NUCLEOSIDES

XXX. SYNTHESIS OF 2-DEOXY-2-FLUORO-D-RIBOSE

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With the successful introduction of fluorine into the ribosyl moiety of nucleosides[1], as in 1-(2-deoxy-2-fluoro-β-D-ribofuranosyl)uracil (2'-deoxy-2'-fluorouridine) (Ib), a route was made available for the synthesis of 2-deoxy-2-fluoro sugars of the *ribo* configuration. Although fluorine had been introduced into the terminal position of several sugars[2,3], it was not until recently that pentoses having a fluorine atom in a nonterminal position were reported with the synthesis of 3-deoxy-3-fluoro derivatives in both the *xylo*[4,5] and *arabino*[5] series. This paper reports the synthesis of 2-deoxy-2-fluoro-D-ribose (IVb). It was anticipated that IVb, as an analog of the biologically important 2-deoxy-D-*erythro*-pentose ("2-deoxy-D-ribose") (IVa), might, either as the free sugar or as an appropriate derivative, possess interesting biological properties*.

As a model compound in this synthesis, 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-uracil (2'-deoxyuridine) (Ia) was reduced using rhodium-on-alumina catalyst, according to the method of Cohn and Doherty[6], to give the known 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-5,6-dihydrouracil (IIa)[7] as colorless crystals (see flow chart). Alkaline treatment which would be expected to give a ureidopropionic acid[7,8], followed by heating in dilute acid[9], gave a solution which gave a positive test with Fehling solution. Thin-layer chromatography (t.l.c. in solvent B) revealed a single spot[10] migrating at the same rate as an authentic sample of IVa. Benzoylation of the dried residue, followed by fractional recrystallization, gave both anomers of 1,3,4-tri-*O*-benzoyl-2-deoxy-D-*erythro*-pentose (α, Va; β, VIa) in approximately equal yields (combined yield 25%). The physical properties agreed closely with those of compounds prepared by Pedersen, Diehl, and Fletcher[11]. The infrared spectra of authentic samples, kindly supplied by Dr. Fletcher, were identical with those of Va and VIa, and mixtures of samples from both sources gave no depression of melting points. These data establish the identity of Va and VIa.

In a similar manner, 1-(2-deoxy-2-fluoro-β-D-ribofuranosyl)uracil (Ib) was reduced to 1-(2-deoxy-2-fluoro-β-D-ribofuranosyl)-5,6-dihydrouracil (IIb), which, although analytically pure, was isolated only as a gum. The di-*O*-benzoyl derivative III, however, was obtained from IIb in high yield, as colorless needles. In

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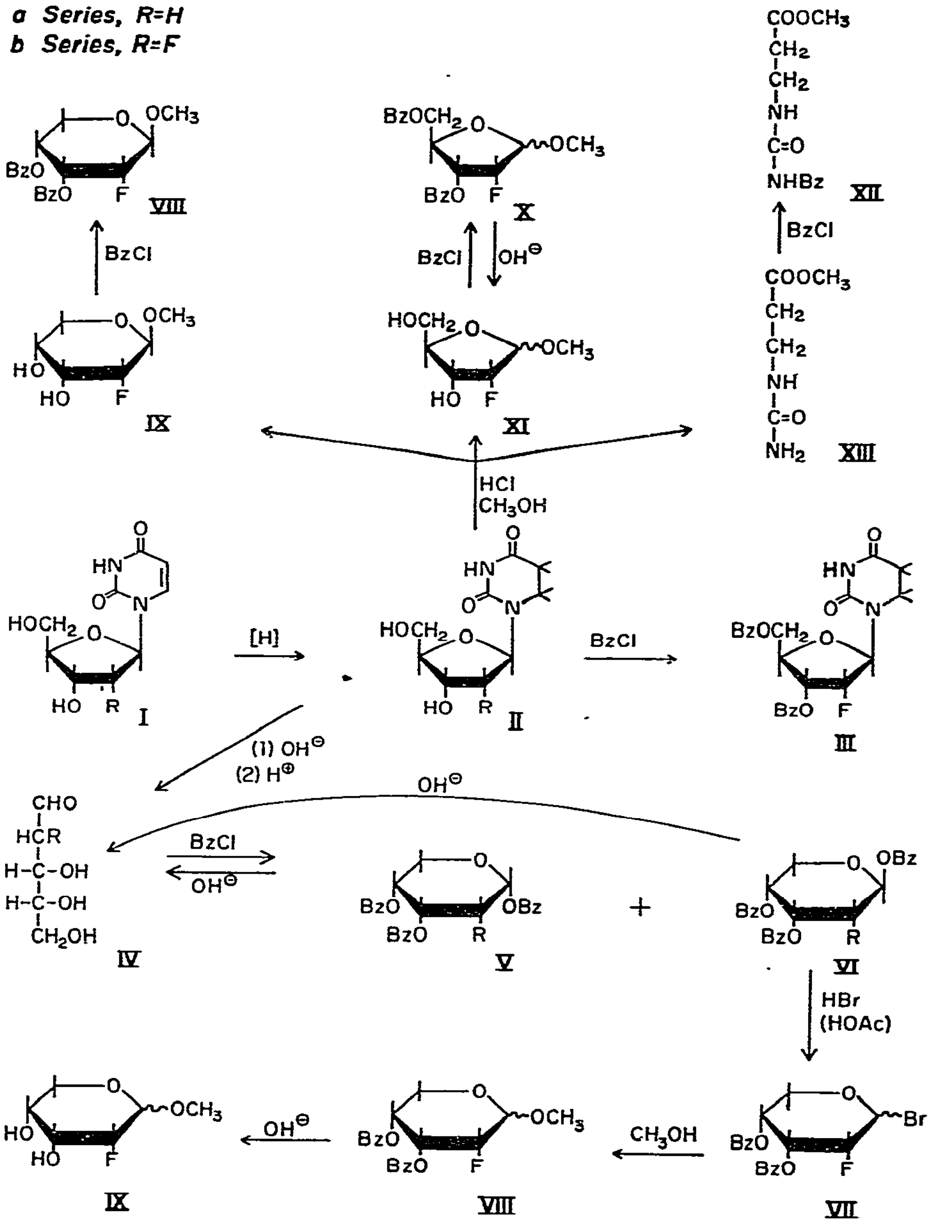
*A study of the biological properties of IVb and certain of its derivatives is under way in this Institute.

