PREPARATION OF SOME 2'-DEOXY-5-FLUOROURIDINE DERIVATIVES BY A DIRECT FLUORINATION*

D.CECH[a] and A.HOLÝ[b]

[a] *Sektion Chemie, Humboldt-Universität Berlin, German Democratic Republic*

[b] *Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6*

Received March 31st, 1976

By the action of an equimolar amount of elemental fluorine in acetic acid and the subsequent refluxing with triethylamine, 2'-chloro-2'-deoxyuridine (*IIIa*), its 3',5'-di-O-benzoyl derivative *IVa*, and 3',5'-di-O-benzoyl-2'-bromo-2'-deoxyuridine (*IVb*) afford the corresponding 2'-halo--2'-deoxy-5-fluorouridine derivatives *VIa*, *VIIa*, and *VIIb*. Similarly, 3',5'-di-O-benzoyl-2'-deoxyuridine (*V*) affords under analogous conditions 3',5'-di-O-benzoyl-2'-deoxy-5-fluorouridine (*VIII*) as the only product. The reaction proceeds *via* the instable derivatives of 5-fluoro-6-acetoxy-5,6-dihydrouracil; in the case of compound *IV*, 1-(3,5-di-O-benzoyl-2-deoxy-β-D-ribofuranosyl)-5-fluoro-6-acetoxy-5,6-dihydrouracil (*XIII*) was isolated.

Fluorinated derivatives of the pyrimidine heterocyclic bases, especially the derivatives of 5-fluorouracil exhibit a significant bacteriostatic, virostatic, cancerostatic, and immunosuppressant activity[1-3]. Some of these compounds, namely, 5-fluorouracil and the corresponding 2'-deoxyribonucleoside are applied as clinical drugs. In addition to some specific effects, 5-fluoro-2'-deoxyuridine (*I*) is more soluble in water than 5-fluorouracil. The pyrimidine derivatives are successfully fluorinated with trifluoromethyl hypofluorite[4,5] or directly with elemental fluorine[6,7]. Both methods make possible the preparation of 5-fluoro-2'-deoxyribonucleoside *I* from 2'-deoxyuridine. Nevertheless, this route does not appear suitable for the preparation of compound *I* since the fluorination is accompanied by a considerable cleavage of the nucleoside bond and because of the lesser accessibility of the starting 2'-deoxyuridine. Compound *I* has been recently prepared[8] by a transformation of 5-fluorouridine which may be obtained either by the nucleoside synthesis[9] or by fluorination of uridine and its derivatives[10]. It was therefore of interest in this connection to make use of the total synthesis of 2'-deoxyuridine[8,11,12] recently developed in this Laboratory and exhibiting high yields of the particular synthetic steps, to fluorinate the corresponding intermediates and apply the thus-obtained fluoro derivatives to the prepa-

* Part CLXXXVI in the series Nucleic Acid Components and their Analogues; Part CLXXXV: This Journal *41*, 2096 (1976).

