[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH DEPARTMENT, PEARL RIVER LABORATORIES, RESEARCH DIVISION AMERICAN CYANAMID CO.]

# 5-Deoxy-5-fluoro-D-ribofuranosyl Derivatives of Certain Purines, Pyrimidines and 5,6-Dimethylbenzimidazole

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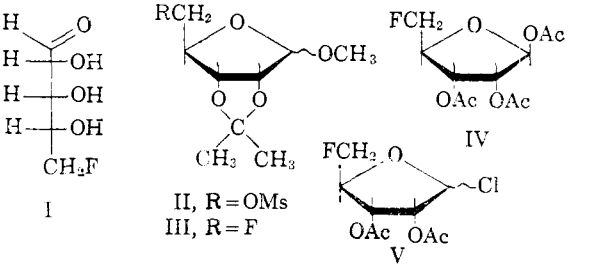
1-Chloro-2,3-di-*O*-acetyl-5-deoxy-5-fluoro-D-ribofuranose (V) was obtained from 5-deoxy-5-fluoro-D-ribose (I) *via* 1,2,3-tri-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranose (IV). Condensation of V with chloromercuri-6-chloropurine afforded 6-chloro-9-(2,3-di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine (VI) which, by appropriate procedures, was converted to the 9-(5-deoxy-5-fluoro-β-D-ribofuranosyl) derivatives of adenine (IX), 6-chloropurine (X), 6-mercaptopurine (XI) and purine (XII). Condensation of chloro sugar V with chloromercuri-4-ethoxy-2(1H)-pyrimidinone yielded 1-(2,3-di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-4-ethoxy-2(1H)-pyrimidinone (XV) which was transformed into 5'-fluorocytidine (XIII) and 5'-fluorouridine (XIV). Condensation of chloromercuri-5,6-dimethylbenzimidazole with V afforded, after deblocking, 5'-fluoro-β-ribazole (XVI).

In previous papers we have described the synthesis of ribonucleoside analogs which differed from the naturally occurring nucleosides by the nature of the substituent on carbon 5 of the ribofuranose moiety. Thus, the 5-deoxy-D-ribofuranosyl derivatives of several purines[1] and the 5-amino-5-deoxy-D-ribofuranosyl derivatives of certain purines[2] and pyrimidines[3] have been reported. A few β-ribazole analogs containing these two sugars also have been prepared.[2,4] These structural variations are of interest since it is impossible for the resulting purine and pyrimidine nucleoside analogs to form normal 5'-phosphate bonds as are found in the nucleic acids and in certain coenzymes. In continuation of this line of research, we have now prepared the 5'-fluoro analogs of several purine and pyrimidine nucleosides, and also of β-ribazole.

The 5-deoxy-5-fluoro-D-ribose (I) required for the synthesis of these 5'-fluoronucleosides was not known at the start of this investigation. It was prepared in two steps from methyl 2,3-*O*-isopropylidene-5-*O*-mesyl-D-ribofuranoside (II).[1,5] Originally, II was treated with anhydrous potassium fluoride in refluxing dimethylformamide to give methyl 2,3-*O*-isopropylidene-5-deoxy-5-fluoro-D-ribofuranoside (III) as a crude oil, which could be converted in poor yield to crystalline 5'-fluoroadenosine (IX) *via* the intermediates described below. While this work was in progress, Taylor and Kent,[5] in a preliminary report, described a superior preparation of the 5-fluoro derivative III, and the hydrolysis of III to 5-deoxy-5-fluoro-D-ribose (I). These authors treated mesylate II with potassium fluoride dihydrate in methanol at 150° for 18 hours and obtained III as an analytically pure oil. Acid hydrolysis gave the free sugar I as a pure sirup which was characterized as a crystalline 2,5-dichlorophenylhydrazone. By using these conditions we were able to obtain III and I in good yields and in relatively large quantities. Acetylation[6] of the free sugar I with acetic anhydride in pyridine afforded, after distillation, a partially crystalline mixture from which 1,2,3-tri-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranose (IV) could be isolated as a crystalline solid.[9] The triacetate was converted to 1-chloro-2,3-di-*O*-acetyl-5-deoxy-5-fluoro-D-ribofuranose (V) with ethereal hydrogen chloride at 3°. This chloro sugar was a suitable intermediate for nucleoside formation.




Condensation of halogenose V with chloromercuri-6-chloropurine[10] in refluxing xylene afforded the 6-chloro-9-(2,3-di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine (VI) as a crystalline solid in 54% yield. This intermediate was used for the preparation of four different nucleosides. Treatment with methanolic ammonia in a steel bomb at 100° for 7 hours[11] afforded **5'-fluoroadenosine** [6-amino-9-(5-deoxy-5-fluoro-β-D-ribofurano-

(1) H. M. Kissman and B. R. Baker, THIS JOURNAL, **79**, 5534 (1957).