anticipation that cleavage of the dihydronucleoside IIb would occur in a manner similar to that found for its deoxy analog IIa. compound IIb was subjected to the alkaline and acid hydrolytic treatments which had been successfully applied to IIa.



Positive Fehling and aniline acid phthalate[10] tests suggested the presence of the desired 2-deoxy-2-fluoro-D-ribose (IVb) in the crude mixture. Attempts to isolate IVb in pure form from this mixture were however, unsuccessful.

After removal of the solvent, the residue containing IVb was benzoylated in pyridine solution. The resulting mixture showed two major components (t.l.c. in solvent A). A third compound was also present, but in small proportion. The major components were separated by chromatography on an alumina column, with chloroform as the eluant. One of these components (VIb) was isolated as colorless needles, $[\alpha]_D$ −146°, in 13–21% yield. The elementary analysis corresponded to that of a tribenzoyldeoxyfluoropentose. Two crystalline forms of VIb, having different melting points and infrared spectra (KBr discs) were isolated. Heating of the KBr disc of the lower-melting isomorph at 110–115° readily changed its infrared spectrum to that of the higher-melting form. The other major component isolated from the alumina column was present in about 6% yield. It was obtained only as an amorphous material, which was contaminated with a small proportion of the third product as shown by t.l.c. chromatography. Attempts to crystallize this material failed. Like VIb, this amorphous material, $[\alpha]_D$ −10°, showed three benzoyl groups on titration. Since only the α-D- and β-D-pyranoses, Va and VIa, were isolated in the 2-deoxy series, it seems probable that the second major component present after benzoylation of IVb is 1,3,4-tri-*O*-benzoyl-2-deoxy-2-fluoro-α-D-ribose (Vb). Strict conformity to Hudson's rule[12,13] (based upon known values in the 2-deoxy and 2-deoxy-2-fluoro series: Va +47°, VIa −192° and VIb −146°) would lead to prediction of a positive rotation (+92°) for the α-D anomer Vb. The value of −10°, however, suggests the probable presence of a contaminant having a high, negative rotation.

The relatively small yield of benzoylated sugars obtained by this method in both the 2-deoxy and 2-deoxy-2-fluoro series may possibly be attributable to ring closure of the β-ureidopropionic acid intermediate under acid conditions. Such a reaction was noted by Batt *et al.*[8] and, later, by others[14].