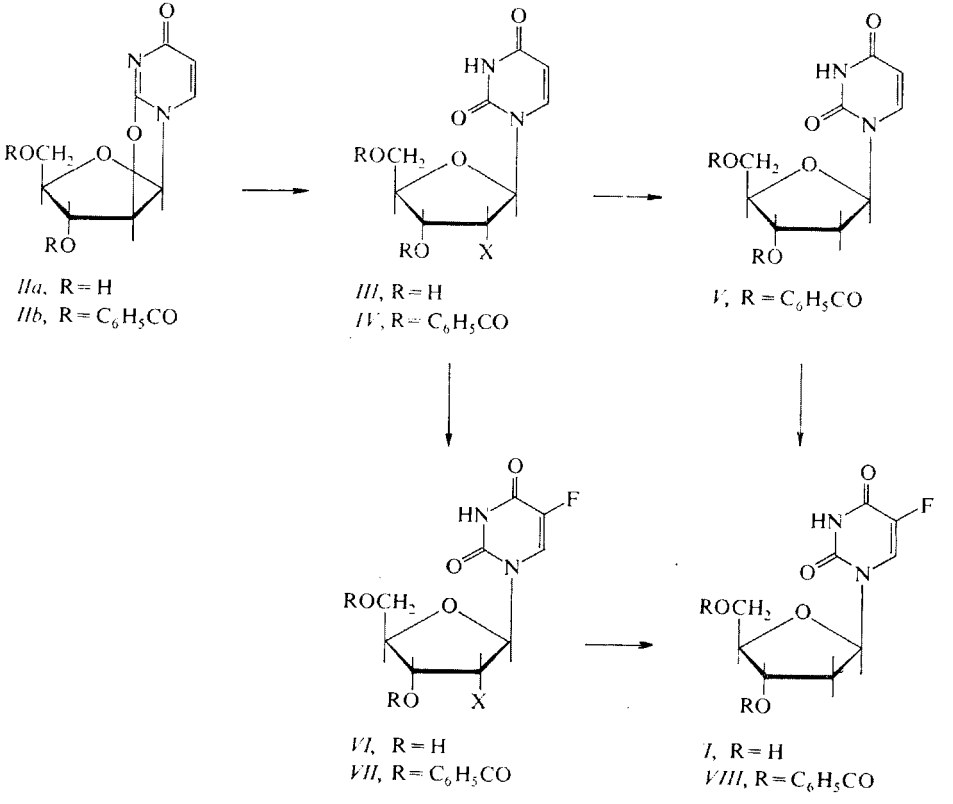
ration of compound *I* with the use of the reported procedures[8]. In the present paper, we wish to describe fluorination of the readily accessible 2′-halo-2′-deoxyuridines and their dibenzoyl derivatives as well as 3′,5′-di-O-benzoyl-2′-deoxyuridine (*V*) (see ref.[13,14]).

The fluorination of uracil and its nucleosides with elemental fluorine diluted with nitrogen in acetic acid solutions at room temperature[6,7,10] may be regarded as the method of choice. As shown, however, by preliminary experiments, the fluorination of our starting compounds mentioned above (similarly to the fluorination of unprotected and peracetylated nucleosides[10]) is accompanied by a considerable cleavage of the nucleoside bond resulting in lower yields of the fluoro derivatives and the need of an additional purification of products. It proved much more advantageous to saturate previously the acetic acid with fluorine, to determine (iodometrically) the fluorine content of this solution, and to treat the acetic acid solution of the compound to be fluorinated with an equimolar amount of this reagent. At room temperature, the reaction is very rapid and almost quantitative being not accompanied by cleavage of the nucleoside bond.

Replacement of acetic acid by other solvents did not prove advisable. In Freons (*e.g.*, in Freon-11, fluorotrichloromethane), the starting compounds are not soluble enough and in chloroform, 5-chlorouracil derivatives are formed as by-products by the action of elemental chlorine which is produced by oxidation of chloroform with fluorine. Thus, the 5-chloro derivative *XII* was isolated as by-product of the fluorination of 3′,5′-di-O-benzoyl-2′-chloro-2′-deoxyuridine (*IVa*) in chloroform as solvent. Consequently, all the remaining fluorinations were performed in acetic acid.