(2) H. M. Kissman and B. R. Baker, Abstracts of Papers, 130th Meeting of the A. C. S., Atlantic City, N. J., September, 1956, p. 19D. Paper in preparation.

(3) H. M. Kissman and M. J. Weiss, THIS JOURNAL, **80**, 2575 (1958).

(4) H. M. Kissman, R. G. Child and M. J. Weiss, *ibid.*, **79**, 1185 (1957).

(5) N. F. Taylor and P. W. Kent, *Research Correspondence*, Suppl. to *Research* (*London*), **9**, No. 7, S 28 (1956); *C. A.*, **51**, 227 (1957); subsequent paper, *cf. idem.*, *J. Chem. Soc.*, 872 (1958).

(6) Although it had been shown that *O*-benzoyl blocked sugar halides give better yields in nucleoside condensation reactions,[7] it was thought at the time that the use of benzoyl groups in this case would require several additional chemical steps. It would have been necessary to benzoylate I and then to replace the 1-*O*-benzoyl group with acetate in one or two steps so that the chloro sugar (obtained on treatment with ethereal hydrogen chloride) would be contaminated only with volatile acetic acid. However, in the meantime, it has been demonstrated by Baker and Hewson[8] that contamination of a chloro sugar with benzoic acid does not interfere in the condensation reaction with a chloromercuri-purine derivative. Therefore, a completely benzoylated sugar derivative probably could have been used, perhaps more effectively, for the synthesis of the nucleosides described in this paper.

(7) H. M. Kissman, C. Pidacks and B. R. Baker, THIS JOURNAL, **77**, 18 (1955).

(8) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

(9) It is probable that this crystalline solid has the β-configuration because the oil isolated from the mother liquors has a much more positive rotation. However, this evidence is not quite satisfactory because combustion analyses indicate that the oil is not a pure substance.

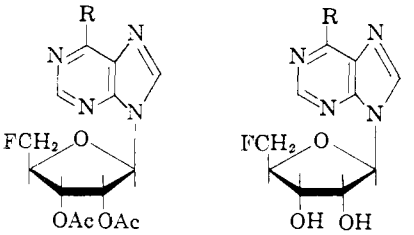
(10) B. R. Baker, K. Hewson, H. J. Thomas and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

(11) G. B. Brown and V. S. Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

syl)-purine, IX] as a crystalline, partially hydrated solid. Under milder conditions (0° for 16 hours[10,11]) the reaction of the blocked nucleoside VI with methanolic ammonia gave **6-chloro-9-(5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine** (X) in 48% yield. Crystalline material could be isolated only after partition chromatography even though seed crystals were available. No attempt was made to isolate the 5′-fluoroadenosine which undoubtedly contaminated this complex reaction mixture.[10]

Since the 9-β-D-ribofuranosyl derivative of 6-mercaptopurine[12] has been reported[13] to have approximately the same antitumor activity as 6-mercaptopurine itself, it was of interest to prepare the corresponding 5-fluororibofuranosyl derivative of this purine. For this purpose, the blocked 6-chloronucleoside VI was allowed to react with thiourea in refluxing ethanol[14] affording 6-mercapto-9-(2,3-di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine (VII) which crystallized from the reaction mixture in almost quantitative yield.[15] The acetyl groups were removed with cold methanolic ammonia and the free nucleoside, **6-mercapto-9-(5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine** (XI), was isolated as a crystalline monomethanolate in 80% yield.

The fourth nucleoside prepared from the blocked 6-chloro compound VI was the 5′-fluoro analog of 9-β-D-ribofuranosylpurine (nebularine).[11,16] Reductive dehalogenation of VI with palladium-on-charcoal catalyst and hydrogen at atmospheric pressure in the presence of magnesium oxide as acid acceptor[11] yielded crystalline 9-(2,3-di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine (VIII). This compound was de-*O*-acylated with methanolic ammonia at 3° to afford crystalline **9-(5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine** [5′-fluoronebularine, XII]. Alternatively, the deblocked compound XII also could be obtained through the reductive dehalogenation of 6-chloro-9-(5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine (X) with palladium-on-charcoal catalyst and magnesium oxide as acid acceptor. Separation of the product from magnesium chloride was difficult by crystallization procedures but could be achieved satisfactorily by partition chromatography. The crystalline product so obtained (55% yield) was identical in all respects with 5′-fluoronebularine (XII) prepared by the other route.[17] Gordon, Magrath and Brown[18] have shown that the very toxic 9-β-D-ribofuranosylpurine is transformed to the corresponding 5′-phosphate in the rat, and they have suggested that the non-toxic character of 9-(5-deoxy-β-D-ribofuranosyl)-purine[1] is due to the fact that this compound cannot undergo phosphorylation in the 5′-position. This hypothesis finds support in the fact that compound XII is also non-toxic and has no antitumor activity.