Compound VIb was shown to have a pyranoid structure as follows: Conversion of VIb to the methyl glycoside VIII through the 1-bromo derivative VII was accomplished by treatment with hydrogen bromide–acetic acid (32%) in dichloromethane followed by treatment of VII with methanol in the presence of a little pyridine as the acid acceptor. These reactions were followed polarimetrically. The methyl dibenzoyl glycoside VIII was obtained as a gum, $[\alpha]_D$ −133°. Titration data indicated two benzoyl groups. The unprotected methyl glycoside IX (Fehling negative) was treated with sodium metaperiodate. After 2 h, exactly one mole of periodate had been consumed per mole of compound. This value remained constant during the next several hours, and then rose slowly. After seven days, 2.7 mole of periodate per mole had been consumed. The continued slow oxidation of the molecule may be related to the observation by Huebner and co-workers[15] of the periodate oxidation of active methylene groups. The primary oxidation product, a monoacetal of α-fluoro malonaldehyde, would probably be expected to consume periodate, in view of the uptake reported for malonaldehyde[16] and α-ethylmalonic acid[15]. The uptake of one mole per mole of periodate at 2–6 h proves conclusively the pyranoid ring-structure of IX and establishes VIb as being 1,3,4-tri-*O*-benzoyl-2-deoxy-2-fluoro-D-ribose.

Although the anomeric form of VIb has not yet been definitely determined, its high negative rotation (—146°) indicates that it is probably of the β-D configuration[12]. The corresponding deoxypyranosides[11] are characterized by a high negative rotation (—195°) for the β-D anomer and a positive rotation (+42°) for the α-D anomer.

In view of their high, negative rotations, it seems probable that both 3,4-di-*O*-benzoyl-2-deoxy-2-fluoro-D-ribosyl bromide (VII) (—225°) and methyl 3,4-di-*O*-benzoyl-2-deoxy-2-fluoro-D-riboside (VIII) (—133°) are mainly of the β-D configuration[13,17]. A β-D configuration for the di-*O*-benzoylpyranosyl bromide VII conforms to the rule, formulated by Haynes and Newth[17] and further discussed by Bhattacharya *et al.*[13], that, in poly-*O*-acylglycopyranosyl halides, the halogen atom at C-1 is *trans* to the acyloxy group at C-3.

Crystalline 2-deoxy-2-fluoro-D-ribose (IVb)* was obtained in almost quantitative yield by debenzoylation of VIb. Reaction of VIb with dilute, ethanolic sodium hydroxide, removal of the contaminating material, and evaporation of water *in vacuo* gave a colorless gum which crystallized as fernlike structures. The compound showed a melting point of 106–112° and an optical rotation of —37°. No mutarotation of IVb was observed in either dilute acid or base. The infrared spectrum of IVb, shown in the figure, is characterized by the absence of carbonyl absorption. Compound IVb migrates (t.l.c. in solvent B) as a single spot (R_F 0.50) at a higher rate than 2-deoxy-D-*erythro*-pentose (IVa) (R_{IVa}, 1.25). Good yields of crystalline IVb were obtained by the same method from the amorphous tribenzoylated material (probably, mainly Vb) isolated from the reaction mixture producing VIb (see above).

Methanolysis[18,19] of IIb was performed in the hope of obtaining IVb from the resulting methyl glycosides in an overall yield higher than had been obtained by the method described above (IIb to VIb and Vb, then to IVb). The amorphous product contained three components as shown by t.l.c. in solvent B. It was benzoylated in pyridine solution. The crude mixture gave six spots on t.l.c. developed with solvent A. The mixture was partially separated by chromatography on an alumina column using chloroform as the eluant. Three components were isolated, and their structures elucidated.

The first component to be eluted was isolated as colorless prisms in 8% yield. Debenzoylation of this compound with dilute, ethanolic sodium hydroxide gave a product which crystallized as colorless needles. The results of elementary analysis were consistent either with the methyl pyranoside IX or the (isomeric) methyl furanoside XI. The furanoid structure was established by the fact that the compound consumed essentially no periodate during 60 min, whereas the pyranoside IX consumed 0.8 mole of oxidant per mole during the same period. Thus, the debenzoylated glycoside is established as being methyl 2-deoxy-2-fluoro-D-ribofuranoside (XI) and the benzoylated derivative as methyl 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-D-riboside (X).

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*For convenience, compounds IVa and IVb are represented on the flow chart in the aldehydo form, although it is improbable that they exist mainly in this form either as crystals or in solution.