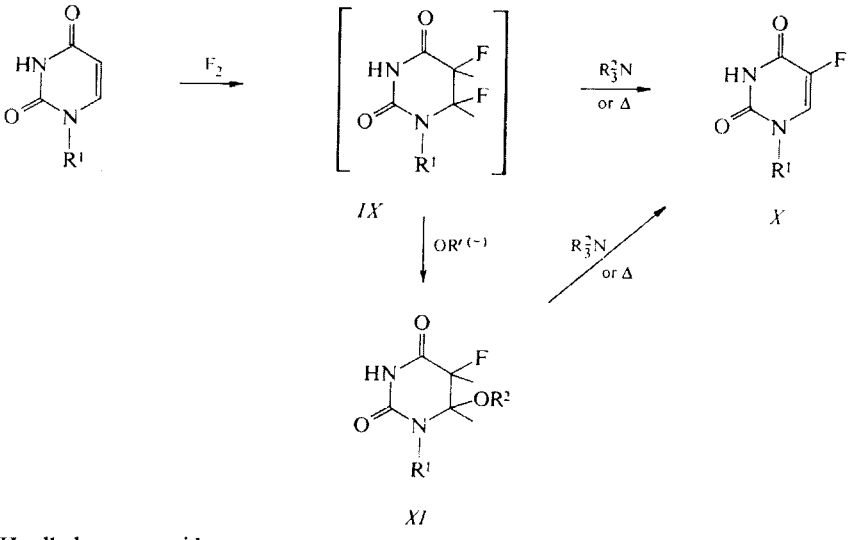
The fluorination of all intermediate types (see ref.[8,12]) in the total synthesis of 2′-deoxyuridine derivatives has been examined, comprising 2′,5′-di-O-benzoyl-$O^{2,2'}$-anhydrouridine (*IIb*), 2′-deoxy-2′-halo derivatives *III* and *IV*, and 3′,5′-di-O-benzoyl-2′-deoxyuridine (*V*). The anhydronucleoside *IIb* is not suitable as the starting compound because of the low solubility in the reaction medium. The fluorination of 2′-halo-2′-deoxyuridines is more advantageous in this respect; the derivatives of 5-fluoro-2′-deoxyuridine (*I*) are accessible from intermediates by reaction with tri-n-butyltin hydride[8,12]. In this group of compounds, the fluorination was examined of the free 2′-halo-2′-deoxynucleosides *III* as well as the corresponding 3′,5′-di-O-benzoyl derivatives *IV*. The 2′-chloro-2′-deoxyuridine derivatives *IIIa* and *IVa* have been reported earlier; the bromo derivatives *IIIb* and *IVb* can be prepared analogously, namely, by a stereospecific opening of the $O^{2,2'}$-anhydronucleoside ring of compounds *II* by the action of hydrogen bromide in dimethylformamide. The structure of compounds *IIIb* and *IVb* is in accordance with elemental analysis and ^{1}H-NMR spectra that also confirm the isomeric purity and the *ribo* configuration of both compounds.

The fluorination of compounds *III* and *IV* with an equimolar amount of fluorine in acetic acid is not a simple substitution reaction. With both types of compounds, the



In formulae *I*, *III*—*VIII* *a*: X = Cl, *b*: X = Br.

primary reaction product is represented by a less polar substance (lacking the UV-absorption in the case of the non-benzoylated compound *III*) which requires a sharp drying, heating or treatment with a tertiary base to be transformed into the required 5-fluorouracil derivative. Analogously to the reaction with trifluoromethyl hypofluorite[4,5] or fluorination of uracil, thymine or 5-halouracils with elemental fluorine[15], the reaction course may be assumed to include the primary addition of fluorine to the 5,6-double bond and formation of the 5,6-dihydro-5,6-difluorouracil derivative *IX*. Elimination of hydrogen fluoride directly affords the 5-fluorouracil derivative *X*; however, nucleophilic attack of an alkoxide ion[16] in an alcoholic medium or of an acetate ion in acetic acid may result in a rapid replacement of the fluoro atom at position 6 by an alkoxy or acetoxy group with the formation of compounds *XI*. Also this type of compounds is then transformed (when heated or sharply dried) by a spontaneous reaction into the 5-fluorouracil derivative *X*; a faster conversion takes place by the action of a tertiary base. We did not succeed in isolating

