# 2-DEOXY-2-FLUORO-D-GLUCOSIDES. PREPARATION OF 17-OXOESTRA-1,3,5(10)-TRIEN-3-YL 2-DEOXY-2-FLUORO-β-D-GLUCOPYRANOSIDE*

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2-Deoxy-2-fluoro-D-glucopyranosides derived from phenol, estrone and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose were prepared and the rates of acid hydrolysis of phenyl β-D-glucopyranoside and phenyl 2-deoxy-2-fluoro-β-D-glucopyranoside compared.

In one of our previous papers we described the preparation of methyl 2-deoxy-2-fluoro-β-D-glucoside[1]. This compound is relatively very resistant to acid hydrolysis, and neither is it split by emulsin, owing to the presence of the fluorine atom on $C_{(2)}$. In this paper we describe the preparation of such 2-deoxy-2-fluoro-D-glucopyranosides in which the aglycone should be more firmly bound to the sugar residue in consequence of the above mentioned effect of the fluorine atom, which could lead, theoretically, to pharmacologically interesting compounds if biologically active aglycones were involved, such as estrone or testosterone. In addition to the mentioned estrone and testosterone we also used phenol, cholesterol and 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose as aglycone components. Of a series of synthetic methods for glycosides preparation two came into consideration primarily, *i.e.* the method of Koenigs–Knorr and then that of Helferich, including their modifications[2-7].

The preparation of one of the starting compounds, 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl bromide (*III*), described as a syrup[1], was modified so that first a mixture of anomeric peracetates of 2-deoxy-2-fluoro-D-glucopyranose (*II*) was prepared by acetolysis of 1,6-anhydro-4-O-benzyl-2-deoxy-2-fluoro-β-D-glucopyranose[8] (*I*) with acetic anhydride in the presence of perchloric acid, and the mixture was converted with hydrogen bromide in a mixture of acetic acid and acetic anhydride to crystalline 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl bromide (*III*).

As a model reaction for the preparation of 2-deoxy-2-fluoro-D-glucoside of estrone we investigated the preparation of phenyl 3,4,6-tri-O-acetyl-2-deoxy-2-

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-fluoro-β-D-glucopyranoside (*IV*). Of all attempts at its preparation the heating with peracetylated 2-deoxy-2-fluoro-α-D-glucopyranosyl bromide (*III*) and phenol with silver oxide at 60–65°C in quinoline, according to ref.[9], was most successful, leading to glycoside *IV* in about 40% yield, while the yield was lower when the procedure was different. The structure *IV* was demonstrated by $^1$H-NMR spectroscopy. The coupling constant values $J_{1,2}$, $J_{2,3}$, $J_{3,4}$ and $J_{4,5}$ ranged from 7·5–9·5 Hz, indicating thus the existence of a compound in $^4C_1$(D) conformation and the presence of a β-glycosidic bond. This is in agreement with the optical rotation, because the values $[\alpha]_D$ for *IV* and for the peracetylated phenyl β-D-glucopyranoside are similar (Table I). In an attempt at the improvement of the preparation of phenyl 3,4,6-tri--O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranoside by substituting silver salicylate for silver oxide, according to ref.[7], we obtained the corresponding peracetylated 1-O--(2-hydroxybenzoyl) derivative *V* instead of the expected glucoside[10].

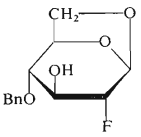
The experiments aimed at the preparation of peracetylated glucopyranoside *IV* from glucosyl bromide *III* and phenol in boiling toluene and in the presence of cadmium carbonate[11] were quite unsuccessful. While 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide reacted with phenol under the mentioned conditions relatively rapidly and in good yield (about 65%), compound *III* reacted with phenol much more slowly, as is evident from the study of the glycosylation course by means of thin-layer chromatography; thermal degradation of bromide *III* under the conditions used evidently competes with this reaction. Orienting attempts were also made with Helfe-