The second component eluted from the column was isolated only as a gum, in 22% yield (based on IIb). It traveled as a single spot, R_F 0.64 (t.l.c. in solvent A) at a lower rate than XI, R_F 0.75. The elementary analysis of it was consistent with structure VIII, and a benzoyl determination indicated two benzoyl groups per molecule. An optical rotation of −156° was observed. This is somewhat more negative than that of the corresponding amorphous material obtained from the pyranosyl bromide VII (see above). The infrared spectra of the two gums were identical, although the bands were not sharp. On the basis of the optical rotation[12], it may be concluded that this sample of VIII is most probably the β-D-anomer. The debenzoylated product IX consumed approximately one mole of periodate per mole in two h, consistent with a pyranoid structure. These data strongly suggest that the second component is the β-D anomer of methyl 3,4-di-*O*-benzoyl-2-deoxy-2-fluoro-D-riboside (VIII). It is noteworthy that, in the methanolysis of IIb, methyl glycosides of both the pyranoid (IX) and furanoid structure (XI) are formed.

An effort was made to obtain 2-deoxy-2-fluoro-D-ribose (IVb) from VIII. A product giving positive Fehling and aniline acid phthalate tests[10], and migrating at the same rate as IVb, was obtained, but the yields were poor, and analytically pure material was not obtained.

A considerable proportion of the benzoylated material was obtained from the column as a third fraction. Trituration of the residual gum with a small amount of ethanol produced a third component as colorless prisms, in 8% yield. This compound contained nitrogen, but no fluorine. Its elementary analysis was consistent with that calculated for XII, methyl 3-(*N*-benzoylureido)propionate. This component was probably formed during the methanolysis reaction as the methyl ester of ureidopropionic acid (XIII), which had presumably resulted from cleavage between C-3 and C-4 of the dihydrouracil moiety[7,8]. In a second methanolysis experiment, dihydrouracil was, in fact, isolated from the reaction mixture prior to separation on an alumina column.

EXPERIMENTAL

Solvent A for t.l.c. was prepared by the addition of *n*-heptane (108 ml) and ethyl acetate (208 ml) to the upper layer (340 ml) obtained from a mixture of *n*-heptane (400 ml) and methanol (200 ml). Solvent B is 1-butanol–water (86:14). All t.l.c. plates were prepared with Silica Gel G, according to Stahl (Brinkmann Instruments, Inc., Westbury, New York, U.S.A.). After the developed plate had been completely freed of solvent, it was sprayed with sulfuric acid–water (1:1) and heated at 100°. Reducing-sugar spots were identified by spraying with aniline acid phthalate reagent, followed by heating[10].

Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are corrected. Elementary analyses were made by Spang Microanalytical Laboratory, Ann Arbor, Michigan. Infrared spectra were made on a Perkin–Elmer spectrophotometer, Model 221.

Benzoyl determinations were made by stirring a weighed sample at 25–30° with a measured amount of 0.1 N sodium hydroxide in dilute aqueous ethanol. Unreacted base was determined by titrating with 0.1 N hydrochloric acid (phenolphthalein).

*1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5,6-dihydrouracil (IIa)*

In accordance with the method of Cohn and Doherty[6], a mixture of 2'-deoxyuridine (Ia) (1.0 g, 4.4 mmole) and rhodium on alumina (5%) (0.70 g) in ethanol (60 ml) absorbed 113 ml of hydrogen at atmospheric pressure within 106 min (theoret., 106 ml). The product, m.p. 133–138° (reported[7] 136–138°), weighed 1.0 g (99%), $[\alpha]_D^{24}$ −7° (*c* 1.1 in water).

1-(2-Deoxy-2-fluoro-β-D-ribofuranosyl)-5,6-dihydrouracil (IIb)

A mixture of 2'-deoxy-2'-fluorouridine (Ib) (0.20 g, 0.82 mmole) and rhodium on alumina (5%) (0.15 g) in ethanol (25 ml) was shaken under one atmosphere of hydrogen for 41 min. An uptake of 23 ml of hydrogen (theoret., 19.7 ml) was recorded. After removal of the catalyst, the filtrate was evaporated to dryness *in vacuo*, leaving a colorless gum, $[\alpha]_D^{24}$ −17° (*c* 0.4 in water). U.v. absorption data (H_2O): shoulder, 205–210 mμ, ratio 220/260 mμ, 87.

Anal. Calc. for $C_9H_{13}FN_2O_5$: C, 43.57; H, 5.28; F, 7.66; N, 11.29. Found: C, 43.56; H, 5.74; F, 7.59; N, 11.15.

1-(3,5-Di-O-benzoyl-2-deoxy-2-fluoro-β-D-ribosyl)-5,6-dihydrouracil (III)

A solution of IIb (0.30 g, 1.22 mmole) in pyridine (8 ml) was cooled to 0–5°, and benzoyl chloride (0.53 g, 3.8 mmole) was added dropwise with stirring. The solution was kept 23 h at about 5° and a small piece of ice was added. Removal of solvent *in vacuo*, followed by addition of ice-water (100 ml) with stirring, gave a colorless solid. This was collected and crystallized from ethanol, yielding colorless needles, 0.40 g (73%), m.p. 160–162°. Additional material (0.05 g), m.p. 155–160°, was obtained from the mother liquor. Recrystallization from ethanol gave colorless needles, m.p. 162–163°, $[\alpha]_D^{24}$ −1° (*c* 0.7 in chloroform).

