14·83% F, 21·87% N; found: 47·96% C, 3·58% H, 14·91% F, 22·01% N. Mass spectrum: *m/e* 129 (MH^+). UV spectrum, pH 2 and pH 7: λ_{max} 322 nm (ε_{max} 1250); pH 12: λ_{max} 323 nm.

B. *Methylation of compound* IIa. Methyl iodide (1 ml) was added to a solution of compound *IIa* (0·23 g; 2 mmol) in 7 ml of methanol containing 2 mmol of sodium methoxide. The mixture was stirred at room temperature for 6 h and evaporated under diminished pressure. The residue was chromatographed on a layer of loose silica gel in the solvent system S_3. The product was eluted with methanol and the eluate evaporated under diminished pressure. Yield, 0·17 g (66·5%) of the foamy product *IIb* which was on chromatography in S_3 and UV spectra identical with the specimen obtained in paragraph *A*.

1-Benzyl-5-fluoro-2-pyrimidinone (*IIc*)

1-Benzyl-2-pyrimidinone (*Ic*; 0·53g; 3 mmol) was processed analogously to the preparation of compound *IIb*, paragraph *A*. The crude product was chromatographed on a layer of loose silica gel in S_3 and the elution was performed with methanol. Yield, 0·38 g (66%) of compound *IIc*, m.p. 127—129°C. R_F value: 0·54 in S_3 (*Ic*, 0·38 in S_3). For $C_{11}H_9FN_2O$ (204·2) calculated: 64·70% C, 4·44% H, 9·30% F, 13·72% N; found: 64·90% C, 5·70% H, 8·78% F, 13·78% N. Mass spectrum: *m/e* 204 (M^+). UV spectrum, pH 2 and pH 7: λ_{max} 330 nm (ε_{max} 2500).

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-5-fluoro-2-pyrimidinone (*IId*)

A solution of fluorine (83·6 mg; 2·2 mmol) in acetic acid was added to a solution of compound[18] *Id* (1·1 g; 2 mmol) in acetic acid (200 ml). The mixture was kept at room temperature for 1 h and evaporated under diminished pressure. The residue was coevaporated with acetic acid, toluene, and ether (50 ml each) and dissolved in chloroform (100 ml). Triethylamine (2 ml) was added and the solution kept at room temperature for 1 h. The solution was then washed twice with 100 ml portions of water and aqueous sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated under diminished pressure. Crystallisation of the

residue from ethanol yielded 1·0 g (90%) of compound *IId*, m.p. 91—93°C, $[\alpha]_D^{25}$ +19·3° (*c* 0·50, dimethylformamide). For $C_{30}H_{23}FN_2O_8$ (558·5) calculated: 64·51% C, 4·15% H, 3·40% F, 5·02% N; found: 63·58% C, 4·95% H, 3·54% F, 4·85% N. R_F value: 0·48 in S_4. UV spectrum (methanol): λ_{max} 324 nm (ε_{max} 1150).

1-(2,3,5-Tri-O-benzoyl-β-D-xylofuranosyl)-5-fluoro-2-pyrimidinone (*IIe*)

Compound[18] *Ie* (1·1 g; 2 mmol) was processed with fluorine analogously to the preparation of compound *IId*. The crude product was chromatographed on a layer of loose silica gel in the solvent system S_5. Elution with methanol yielded 0·90 g (81%) of amorphous *IIe*, $[\alpha]_D^{25}$ −8·9° (*c* 0·49. dimethylformamide), R_F 0·48 in S_4. For $C_{30}H_{23}FN_2O_8$ (558·5) calculated: 64·51% C, 4·15% H, 3·40% F, 5·02% N; found: 63·78% C, 4·66% H, 3·27% F, 4·44% N. UV spectrum (methanol): λ_{max} 323 nm (ε_{max} 1200).

1-(2,3,4-Tri-O-benzoyl-β-D-ribopyranosyl)-5-fluoro-2-pyrimidinone (*IIf*)

Compound[18] *If* (1·1 g; 2 mmol) was processed with fluorine analogously to the preparation of compound *IId*. The crude product was chromatographed on a layer of loose silica gel in the solvent system S_5. Elution with methanol yielded 0·90 g (81%) of compound *IIf*, m.p. 102—104°C, $[\alpha]_D^{25}$ −31·7° (*c* 0·50, dimethylformamide), R_F 0·48 in S_4. For $C_{30}H_{23}FN_2O_8$ (558·5) calculated: 64·51% C, 4·15% H, 3·40% F, 5·02% N; found: 64·29% C, 5·27% H, 3·75% F, 4·41% N. UV spectrum (methanol): λ_{max} 323 nm (ε_{max} 1200).

1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-5-fluoro-2-pyrimidinone (*IIg*)

Compound[18] *Ig* (1·4 g; 4 mmol) was fluorinated analogously to the preparation of *IId* but the mixture was not kept in chloroform with triethylamine for 1 h: the mixture was instantaneously washed with water and aqueous sodium hydrogen carbonate. The resulting product was homogeneous on chromatography, R_F 0·71 in S_3. Yield, 1·0 g (67%) of amorphous *IIg*, $[\alpha]_D^{25}$ +3·8° (*c* 0·50, dimethylformamide). For $C_{15}H_{17}FN_2O_8$ (372·3) calculated: 48·39% C, 4·60% H, 5·10% F, 7·53% N; found: 47·24% C, 5·47% H, 5·24% F, 6·81% N. UV spectrum (methanol): λ_{max} 321 nm (ε_{max} 1850).