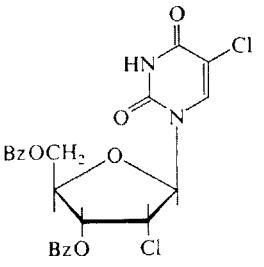


R^1 = H, alkyl, sugar residue
R^2 = alkyl, alkoxyl group

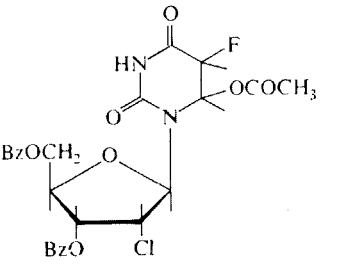
the very unstable primary addition products. On the other hand, compounds produced by the secondary nucleophilic reaction at position 6 are more stable and readily detectable in the reaction by thin-layer chromatography. The 2′-halo-2′-deoxy derivatives even appear to exhibit an enhanced stability; from the reaction mixture after the fluorination of compound *IVa*, a substance was isolated under mild conditions, the elemental analysis and mass spectrum of which is in accord with the structure *XIII*. Furthermore, the ^{1}H-NMR spectrum of the isolated substance exhibits (in addition to signals attributable to the intact sugar moiety) a characteristic shift of the H_6 proton of the uracil ring and the presence of a methyl group with a chemical shift corresponding to the acetoxy group. By heating, drying, or, preferably, treatment with anhydrous triethylamine, compound *XIII* is converted to the 5-fluorouracil derivative *VIIa*, in accordance with expectation.

The last mentioned method, *i.e.* heating of the dried and hydrogen-fluoride free reaction mixture with anhydrous triethylamine proved to be the most advantageous processing after the fluorination in acetic acid as solvent. Noteworthy, no $O^{2,2'}$-anhydro bond is formed from 2′-halo-2′-deoxy derivatives *VI* and *VII* of the *ribo* C-Hal bond under these conditions.

The fluorination of 2′-halo-2′-deoxy derivatives *III* and *IV* in acetic acid has not been in any case accompanied by a halogen exchange at position 2′ of the sugar moiety which would result in the formation of a 2′-fluoro-2′-deoxy derivative. The reaction thus exclusively affords a product of the fluorination on the uracil ring, *i.e.*, a 5-fluorouracil derivative.



XII



XIII

In formulae *XII*, *XIII* Bz = benzoyl group.

Similarly to the halo derivatives *III* and *IV*, the direct fluorination of 3′,5′-di-O-benzoyl-2′-deoxyuridine (*V*) with a solution of fluorine in acetic acid represents an unambiguous and quantitative reaction. An intermediate of the type *IX* or *XI* was neither detected nor isolated. Evaporation of the reaction mixture and work-up of the residue with triethylamine affords 3′,5′-di-O-benzoyl-5-fluoro-2′-deoxyuridine (*VIII*) in a high yield. The L-enantiomer of compound *V* (*cf.*[12]) affords analogously the corresponding L-enantiomer of the 5-fluoro-2′-deoxyuridine derivative (L-*VIII*) as the starting compound for the synthesis of biologically interesting substances of the 5-fluorouracil series.

It may be seen from the above experiments that the direct fluorination with a solution of elemental fluorine in acetic acid is smooth not only with 3′,5′-di-O-benzoyl-2′-deoxyuridine (*V*) but also with the corresponding 2′-halo-2′-deoxy compounds of the type *III* and *IV*. As the latter derivatives are accessible on a large scale and are readily converted to the corresponding 2′-deoxynucleoside *I* or *VIII* by dehalogenation with tri-n-butyltin hydride[8] without any attack on the C—F bond, the use of the present fluorination technique and of the two mentioned types of starting compounds opens an attractive preparative approach to the synthesis of the biologically and clinically significant 5-fluoro-2′-deoxyuridine (*I*).