Anal. Calc. for $C_{23}H_{21}FN_2O_7$: C, 60.55: H, 4.62; F, 4.17; N, 6.13. Found: C, 60.41; H, 4.63; F, 4.21; N, 6.33.

*2-Deoxy-D-*erythro*-pentose (IVa)*

A solution of IIa (0.23 g, 1.0 mmole) in 0.2 N sodium hydroxide (10 ml) was allowed to stand for 20 min at room temperature, and then treated with Dowex 50 (H^+). After removal of the resin, 1 N sulfuric acid was added (3 ml, total volume 12 ml), and the resulting solution was heated at 85° for 20 min. Anions were removed with Dowex 1 (OH^-). The filtrate was evaporated to dryness *in vacuo*. The residue was co-distilled several times with anhydrous benzene, and dried well *in vacuo*. The product gave positive Fehling and diphenylamine[20] tests and migrated on t.l.c.

in solvent B at the same rate as an authentic sample of 2-deoxy-D-*erythro*-pentose, R_F 0.40.

*1,3,4-Tri-O-benzoyl-2-deoxy-α-D-*erythro*-pentose (Va) and 1,3,4-tri-O-benzoyl-2-deoxy-β-D-*erythro*-pentose (VIa)*

Benzoylation was performed in a manner similar to that described by Pedersen, Diehl, and Fletcher[11]. The dried product (IVa) described above was dissolved in pyridine (11 ml) and treated with benzoyl chloride (0.50 g, 3.6 mmole) at 0–5° with stirring, then kept refrigerated for an additional 17 h. After hydrolysis of the remaining benzoyl chloride with a small piece of ice, and removal of solvent, ice-water was added to the residue. As the product did not crystallize, the mixture was extracted with ether, and the ethereal solution dried. Colorless needles, 0.06 g, m.p. 140–150°, were filtered from 2–3 ml of ether. Recrystallization from ethanol gave 0.05 g (11%) of colorless needles, m.p. 159–160°, $[\alpha]_D^{24}$ −192° (*c* 0.2 in chloroform). Pedersen *et al.*[11] report m.p. 159–161° and $[\alpha]_D^{20}$ −195° (chloroform) for the β-D pyranose VIa. A mixture of an authentic sample[11], m.p. 158.5–159.5°, with the above sample, m.p. 159–160°, melted at 159–160°. Infrared spectra (KBr discs) of the two samples showed significant differences in the 10–15 μ region. Upon heating the KBr disc (sample prepared as described above and recrystallized from ethanol) at 110–115° for 60 min, its infrared spectrum was identical with that of a sample prepared by Pedersen *et al.*, which had been crystallized from methanol.

The ether-soluble fraction was crystallized from ethanol to give 0.06 g (14%) of long, colorless needles melting at 147–149°. Recrystallization from methyl Cellosolve gave colorless needles, m.p. 150.5–151.5°, $[\alpha]_D^{23}$ +47° (*c* 0.2 in chloroform). Reported[11] constants for the α-D anomer were m.p. 151–152° and $[\alpha]_D^{20}$ +42° (chloroform). A mixture of a sample prepared as above, m.p. 150.5–151.5°, with an authentic sample[11], m.p. 150.5–151.5°, melted at 150.5–151.5°. Infrared spectra (KBr discs) of the two samples showed significant differences. The KBr disc of the sample prepared as described above (crystallized from methyl Cellosolve) was heated at 110–115° for 60 min. Its infrared spectrum was then identical with that of an authentic sample (crystallized from methanol)[11].

1,3,4-Tri-O-benzoyl-2-deoxy-2-fluoro-β-D-ribose (VIb)

An alkaline solution (40 ml, 0.2N NaOH) of IIb (0.76 g, 3.07 mmole) was allowed to stand at 23–25° for 40 min. Neutralization with 2N sulfuric acid (4 ml) was followed by a further addition of 2N sulfuric acid (4.9 ml). The solution was heated at 85–90° (internal temp.) for 35 min and then treated, while hot, with solid barium carbonate until neutral. Filtration gave a clear solution which was treated with Dowex 50 (H^+), and the filtrate was evaporated to dryness *in vacuo*. The gummy residue gave positive tests with Fehling and aniline acid phthalate[10] reagents. Addition of pyridine to the residue, followed by its removal *in vacuo*, was repeated twice.