1-(β-D-Ribofuranosyl)-5-fluoro-2-pyrimidinone (*IIh*)

A solution of compound *IId* (0·56 g; 1 mmol) in methanol (20 ml) was adjusted to pH 9 (moistened pH-paper) by the addition of 0·1M methanolic sodium methoxide. The mixture was kept at room temperature overnight, neutralised with Dowex 50X8 (H^+) ion exchange resin, filtered, and the material on the filter washed with methanol. The filtrate and washings were combined and evaporated under diminished pressure. The residue was dissolved in water (20 ml), the aqueous solution washed with three 20 ml portions of ether, applied to a column (20 × 1·5 cm) of DEAE-cellulose (Cellex D, high capacity), and the column eluted with water (2 ml/min). The UV-absorbing fractions were pooled, concentrated under diminished pressure, and the residue freeze-dried. Yield, 0·18 g (73%) of compound *IIh*, chromatographically homogeneous (R_F 0·23 in S_2) and identical with an authentic[7] material. For $C_9H_{11}FN_2O_5$ (246·2) calculated: 43·90% C, 4·50% H, 7·72% F, 11·38% N; found: 43·61% C, 4·27% H, 7·01% F, 11·21% N. UV spectrum (pH 2 and pH 7): λ_{max} 325 nm (ε_{max} 1720).

1-Benzyl-4,6-dihydro-4,6-diethoxy-5-fluoro-2-pyrimidinone (*VI*)

Into a solution of compound *Ic* (1·4 g; 7·5 mmol) in acetic acid (100 ml), fluorine was introduced in a stream of nitrogen at room temperature until the reaction was complete (as determined by chromatography in the solvent system S_4). The mixture was evaporated under diminished pressure and the residue coevaporated with three 25 ml portions of acetic acid. The final residue was heated with ethanol (20 ml) to the boiling point and the ethanol evaporated under diminished pressure. The residue was chromatographed on a layer of loose silica gel in the solvent system S_5 (*vide supra*). The product was eluted with the same solvent mixture, the eluate evaporated, and the residue dried *in vacuo*. Yield, 0·60 g (27%) of compound *VI* (R_F 0·82 in S_4). For $C_{15}H_{21}FN_2O_3$ (296·3) calculated: 60·80% C, 7·14% H, 6·41% F, 9·46% N; found: 59·01% C, 5·87% H, 7·01% F, 9·01% N. Mass spectrum (*m/e*): 296 (M^+), 250 ($M^+ - C_2H_5OH$), 204 ($M^+ - 2\,C_2H_5OH$).

REFERENCES

1. Oftebro R., Grimmer Ø., Øyen T. B., Laland S. G.: Biochem. Pharmacol. *21*, 2451 (1972).
2. Budějínský Z., Přikryl J., Jelínek V.: Czech. 1 227 776; Chem. Abstr. *68*, 29719 (1968).
3. Hoffmann La Roche Inc.: US 3 317 532; Chem. Abstr. *68*, 29715 (1968).
4. Reichardt Ch., Halbritter K.: Justus Liebigs Ann. Chem. *1975*, 470.
5. Undheim K., Gacek M.: Acta Chem. Scand. *23*, 294 (1969).
6. Uchytilová V., Holý A., Cech D., Gut J.: This Journal *40*, 2347 (1975).
7. Cech D., Holý A.: This Journal *42*, 2246 (1977).
8. Cech D., Holý A.: Czech. Appl. PV 1054—76; Ger. (GDR) Appl. RC 07d/191394 (1976).
9. Cech Holý A.: Czech. Appl. PV 1055—76; Ger. (GDR) Appl. WPC 07d/191395 (1976).
10. Crosby D. G., Berthold R. V.: J. Org. Chem. *25*, 1916 (1960).
11. Tee O. S., Banerjee S.: Can. J. Chem. *52*, 451 (1974).
12. Cech D., Meinert H., Etzold G., Langen P.: J. Prakt. Chem. *315*, 149 (1973).
13. Cech D., Holý A.: This Journal *41*, 3335 (1976).
14. Cech D., Hein L., V. Janta Lipinski M., Otto A., Langen P.: Nucleic Acids Res. *2*, 2177 (1975).
15. Barbieri W., Bernardi L., Palmidessi G., Venturi M. T.: Tetrahedron Lett. *2931* (1968).
16. Wang S. G.: J. Org. Chem. *24*, 11 (1968).
17. Protopopova T. V., Skoldinov A. P.: Zh. Obshch. Khim. *27*, 1276 (1957).
18. Holý A.: This Journal *42*, 902 (1977).
19. Holý A., Beerbaum H., Cech D.: Czech. Appl. PV 7045—76 (1976).
20. Fox J. J., Van Praag D.: J. Amer. Chem. Soc. *82*, 486 (1960).

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