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Boetius Mikroheiztisch) and are not corrected. Solutions were taken down on a rotatory evaporator at 40°C/15 Torr. Substances were dried over phosphorus pentoxide at 0·1 Torr. Thin-layer chromatography on silica gel was performed on the Kieselgel HF_{254} plates (Merck, Darmstadt, Federal Republic Germany) or on Silufol UV_{254} foils (Kavalier Glassworks, Votice, Czechoslovakia) in the solvent systems S_1, 8 : 1 : 4 ethyl acetate–2-propanol–water (upper phase); S_2, 97 : 3 chloroform–ethanol; S_3, 9 : 1 chloroform–ethanol; S_4, 9 : 1 benzene–ethyl acetate; and S_5, 7 : 3 benzene–ethyl acetate. Column chromatography was carried out on the Kieselgel 60 (Merck) silica gel in solvent systems S_1 and S_2. Loose-layer chromatography was performed on 40 × 16 × 0·4 cm layers of the fluorescent-indicator-containing silica gel (particle size, 30—50 micron; produced by Service Labora-

tories of this Institute). The UV spectra were recorded in water or methanol on Spekord apparatus (Carl Zeiss, Jena, German Democratic Republic). The ^{1}H-NMR spectra were measured in deuteriochloroform (hexamethyldisiloxane as internal standard) on a Varian 100 apparatus (δ values in p.p.m. and coupling constants in Hz). The solution of fluorine in acetic acid was prepared at room temperature by introduction of diluted (1 : 10, with pure nitrogen) elemental fluorine into dry acetic acid. The content of fluorine was determined iodometrically.

2′-Bromo-2′-deoxyuridine (*IIIb*)

A mixture of $O^{2,2'}$-anhydrouridine[12] (*IIa*; 1·0 g; 4·4 mmol) and 2M hydrogen bromide in dimethylformamide (10 ml; 20 mmol; prepared by introducing dry hydrogen bromide into dimethylformamide at 0°C and diluting to the required concentration) was heated at 100°C under calcium chloride tube for 1 h, diluted with acetone (100 ml), and adjusted to pH 7·5 (moistened pH-paper) by the addition of triethylamine with stirring. The precipitate was filtered off and washed with acetone (50 ml). The filtrate and washings were combined and evaporated under diminished pressure. The residue was kept under ether (200 ml) at 0°C overnight, the solvent decanted, and the residue chromatographed on a layer of silica gel in the solvent system S_3. The band of the product was eluted with methanol (500 ml), the eluate evaporated, the residue dissolved in water (20 ml), and the aqueous solution applied to a column (50 ml) of Amberlite IR 4B (acetate) ion exchange resin. The column was eluted with water and the elution checked by the Uvicord apparatus. The UV-absorbing fraction was evaporated and the residue applied to a column (50 ml) of Dowex 50 X 8 (H^+) ion exchange resin. A similar work-up afforded a solid which was crystallised from ethanol. Yield, 0·60 g (44·7%) of compound *IIIb*, m.p. 192 to 193°C. For $C_9H_{11}BrN_2O_5$ (307·2) calculated: 35·18% C, 3·61% H, 26·02% Br, 9·12% N; found: 35·28% C, 3·98% H, 25·89% Br, 8·61% N. R_F, 0·47 in S_3.

3′5′-Di-O-benzoyl-2′-bromo-2′-deoxyuridine (*IVb*)