The residue was dissolved in dry pyridine (50 ml) and treated dropwise with benzoyl chloride (2.4 g, 17.1 mmole) at 0–5° with stirring. After 16 h at 5–7°, the mixture was warmed at 35–40° for 60 min. A small piece of ice was added with stirring. Later, the pyridine was removed *in vacuo*, and the residue dissolved in chloroform. The solution was extracted with dilute sodium bicarbonate solution and water, and dried over sodium sulfate.

A chloroform solution (10 ml) of the above material was placed on an alumina (acid washed) column (3 × 42 cm), and the column eluted with chloroform. Fractions containing benzoylated material were eluted in the 484–724 ml portion of effluent. The 484–596 ml fraction was evaporated to dryness *in vacuo*, and the residue crystallized as colorless needles which were triturated with water and filtered, 0.21 g (15%), m.p. 113–115°. An additional 0.05 g (total yield 18%) of VIb was isolated from the second fraction (see below). Recrystallization (0.21 g) from ethanol gave elongated rods, 0.17 g, m.p. 146–147°, $[\alpha]_D^{25}$ −146° (*c* 0.1 in chloroform). Certain samples from other runs exhibited two melting points: initial melting at 112–116°, followed by resolidification and then remelting at 144–145°. The infrared spectra (KBr discs) of the two isomorphic forms were markedly different. Heating the KBr disc of the lower-melting form at 110–115° for 30 min changed its infrared spectrum to that of the higher-melting isomorph.

Anal. Calc. for $C_{26}H_{21}FO_7$: C, 67.25; H, 4.55; F, 4.09. Found: C, 67.49; H, 4.62; F, 4.77.

The 612–724 ml fraction was evaporated to dryness *in vacuo*, giving a yellow gum. This exhibited, on t.l.c., three spots of R_F values 0.73 (corresponding to VIb), 0.66, and 0.25, a very weak spot. The gum was dissolved in chloroform and passed through an alumina column (1.7 × 32 cm) as above. Fraction I (86–116 ml) yielded colorless crystals which, on recrystallization from ethanol, gave 0.05 g of VIb, m.p. 144.5–145.5°. Fraction IV (161–176 ml) yielded a gum (30 mg), $[\alpha]_D^{24}$ −10° (*c* 0.2 in chloroform). This separated into two spots on t.l.c. plates, one corresponding to that of the second major component (R_F 0.66), and the other, a weak spot at R_F 0.25. Compound VIb was absent. The two intermediate fractions, II and III, 70 and 72 mg, respectively, contained both VIb and the second major component, R_F 0.66.

Anal. of Fraction IV: Calc. for $C_{26}H_{21}FO_7$: benzoyl groups, 3.0. Found: benzoyl groups, 2.93.

*2-Deoxy-2-fluoro-*D*-ribose (IVb)*

The debenzoylation of VIb was observed in a polarimeter cell. A mixture of VIb (0.088 g, 0.19 mmole), ethanol (1.5 ml) and 1 N sodium hydroxide (1.5 ml) was shaken for 60 min before dissolution was complete. At that time, the specific rotation had diminished to −11°, based upon IVb (from −146°). The specific rotation increased during the next two h and became constant at −30° (based upon IVb). Ethanol was removed from the solution under reduced pressure, water (6 ml) was added, and the solution was treated with Dowex 50 (H^+). After filtration, benzoic acid was removed by repeated extraction with ether. The solution was adjusted to 3 ml and its rotation was found to be −36°, based on a theoretical yield of IVb. On removal of the water *in vacuo*, a colorless gum remained which, on standing, crystallized as a fern-like structure, yield 27 mg (96%), m.p. 106–112°, $[\alpha]_D^{24}$ −37°, R_F 0.50, R_{IVa} 1.25 (t.l.c. in solvent B).

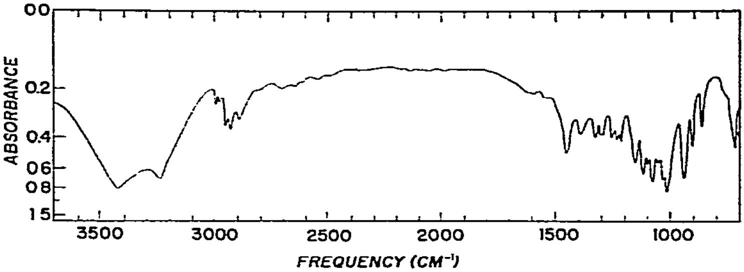

Fig. 1. Infrared spectrum (KBr disc) of 2-deoxy-2-fluoro-D-ribose (IVb).