TABLE I

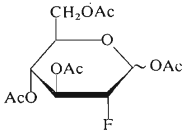
Specific Rotations of Some β-D-Glucopyranosides and 2-Deoxy-2-fluoro-β-D-glucopyranosides

| Aglycone | Peracetyl Glcid[c] | Glcid[a] | Peracetyl FGlcid[d] | FGlcid[b] |
|---|---|---|---|---|
| Methyl | −23° (lit.[20]) | −32° (lit.[21]) | +33° (lit.[1]) | −29° (lit.[1]) |
| Phenyl | −22° (lit.[22]) | −73° (lit.[23]) | −12° | −59° |
| 17-Oxoestra-1,3,5(10)-trienyl | +65° (lit.[11]) | +63° (lit.[24]) | +64° | +48° |
| 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranosido | −53° (lit.[25]) | – | −11° | – |

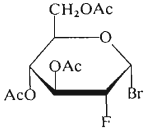
[a] β-D-Glucopyranoside; [b] 2-deoxy-2-fluoro-β-D-glucopyranoside; [c] 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside; [d] 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranoside.



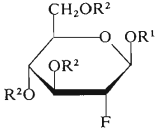

*I*



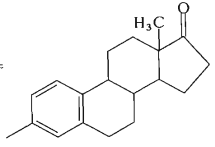

*II*



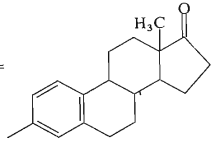

*III*



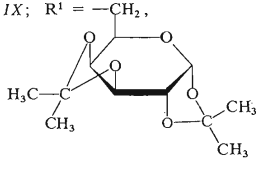

*IV*; $R^1 = C_6H_5$, $R^2 = Ac$
*V*; $R^1 = C_6H_4(OH)CO$, $R^2 = Ac$
*VI*; $R^1 = C_6H_5$, $R^2 = H$

*VII*; $R^1$ = 

, $R^2 = Ac$

*VIII*; $R^1$ = 

, $R^2 = H$

*IX*; $R^1 = -CH_2$, 

$R^2 = Ac$

Ac = $CH_3CO$
Bn = $C_6H_5CH_2$

rich's method of preparation of glycosides with peracetylated 2-deoxy-2-fluoro-D-glucopyranose (*II*). The latter was heated with phenol and *p*-toluenesulfonic acid as catalyst in tetrachloromethane. According to thin-layer chromatography the required product was formed, it is true, but even after 10 h heating about 40% of the starting peracetate *II* were still present in the mixture. Therefore we did not further investigate this approach.

Using the deacetylation of the peracetylated glycoside *IV* by Zemplén's method we prepared phenyl 2-deoxy-2-fluoro-β-D-glucopyranoside (*VI*).

On the basis of the experiences obtained with model preparation of phenyl 2-deoxy-2-fluoro-β-D-glucopyranoside we also synthetized 17-oxoestra-1,3,5-(10)-trien-3-yl 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranoside (*VII*) in an analogous manner. While the application of Klyne's rule[12] did not demonstrate conclusively that it was a β-anomer, the β-configuration is supported by its $^1$H-NMR spectrum ($J_{1,2}$ = 7·5 Hz) and from the comparison of $[\alpha]_D$ values of β-D-glucopyranosides and 2-deoxy-2-fluoro-β-D-glucopyranosides of phenol and estrone (Table I). In addition to this it is known that in the Koenigs–Knorr synthesis of steroid glycosides, using silver oxide as catalyst, β-anomers are formed almost exclusively[13]. Deacetylation of the product *VII* by Zemplén's method gave 17-oxoestra-1,3,5(10)-trien-3-yl 2-deoxy-2-fluoro-β-D-glucopyranoside (*VIII*).