A solution of 3′,5′-di-O-benzoyl-$O^{2,2'}$-anhydrouridine[12] (*IIb*; 4·35 g; 10 mmol) in dimethylformamide (40 ml) was heated to 100°C and then 4M hydrogen bromide in dimethylformamide (20 ml) was added. The mixture was stirred at 100°C under calcium chloride tube for 1 h and poured into water (500 ml). The solid was collected with suction, washed with water, and dissolved in chloroform (100 ml). The solution was dried over anhydrous magnesium sulfate, evaporated, and the residue crystallised from ethanol (100 ml) to afford 3·0 g (58·3%) of compound *IVb*, m.p. 170—171°C. For $C_{23}H_{19}BrN_2O_7$ (515·4) calculated: 53·60% C, 3·71% H, 15·51% Br, 5·43% N; found: 54·05% C, 3·90% H, 15·89% Br, 5·63% N. The ^{1}H-NMR spectrum: 4·50 to 4·80 (m, 3 H) $H_{4'}$ + 2 $H_{5'}$; 5·01 (t, 1 H, $J_{2',3'} = 6·0$) $H_{2'}$; 5·50—5·70 (m, 1 H) $H_{3'}$; 5·58 (br d, 1 H, $J_{5,6} = 7·5$, $J_{5,NH} \leqq 1·0$) H_5; 6·33 (d, 1 H, $J_{1',2'} = 6·0$) $H_{1'}$; 7·30—7·70 (m, 7 H) H_6 + + arom. protons; 7·95—8·15 (m, 4 H) arom. protons; 11·30 (br. 1 H) NH. R_F, 0·60 in S_2, 0·45 in S_5.

2′-Chloro-2′-deoxy-5-fluorouridine (*VIa*)

A saturated solution of fluorine (152 mg; 4 mmol) in acetic acid was added to 2′-chloro-2′-deoxyuridine[8] (*IIIa*; 1·048 g; 4 mmol) in acetic acid (200 ml). When the reaction was complete (as indicated by thin-layer chromatography in S_1), the solvent was evaporated, the residue repeatedly coevaporated with acetic acid and finally with ethanol, and chromatographed on a column of silica gel (100 g) in the solvent system S_1. The product-containing fractions were evaporated and the residue crystallized from ethanol to afford 0·54 g (48%) of compound *VIa*, m.p. 183°C.

For $C_9H_{10}ClFN_2O_5$ (280·6) calculated: 38·52% C, 3·59% H, 6·77% F, 12·63% Cl, 9·98% N; found: 39·01% C, 3·87% H, 12·96% Cl, 6·52% F, 9·57% N. R_F, 0·73, in S_1. UV spectrum (methanol): λ_{max} 262 nm.

3',5'-Di-O-benzoyl-2'-chloro-2'-deoxy-5-fluorouridine (*VIIa*)

A saturated solution of fluorine (76 mg; 2 mmol) in acetic acid was added to 3',5'-di-O-benzoyl-2'-chloro-2'-deoxyuridine[12] (*IVa*; 0·94 g; 2 mmol) in acetic acid (50 ml), the mixture kept at room temperature for 1 h, and evaporated under diminished pressure. The residue was coevaporated with acetic acid and then refluxed in triethylamine (50 ml) for 1 h. The mixture was cooled down, evaporated to dryness *in vacuo* the residue coevaporated with toluene, and crystallised from ethanol. Yield, 0·77 g (73%) of compound *VIIa*, m.p. 224°C. For $C_{23}H_{18}ClFN_2O_7$ (488·9) calculated: 56·50% C, 3·71% H, 3·88% F, 5·73% N; found: 56·25% C, 3·42% H, 3·80% F, 5·70% N. Mass spectrum: *m/e* 489 (M^+), 452 (M — HCl, $C_{23}H_{17}N_2O_7F$). The ^{1}H-NMR spectrum: 4·50—5·0 (m, 4 H) $H_{3'} + H_{4'} + 2\ H_{5'}$; 5·64 (br t, 1 H, $J_{2',1'} = 5·5$, $J_{2',3'} = 5·0$) $H_{2'}$; 6·20 (dd, 1 H, $J_{1',2'} = 5·5$, $J_{1',F} \leq 1·0$) $H_{1'}$; 7·30—7·80 + 7·95—8·20 (m, 11 H) H_6 + arom. protons. UV spectrum (methanol): λ_{max} 266 nm.