VI, R = Cl
VII, R = SH
VIII, R = H

IX, R = $NH_2$
X, R = Cl
XI, R = SH
XII, R = H

Two pyrimidine nucleoside analogs, 5′-fluorocytidine (XIII) and 5′-fluorouridine (XIV), were prepared by an adaptation of the methods of Fox and co-workers.[19] Chloromercuri-4-ethoxy-2(1H)-pyrimidinone[19] was condensed with the blocked chloro sugar V in refluxing xylene, and the condensation product, 1-(2,3-di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-4-ethoxy-2(1H)-pyrimidinone (XV), was isolated as an impure glass after chromatography on silica gel. Crude XV was converted to crystalline 5′-fluorocytidine [1-(5-deoxy-5-fluoro-β-D-ribofuranosyl)-cytosine, XIII] with methanolic ammonia in a bomb at 100° for 8 hours.[19] The compound was thus obtained in 30% over-all yield from the tri-*O*-acetate IV. Treatment of the crude 4-ethoxy derivative XV with methanolic hydrogen chloride[20] afforded crystalline 5′-fluorouridine [1-(5-deoxy-5-fluoro-β-D-ribofuranosyl)-uracil, XIV] in 20% yield over-all from IV.[21]

For the synthesis of **5′-fluoro-β-ribazole** [1-(5-deoxy-5-fluoro-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole, XVI], chloromercuri-5,6-dimethylbenzimidazole[22] was condensed with the chloro sugar V in the usual manner. The crude condensation product, 1-(2,3-di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole, was de-*O*-acetylated with methanolic sodium methoxide to yield crystalline 5′-fluoro-β-ribazole (XVI) (38% over-all from IV).

The β-configuration of the nucleosides described in this paper has not been established unequivocally but is assumed for the following reasons. The condensation of 1-halo-2-acyloxy sugars with

(12) J. A. Johnson, Jr., and H. J. Thomas, THIS JOURNAL, **78**, 3863 (1956).

(13) H. E. Skipper, J. R. Thomson, D. J. Hutchison, F. M. Schabel, Jr., and J. A. Johnson, Jr., *Proc. Soc. Exp. Biol. Med.*, **95**, 135 (1957).

(14) A. Bendich, P. J. Russell, Jr., and J. J. Fox, THIS JOURNAL, **76**, 6073 (1954).

(15) Johnson and Thomas[12] were unable to use thiourea for the synthesis of 6-mercaptopurine riboside from deblocked 6-chloropurine riboside because the acid formed during the reaction cleaved the nucleoside linkage. This problem did not arise in our work, probably because the *O*-aceylated derivative VII was quite insoluble and crystallized out during the course of the reaction.

(16) N. Löfgren and B. Lüning, *Acta Chem. Scand.*, **7**, 225 (1953); N. Löfgren, B. Lüning and H. Hedström, *ibid.*, **8**, 670 (1954).

(17) The high yield of crystalline material XII obtained in this deblocking reaction with methanolic ammonia would seem to indicate that 5′-fluoronebularine is somewhat more stable toward alkaline conditions then nebularine itself; *cf.* M. P. Gordon, V. S. Weliky and G. B. Brown, THIS JOURNAL, **79**, 3245 (1957).

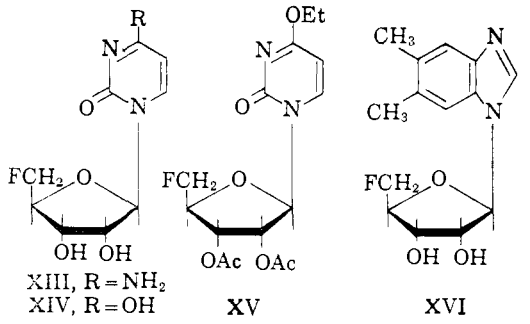
(18) M. P. Gordon, D. I. Magrath and G. B. Brown, *ibid.*, **79**, 3256 (1957); *cf.* J. J. Biesele, M. C. Slautterback and M. Margolis, *Cancer*, **8**, 87 (1955).

(19) J. J. Fox, N. Yung, I. Wempen and I. L. Doerr, THIS JOURNAL, **79**, 5060 (1957).

(20) G. E. Hilbert, *ibid.*, **59**, 330 (1937); G. E. Hilbert and T. B. Johnson, *ibid.*, **52**, 4489 (1930).