Fraction III (72 mg) which was obtained as a gum after chromatography of the benzoylation products of crude IVb on an alumina column (see above) was treated with base under the conditions just described. A good yield of crystalline IVb was obtained.

The product isolated in this fashion exhibited no change in optical rotation on being kept in solution in 0.1 N HCl for 17 h or in 0.1 N NaOH for 3 h.

Anal. Calc. for $C_5H_9FO_4$: C, 39.47; H, 5.96; F, 12.49. Found: C, 39.51; H, 6.03; F, 12.55.

*Conversion of VIb into methyl 3,4-di-O-benzoyl-2-deoxy-2-fluoro-*D*-riboside (VIII)*

To a solution of VIb (0.035 g, 0.075 mmole) in dichloromethane (0.3 ml) were added 5 drops of hydrogen bromide–acetic acid (32%). After being kept at 20–25° for 19 h, the solution was diluted with dichloromethane (5 ml) and rapidly extracted in the cold with water, sodium bicarbonate solution, and water. The solution was dried with sodium sulfate, and, after filtration, the solvent was removed *in vacuo*. The residue was dissolved in dry methanol (3 ml). The optical rotation, $[\alpha]_D^{24}$, after 15 min based upon VII, was −225°. One drop of pyridine was added to the solution. After 5 h at 20–25°, the rotation was −148°, based upon VIII, and after 22 h, −133°.

The solution was evaporated to dryness, leaving a pale-yellow gum which was triturated well with water, and the water decanted. Moisture was removed by co-distillation with ethanol *in vacuo* several times. The residue was dissolved in ether, and filtered to remove a small amount of insoluble material. Upon removal of the ether, a colorless gum remained, $[\alpha]_D^{24}$ −133° (*c* 0.6 in ethanol). The material gave a negative Fehling test. The chromatographic behavior and infrared spectrum of this material were identical with those found for compound VIII, isolated after methanolysis of IIb, followed by benzoylation (see below).

Anal. Calc. for $C_{20}H_{19}FO_6$: benzoyl groups, 2.00. Found: benzoyl groups, 2.08.

*Oxidation of methyl 2-deoxy-2-fluoro-*D*-riboside (XI) with sodium periodate*

To the solution resulting from the determination of the benzoyl groups was added an excess of sodium metaperiodate. Aliquots were buffered at pH 7 and titrated with standard arsenite. The results are given in the table.

Time	*Moles IO_4^- consumed per mole of compound*
0.1	0.21
0.9	0.85
2.1	1.00
3.4	0.98
5.3	1.00
24.0	1.24
71.0	1.80
7 days	2.70

*Methanolysis of 1-(2-deoxy-2-fluoro-β-*D*-ribofuranosyl)-5,6-dihydrouracil (IIb)*

Anhydrous methanol saturated with hydrogen chloride (100 ml) was added to IIb (0.74 g, 2.98 mmole). The solution was heated at reflux for 10 h, then neutralized by the addition of solid silver carbonate. After filtration of silver salts, the solvent was removed *in vacuo*, leaving an amorphous residue. T.l.c. in solvent B showed three spots of R_F values 0.34, 0.52, 0.62.

Benzoylation was carried out in pyridine (25 ml) at 0° with the addition of benzoyl chloride (1.82 g, 13.0 mmoles) with stirring. After 41 h at 0–5° a small piece of ice was added. Pyridine was removed *in vacuo*, and a chloroform solution of the residue was extracted in the cold in turn with water, sodium bicarbonate solution and water. After drying, the chloroform was removed *in vacuo*, leaving a yellow gum. T.l.c. in solvent A revealed six spots of R_F values 0.12, 0.21, 0.26, 0.34, 0.48, 0.60. A chloroform solution of the mixture was placed on a column of alumina, 2.4 × 42 cm, and eluted with chloroform. Fractions of 8 ml each were collected. The benzoylated material was eluted from the column in the 290–464 ml portion of effluent. The effluent was studied in four parts: (A) 290–320 ml, (B) 328–360 ml, (C) 367–410 ml, and (D) 420–460 ml.

The solvent was removed from each fraction, leaving a gum residue from fractions (C) and (D), crystals from fraction (A) and a mixture of crystals and gum from fraction (B). Qualitative analysis revealed nitrogen present only in fraction (D).