The attempts at the preparation of peracetylated 2-deoxy-2-fluoro-D-glucoside of testosterone prepared from glycosyl bromide *III* and testosterone in the presence of cadmium carbonate or also chloride in boiling toluene[11], or in the presence of silver oxide in quinoline[9], failed. An experiment aimed at the preparation of peracetylated derivative of 2-deoxy-2-fluoro-D-glucoside of cholesterol under catalysis with silver salicylate[7] or mercuric cyanide in acetonitrile[14–18] was also unsuccessful. It is worth noting that under the mentioned conditions both peracetylated β-D-glucosides of testosterone and cholesterol are formed smoothly.

In connection with this work we also prepared 1,2:3,4-di-O-isopropylidene-6-O-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosyl)-α-D-galactopyranose (*IX*) on reaction of compound *III* with 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose and with mercuric cyanide in a mixture of acetonitrile and benzene (1 : 1) at 65°C. From the $^1$H-NMR spectrum it follows that – the same as in compound *IV* – the 2-deoxy-2-fluoro-D-glucopyranosyl residue is in the disaccharide *IX* also in the $^4C_1$(D) conformation and bound by a β-glycosidic bond.

The difference in the stability of the glycosides and their deoxyfluorinated analogues against acid hydrolysis[1] was studied on phenyl β-D-glucopyranoside and phenyl 2-deoxy-2-fluoro-β-D-glucopyranoside. The hydrolysis was carried out at 80°C in 0·75M sulfuric acid in aqueous solution; the concentration of the phenol formed was measured spectrophotometrically (at 500 nm at a higher, and at 750 nm at a lower content of phenol), on the basis of the coloration with Folin–Ciocalteu's reagent[19].

From the dependence of the logarithm of the instantaneous concentration of both mentioned glycosides on time approximate rate constant values were determined: for phenyl β-D-glucopyranoside $k = 4{\cdot}2 \cdot 10^{-4}\ s^{-1}$ (ref.[28]) and for phenyl 2-deoxy-2-fluoro-β-D-glucopyranoside $k = 2{\cdot}9 \cdot 10^{-5}\ s^{-1}$. The first compound is thus hydrolysed about 15 times more quickly than its deoxy fluorinated derivative.

## EXPERIMENTAL

The melting points were measured on a Boëtius micromelting point apparatus. Optical rotations were measured at 25°C with a Bendix Ericsson automatic polarimeter, type 143 A. The absorbances in the visible region were measured on a Specord UV VIS spectrophotometer. The $^1$H-NMR spectra were recorded with a Varian HA-100 instrument in deuteriochloroform (hexamethyldisiloxane as internal reference), and the chemical shifts in $\delta$-values are corrected with respect to tetramethylsilane; the parameters $\delta$ (ppm) and $J$ (Hz) were obtained by first order analysis. The solutions were dried over anhydrous magnesium sulfate and the solvents were distilled off under reduced pressure at 40°C. The courses of the reactions were followed by thin-layer chromatography on silica gel G (Merck). The following solvent systems were employed: *A*) tetrachloromethane–ether 3 : 2 with double development[26]; *B*) heptane–ethyl acetate–methanol according to Codington and coworkers[27]; C) benzene–acetone 10 : 1, double development. Detection was carried out by spraying with 50% sulfuric acid and heating. Samples for analysis were dried under reduced pressure over $P_2O_5$.