3',5'-Di-O-benzoyl-2'-bromo-2'-deoxy-5-fluorouridine (*VIIb*)

A saturated solution of fluorine (76 mg; 2 mmol) in acetic acid was added to compound *IVb* (1·03 g; 2 mmol) in acetic acid (200 ml). When the reaction was complete (as indicated by thin-layer chromatography in the solvent system S_3), the mixture was evaporated and the residue processed analogously to the preparation of compound *VIIa*. Crystallisation from ethanol yielded 725 mg (69%) of compound *VIIb*, m.p. > 250°C. For $C_{23}H_{18}BrFN_2O_7$ (533·3) calculated: 51·80% C, 3·40% H, 3·56% F, 5·25% N; found: 51·88% C, 3·41% H, 3·57% F, 5·26% N. Mass spectrum: *m/e* 532 (M^+), 452 (M — HBr), 403 (M — base), 130 (protonated base). UV spectrum, pH 7: λ_{max} 264 nm (ε_{max} 10900); pH 13: λ_{max} 269 nm (ε_{max} 5900). R_F, 0·48 in S_5, 0·70 in S_2.

3',5'-Di-O-benzoyl-2'-deoxy-5-fluorouridine (*VIII*)

A saturated solution of fluorine (114 mg; 3 mmol) in acetic acid was added to compound[8] *V* (1·3 g; 3 mmol) in acetic acid (200 ml), the mixture kept at room temperature for 1 h, and processed analogously to the preparation of compounds *VIIa* and *VIIb*. Crystallisation from ethanol yielded 1·1 g (82%) of compound *VIII*, m.p. >250°C (decomp.). For $C_{23}H_{19}FN_2O_7$ (454·4) calculated: 60·79% C, 4·21% H, 4·18% F, 6·16% N; found: 60·51% C, 4·01% H, 3·99% F, 6·23% N. Mass spectrum: *m/e* 454 (M^+), 325 (M — base), 130 (protonated base). UV spectrum, pH 7: λ_{max} 267 nm (ε_{max} 9000); pH 13: λ_{max} 268 nm (ε_{max} 6700). R_F: 0·63 in S_5.

3',5'-Di-O-benzoyl-2'-deoxy-5-fluoro-L-uridine (L-*VIII*) was prepared analogously to the D-enantiomer *VIII* in 80% yield. Found: 60·32% C, 41·5% H, 5·10% F, 6·30% N. R_F: 0·63 in S_5.

Fluorination of Compound *IVa* in Chloroform

A saturated solution of fluorine (76 mg; 2 mmol) in chloroform was added to compound[12] *IVa* (0·94 g; 2 mmol) in chloroform (150 ml), the mixture kept at room temperature for 1 h, and evaporated. The residue was coevaporated with toluene and then chromatographed (*vide supra*) on a column of silica gel (100 g) in the solvent system S_2. In addition to compound *VIIa*, there was obtained 100 mg (20%) of compound *XII*, m.p. >250°C (decomp.). For $C_{23}H_{18}Cl_2N_2O_7$ (505·3) calculated: 54·67% C, 3·59% H, 14·03% Cl, 5·54% N; found: 54·81% C, 3·67% H, 5·61% N,

13·89% Cl. Mass spectrum: *m/e* 468 (M — HCl), 433, 359 (S^+). The ^{1}H-NMR spectrum: 4·61 (m, 3 H) $H_{4'}$ + 2 $H_{5'}$; 5·13 (t, 1 H, $J_{2',3'}$ = 6·0) $H_{2'}$; 5·68 (m, 1 H) $H_{3'}$; 61·3 (d, 1 H, $J_{1',2'}$ = = 6·0) $H_{1'}$; 7·20—7·75 + 7·80—8·05 (2 m, 11 H) arom. protons + H_6. R_F: 0·18 in S_4, 0·56 in S_5; *IVa*: 0·15 in S_4, 0·30 in S_5.