*Methyl 3,5-di-O-benzoyl-2-deoxy-2-fluoro-*D*-riboside (X)*

Trituration of fraction (A) with water, followed by filtration gave 0.055 g of colorless needles, m.p. 80–88°. Trituration of fraction (B) in a small amount of cold ethanol gave an additional 0.026 g of the same product, m.p. 86–88° (total yield 8%). The compound migrated as a single spot, R_F 0.60 (t.l.c. solvent A).,

*Methyl 2-deoxy-2-fluoro-*D*-ribofuranoside (XI)*

To a solution of X (0.076 g, 0.20 mmole) in ethanol (3 ml) was added 0.50N sodium hydroxide (3 ml), and the solution was stirred for 4.5 h at 20–25°. Treatment with Dowex 50 (H^+), filtration and removal of solvent left an amorphous residue. Upon trituration with petroleum ether (30–60°) colorless crystals formed, 0.021 g (62%), m.p. 74–78°. Crystallization from ethyl acetate–petroleum ether (30–60°) gave colorless needles, m.p. 81–83°. Within 60 min XI consumed 0.083 mole of sodium metaperiodate per mole of XI.

Anal. Calc. for $C_6H_{11}FO_4$: C, 43.35; H, 6.67; F, 11.45. Found: C, 43.46; H, 6.76; F, 11.40.

*Methyl 3,4-di-O-benzoyl-2-deoxy-2-fluoro-*D*-riboside (VIII)*

The amorphous residue from fraction (C) weighed 0.232 g (20%) and traveled as a single spot of R_F 0.63 (t.l.c., solvent A), $[\alpha]_D^{24}$ $-156°$ (c 0.4 in chloroform).

Anal. Calc. for $C_{20}H_{19}FO_6$: C, 64.16; H, 5.12; F, 5.08; benzoyl groups, 2.0. Found: C, 63.05; H, 5.08; F, 5.07; benzoyl groups, 2.0.

Periodate oxidation of VIII after debenzoylation

Consumption of periodate per mole of compound within: 0.1 h, 0.13 mole; 0.6 h, 0.64 mole; 2.0 h, 0.84 mole; 5 h, 0.89 mole; 22 h, 0.94 mole; 48 h, 1.1 mole.

The lower rate of periodate uptake in this experiment, as compared to that for compound IX above, is probably due to the fact that the pH of the reaction mixture was slightly lower in this experiment.

*Methyl 3-(*N*-benzoylureido)propionate (XII)**

The fraction (D) residue (0.38 g) was triturated in ethanol (2 ml) at 0–5°. Colorless crystals, 0.056 g (8%), m.p. 117–118°, were collected. Crystallization from ethanol gave micaceous plates, m.p. 118–119°. The infrared spectrum (KBr disc) of XII was consistent with an *N*-benzoylureido-propionate. Carbonyl bands: $COOCH_3$, 5.75 μ; $NHCOC_6H_5$, 5.91 μ; NHCONH, 5.98 μ.

Anal. Calc. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.33; H, 5.71; N, 11.15.

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*For convenience, the benzoyl group is attached to the terminal nitrogen atom in structure XII, although its exact position has not yet been determined.

SUMMARY

Crystalline 2-deoxy-2-fluoro-D-ribose (IVb) was prepared by debenzoylation of 1,3,4-tri-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribose (VIb). Reduction of 2′-deoxy-2′-fluorouridine (Ib) gave amorphous 1-(2-deoxy-2-fluoro-β-D-ribofuranosyl)-5,6-dihydrouracil (IIb), which was converted into crystalline 1-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-D-ribosyl)-5,6-dihydrouracil (III). Glycosylic cleavage of IIb with dilute alkali, followed by heating with dilute acid, gave a mixture containing IVb. Benzoylation of impure IVb produced crystalline VIb. A second product, in amorphous form, probably 1,3,4-tri-*O*-benzoyl-2-deoxy-2-fluoro-α-D-ribose, was isolated; it also gave crystalline IVb upon debenzoylation. The pyranoid structure of VIb was proved as follows: replacement of the benzoyloxy group on C-1 by a methoxyl group gave methyl 3,4-di-*O*-benzoyl-2-deoxy-2-fluoro-D-riboside (VIII). Debenzoylation gave the unsubstituted glycoside IX, which was shown to be a pyranoside, thus establishing the ring structure of VIb.

Methanolysis of IIb, followed by benzoylation, gave crystalline methyl 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-D-riboside (X) and amorphous VIII, as well as crystalline methyl 3-(*N*-benzoylureido)propionate (XII). Debenzoylation of X produced crystalline methyl 2-deoxy-2-fluoro-D-ribofuranoside (XI).

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