### 3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl Bromide (*III*)

Perchloric acid (70%; 0·03 ml) was added to a solution of 1·3 g of 1,6-anhydro-4-O-benzyl--2-deoxy-2-fluoro-β-D-glucose[8] (*I*) in 5 ml of acetic anhydride and the mixture allowed to stand at 20°C for 24 h. After neutralization with aqueous sodium hydrogen carbonate solution the mixture was extracted with chloroform and the extract dried and evaporated. Benzyl acetate was eliminated by chromatography of the remaining syrup on a silica gel column with light petroleum–acetone 20 : 1. The peracetylated 2-deoxy-2-fluoro-D-glucose (*II*) was obtained in the form of a syrup in a 73% yield (1·7 g). Thin-layer chromatography in system A indicated that it was a mixture of anomers in which the β-anomer predominated. Hydrogen bromide solution in anhydrous acetic acid (39%; 17 ml) was added to a solution of the anomeric mixture *II* (1·7 g) in 4·3 ml of acetic anhydride and the mixture was allowed to stand for 2 h. After pouring onto ice–water mixture the product was extracted with chloroform and the extract neutralized with a saturated aqueous solution of sodium hydrogen carbonate, washed with water, dried and filtered through a small column of active charcoal. Chloroform was then distilled off and the residue crystallized from ether–light petroleum. Yield, 1·3 g (72%), m.p. 82–84°C, $[\alpha]_D$ +203° (*c* 0·66; chloroform). For $C_{12}H_{16}BrFO_7$ (371·2) calculated: 38·83% C, 4·34% H, 21·53% Br, 5·11% F; found: 38·98% C, 4·24% H, 21·40% Br, 5·23% F.

### Phenyl 3,4,6-Tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranoside (*IV*)

A solution of compound *III* (1 g) and freshly distilled phenol (0·4 g) in quinoline (3 ml) was stirred with silver oxide (0·4 g) at 65°C for 30 min. After dilution with chloroform the mixture was filtered through a small column of charcoal and then extracted with 10 ml of 3M-HCl, washed with water, two 20 ml portions of 5% NaOH and again with water. After drying and evaporation

the residue was crystallized from ethanol–light petroleum. Yield, 400 mg (40%), m.p. 126–128°C, $[\alpha]_D$ −12° (*c* 0·82; chloroform). $R_F$ values: 0·60 in system A, 0·30 in B. For $C_{18}H_{21}FO_8$ (384·4) calculated: 56·24% C, 5·52% H, 4·94% F; found: 56·31% C, 5·67% H, 5·28% F. $^1$H-NMR spectrum: 2·04, 2·06, 2·10 s (3 $CH_3COO$); 3·85 m (H-5), $J_{5,6}$ = 2·7 and 5·2, $J_{5,4}$ ~9·7; 4·14 dd (H–6), $J_{6,6}$ ~12, $J_{6,5}$ = 2·7; 4·31 dd (H–6), $J_{6,6}$ ~12, $J_{6,5}$ = 5·2; 4·57 ddd (H–2), $J_{2,F}$ = 50·4, $J_{2,1}$ = 7·7, $J_{2,3}$ = 8·6; 5·095 t (H–4), $J_{4,5}$ ~9·7, $J_{4,3}$ ~9·1; 5·125 dd (H–1), $J_{1,2}$ = 7·5, $J_{1,F}$ = 3·2; 5·42 dt (H–3), $J_{3,2}$ = 8·7, $J_{3,4}$ ~9·1, $J_{3,F}$ = 14·1; 6·95–7·42 m (5 H arom.).

Reaction of Glucosyl Bromide *III* with Silver Salicylate

A solution of 0·5 g of compound *III* and 0·2 g of redistilled phenol in 1·5 ml of quinoline was stirred with 0·3 g of silver salicylate at 65°C for 30 min. The product was isolated in the same way as in the preceding case. From ethanol–light petroleum mixture 350 mg (68%) of 3,4,6-tri--O-acetyl-2-deoxy-2-fluoro-1-O-(2-hydroxybenzoyl)-β-D-glucopyranose (*V*) crystallized out with m.p. 144 to 146°C. IR spectrum: 1755 $cm^{-1}$ ($CH_3COO$), 1700, 1620, 1580 $cm^{-1}$ (aromatic ester). $[\alpha]_D$ +12° (*c* 0·66; chloroform). $R_F$ in B: 0·32. For $C_{19}H_{21}FO_{10}$ (428·4) calculated: 53·27% C, 4·95% H, 4·43% F; found: 53·61% C, 4·98% H, 4·52% F.