1-(3,5-Di-O-benzoyl-2-chloro-2-deoxy-β-D-ribofuranosyl)-5-fluoro-6-acetyloxy--5,6-dihydrouracil (*XIII*)

A saturated solution of fluorine (38 mg; 1 mmol) in acetic acid was added to a solution of compound[12] *IVa* (0·47 g; 1 mmol) in acetic acid, the mixture kept at room temperature for 1 h, and evaporated under diminished pressure. The residue was coevaporated with acetic acid and then chromatographed on a layer of loose silica gel in the solvent system S_4. The band of the product was eluted with ethyl acetate (200 ml), the eluate evaporated, and the amorphous residue dried under diminished pressure; yield, 0·37 g (67·5%). For $C_{25}H_{22}ClFN_2O_9$ (548·9) calculated: 54·70% C, 4·04% H, 6·46% Cl, 3·46% F, 5·10% N; found: 53·46% C, 4·01% H, 6·50% Cl, 3·70% F, 4·80% N. Mass spectrum: *m/e* 452 (M — CH_3COOH—HCl), 359 (sugar residue), 130 (BH), 129 (B). The ^{1}H-NMR spectrum: 2·05 (s, 3 H) $COCH_3$; 4·40—4·80 (m, 3 H) $H_{4'}$ + + 2 $H_{5'}$; 5·14 (m, 1 H) $H_{2'}$; 5·50—5·80 (m, 1 H, $J_{1',2'}$ = 6·0, $J_{1',F} \geqq 0$) $H_{1'}$; 6·60 (br t, 1 H, $J_{5,6} = J_{6,F}$ = 4·0) H_6; 7·20—7·75 + 7·80—8·05 (2 m, 1 H) arom. protons + H_5. R_F: 0·30 in S_4, 0·68 in S_5; *IVa*: 0·15 in S_4, 0·30 in S_5.

REFERENCES

1. Langen P. in the book: *Antimetabolite des Nucleinsäure-Stoffwechsels*, p. 123. Akademie-Verlag, Berlin 1968.
2. Roy-Burman P. in the book: *Analogues of Nucleic Acid Components*, p. 49. Springer Verlag, Berlin 1970.
3. Camiener G. W., Wechter W. J. in the book: *Progress in Drug Research* (E. Jucker, Ed.), Vol. 16, p. 67. Birkhäuser, Basel 1972.
4. Robins M. J., Naik S. R.: J. Amer. Chem. Soc. *93*, 5277 (1971).
5. Barton D. H. R., Hesse R. H., Toh H. T., Pechet M. M.: J. Org. Chem. *37*, 329 (1972).
6. Ger. (GDR) WPC 07d/158630 (1971).
7. Ger. (GDR) WPC 07d/159832 (1971).
8. Holý A., Cech D.: This Journal *39*, 3157 (1974).
9. Wempen I., Fox J. J. in the book: *Synthetic Procedures in Nucleic Acid Chemistry* (W. W. Zorbach, R. S. Tipson, Eds), Vol. 1, p. 425. Interscience, New York 1968.
10. Cech D., Meinert H., Etzold G., Langen P.: J. Prakt. Chem. *315*, 49 (1973).
11. Holý A.: Tetrahedron Lett. *1971*, 189.
12. Holý A.: This Journal 37, *4072* (1972).
13. Cech D., Holý A.: Czech. Appl. PV 1054—76 (1976).
14. Cech D., Holý A.: Czech. Appl. PV 1055—76 (1976).
15. Cech D., Hein L., v. Janta-Lipinski M., Wuttke R., Otto A., Langen P.: Nucleic Acids Res. *2*, 2177 (1975).
16. Duschinsky R., Gabriel T., Tautz W., Nussbaum A., Hoffer M., Grunberg E., Burchenal J. H., Fox J. J.: J. Med. Chem. *10*, 47 (1967).

Translated by J. Pliml.