Phenyl 2-Deoxy-2-fluoro-β-D-glucopyranoside (*VI*)

Methanol (30 ml) and a catalytic amount of sodium methoxide were added to a solution of 400 mg of glucoside *IV* in 30 ml of benzene and the mixture was allowed to stand for half an hour. It was then neutralized with Dowex 50 W, filtered through a small column of active charcoal and evaporated. The product was crystallized from ethyl acetate–light petroleum, yielding 170 mg (65%), m.p. 140–142°C, $[\alpha]_D$ −60° (*c* 0·83; methanol). For $C_{12}H_{15}FO_5$ (258·3) calculated: 55·80% C, 5·86% H, 7·36% F; found: 55·56% C, 5·66% H, 7·27% F.

17-Oxoestra-1,3,5(10)-trien-3-yl 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranoside (*VII*)

A solution of compound *III* (1·5 g) and estrone (1·2 g) in quinoline (4·5 ml) was mixed with silved oxide (0·5 g) and stirred at 65°C for half an hour. The mixture was diluted with chloroform, filtered through a column of charcoal and the filtrate shaken with 30 ml of 3M-HCl, water and sodium hydrogen carbonate solution, then dried and evaporated. Using chromatography on a silica gel column and tetrachloromethane–ether 2 : 1 mixture as eluent about 300 mg of unreacted estrone were separated from the product. The latter was crystallized from ethanol–light petroleum. Yield 1 g (45%), m.p. 205–206°C, $[\alpha]_D$ +64° (*c* 0·88; chloroform). $R_F$ values: 0·30 in A, 0·15 in B. For $C_{30}H_{37}FO_9$ (560·7) calculated: 64·26% C, 6·67% H, 3·39% F; found: 63·91% C, 6·40% H, 3·49% F. $^1$H-NMR spectrum: the glycosyl part — 2·05, 2·08, 2·11 s (3 $CH_3COO$); 3·85 o (H–5), $J_{5,4}$ = 9·5, $J_{5,6}$ = 3·0, $J_{5,6}$ = 5·0; 4·15 dd (H–6), $J_{6,6}$ = 12·0, $J_{6,5}$ = 3·0; 4·30 dd (H–6), $J_{6,6}$ = 12, $J_{6,5}$ = 5·0; 4·55 dt (H–2), $J_{2,F}$ = 50·0, $J_{2,1}$ = 7·5, $J_{2,3}$ = 9·0; 5·09 t (H–4), $J_{4,3}$ = 9·5, $J_{4,5}$ = 9·5; 5·11 dd (H–1), $J_{1,2}$ = 7·5, $J_{1,F}$ = 3·0; 5·41 dt (H–3), $J_{3,F}$ = 14·5, $J_{3,2}$ = 9·0, $J_{3,4}$ = 9·5; aglycone — 0·91 s ($CH_3$–18); 6·82 bs ($C_{(4)}$—H); 6·87 bd ($C_{(2)}$—H), 7·23 bd ($C_{(1)}$—H); the remaining protons were not identified.

17-Oxoestra-1,3,5(10)-trien-3-yl 2-Deoxy-2-fluoro-β-D-glucopyranoside (*VIII*)

A catalytic amount of sodium methoxide in 60 ml of methanol was added to a solution of 800 mg of glucoside *VII* in a small amount of dichloromethane and the mixture was allowed to stand for 30 min. After neutralization with Dowex 50 W the solution was filtered through a small

column of active charcoal and evaporated. The residue was dissolved in boiling 75% aqueous ethanol. After cooling glucoside *VIII* crystallized out, yield 420 mg (68%), m.p. 240–243°C, $[\alpha]_D$ +48° (*c* 0·87; pyridine). For $C_{24}H_{31}FO_6$ (434·5) calculated: 66·33% C, 7·20% H, 4·37% F; found: 65·94% C, 7·10% H, 4·16% F.

1,2 : 3,4-di-O-Isopropylidene-6-O-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-β-D-glucopyranosyl)--α-D-galactopyranose (*IX*)

Acetonitrile (21 ml), compound *III* (1·4 g) and mercuric cyanide (0·9 g) were added to a solution of 1 g of 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose in benzene (21 ml) and the mixture was heated at 65°C for 6 h. After distillation off of the solvents 70 ml of chloroform were added and the solution filtered, then washed with a saturated sodium chloride solution, with water, dried and evaporated. Chromatography on a silica gel column in benzene–acetone 25 : 1 gave a product which was crystallized from chloroform–heptane to afford 500 mg (24%) of a chromatographically pure product. M.p. 149–150°C, $[\alpha]_D$ −11° (*c* 1·03; chloroform). $R_F$ value in system C was 0·50. For $C_{24}H_{35}FO_{13}$ (550·6) calculated: 52·42% C, 6·42% H, 3·45% F; found: 52·68% C, 6·23% H, 3·58% F. $^1$H-NMR spectrum: the D-glucopyranosyl part — 2·02, 2·06, 2·07 s (3.$CH_3$COO); 3·72 m (H−5), $J_{5,6}$ = 2·8, $J_{5,4}$ = 10·0; 4·68 dd (H−1), $J_{1,2}$ = 7·8, $J_{1,F}$ = 3·2; 5·02 t (H−4), $J_{4,3}$ = 9·6, $J_{4,5}$ = 9·6; 5·325 dt (H−3), $J_{3,2}$ = 8·8, $J_{3,4}$ = 8·8, $J_{3,F}$ = 14·2; the D-galactopyranosyl part — 1·33 s (2 $CH_3$); 1·44, 1·53 s (2 $CH_3$); 5·52 d (H−1), $J_{1,2}$ = 4·8.

Measurement of the Rate of Hydrolysis using Folin–Ciocalteu's Reagent

The Folin–Ciocalteu's reagent and other necessary solutions, A, B and C, were prepared according to literature[19].

TABLE II

Concentration of Phenol Formed on Hydrolysis of Phenyl β-D-Glucoside (*A*) and Phenyl 2-Deoxy-2-fluoro-β-D-glucoside (*B*)

| Time of hydrolysis min | Amount of p henol set free | |
|---|---|---|
| | A | B |
| 5 | 5·13 | — |
| 10 | 8·60 | — |
| 15 | 12·25 | 0·99 |
| 20 | 14·90 | — |
| 25 | 18·20 | — |
| 30 | 20·60 | 1·82 |
| 45 | — | 2·98 |
| 60 | — | 3·80 |

*Calibration curves*: 3 ml-portions of solution C were pipetted into test tubes and a measured volume (3, 5, 7, 10 or 15 μl) of a solution prepared from 10 mg of distilled phenol in 10 ml of water was added to it. After stirring the solution formed was allowed to stand for 10 min. Folin–Ciocalteu's reagent (0·3 ml) was then added and the mixture stirred thoroughly. After 30 min standing absorbance was measured at 500 and 700 nm wavelength. Calibration curves were obtained by plotting absorbance values against molar concentration of phenol.

*Hydrolysis of phenyl β-D-glucoside*: Phenyl β-D-glucoside (10 mg; 0·039 mmol) and 0·75M-$H_2SO_4$ (1 ml) were heated in a ground-glass joint test tube immersed in a bath 80°C warm. Immediately after immersion phenyl β-D-glucoside dissolved completely. At 5 minute intervals, over half an hour, 10 μl of this solution were always added to 3 ml of solution C. After mixing and ten minutes' standing 0·3 ml of Folin–Ciocalteu's reagent were added and the solution stirred. Absorbance of the solution at 500 nm was measured after 30 min. The amount of phenol set free at various time intervals is given in Table II.

*Hydrolysis of phenyl 2-deoxy-2-fluoro-β-D-glucoside*: 10 mg (0·039 mmol) of the glucoside *VI* were hydrolyzed in 1 ml of 0·75M-$H_2SO_4$. The procedure was similar as in the preceding case, with the difference that the samples were withdrawn at 15 min intervals over 1 h. Absorbance was measured at 750 nm. The amount of phenol set free at various time of hydrolysis is given in Table II.

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