(21) The 4-ethoxy group of XV was surprisingly resistant to the action of methanolic hydrogen chloride. Maximum yields of 5′-fluorouridine (XIV) were obtained when crude XV was exposed to methanolic hydrogen chloride for three days instead of the more usual 24 hours.[8,20]

(22) J. Davoll and G. B. Brown, THIS JOURNAL, **73**, 5781 (1951).




the mercury derivatives of various purines,[23] pyrimidines[19] and benzimidazoles[4,22] has in all reported cases given, at least as the major product,[24] nucleosides wherein the substituents at $C_1$–$C_2$ are *trans*.[25] Therefore, in view of the relatively high yields obtained for the nucleoside condensation reactions reported in this paper, it is a reasonable supposition that these nucleosides have the β-configuration ($C_1$–$C_2$ *trans*).

The unblocked nucleosides IX-XIV, XVI had no activity when tested against sarcoma 180, lymphosarcoma $6C_3HED$ and the $C_3H$ mammary adenocarcinoma in mice. The inactivity of the 6-mercaptopurine nucleoside (XI) is interesting because it indicates the possibility that the antitumor activity of 6-mercaptopurine riboside[13] involves phosphorylation at the 5′-position. In this connection, the statement made earlier in this paper, concerning the lack of activity of 5′-deoxy- and 5′-fluoronebularine, may be recalled.

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## Experimental[26]

**Methyl 2,3-*O*-Isopropylidene-5-*O*-mesyl-D-ribofuranoside** (II).—The synthesis of this compound[1] has been improved and adapted for large scale preparations. To an ice-cold solution of 138 g. (0.68 mole) of methyl 2,3-*O*-isopropylidene-D-ribofuranoside in 350 cc. of anhydrous pyridine was added, dropwise with stirring and cooling, 80 cc. (0.96 mole) of methanesulfonyl chloride. The mixture was kept at 3° overnight and then was drowned in 1500 cc. of ice-water. The solid, which formed on agitation, was collected and was washed thoroughly with ice-water. The solid was resuspended in 500 cc. of cold water and was filtered. This treatment removed all traces of color and left a white, crystalline solid, which, after drying over $P_2O_5$ *in vacuo*, weighed 137 g. (71%), m.p. 73–74° (lit.[1] m.p. 78–79°). The substance was used as such for subsequent reactions.

**Methyl 2,3-*O*-Isopropylidene-5-deoxy-5-fluoro-D-ribofuranoside** (III).[5]—A mixture of 4.23 g. (1.5 mmoles) of the mesylate II, 4.2 g. of finely ground potassium fluoride dihydrate and 50 cc. of methanol was heated in a stainless steel bomb at 150–160° for 18 hours. When cool, the bomb was opened and the contents washed out with methanol. The thick suspension (170 cc.) was filtered and the precipitate was washed with a little methanol. Filtrate and washings were freed from methanol on the steam-bath, and the residue was triturated with 100 cc. of ether and filtered through Norit.[27] The colorless filtrate was freed from ether under reduced pressure and the oily residue was distilled *in vacuo* to afford 2.11 g. (68%) of a colorless oil with b.p. 62–67° (0.3–0.2 mm.), $n^{19}D$ 1.4325 (lit.[5] b.p. 58° (0.035 mm.), $n^{20}D$ 1.4340).[28]

**5-Deoxy-5-fluoro-D-ribose** (I).—A mixture of 4.12 g. (20 mmoles) of methyl 2,3-*O*-isopropylidene-5-deoxy-5-fluoro-D-ribofuranoside (III) and 30 cc. of 0.02 *N* sulfuric acid[5] was heated on the steam-bath for 3.5 hours with stirring. The yellow, homogeneous solution was neutralized with solid barium carbonate and was freed from barium sulfate by centrifugation. The supernatant was filtered through Celite[29] and the filtrate was evaporated under reduced pressure at 60°. The residue was dissolved in methanol and was filtered through a layer of Norit. Evaporation *in vacuo* left a sirup which was dried to constant weight over phosphorus pentoxide *in vacuo* to afford 3.025 g. (theory 3.04 g.). Paper chromatography in butanol–ethanol–water 4:1:5 (v./v.) showed a large spot with $R_f$ 0.62 and a small spot with $R_f$ 0.46. In the same system, D-ribose had $R_f$ 0.48.[30] Taylor and Kent[5] reported $R_f$ 0.6 and $R_f$ 0.4 for compound I and D-ribose, respectively. A 2,5-dichlorophenylhydrazone with m.p. 74–76° (lit.[5] m.p. 76°; in the more recent paper this m.p. has been reported as 130°) was prepared in refluxing methanol.

**1,2,3-Tri-O-acetyl-5-deoxy-5-fluoro-β-D-ribofuranose** (IV).[9]—To a solution of 3.02 g. of crude 5-deoxy-5-fluoro-D-ribose (I), prepared as described above from 4.12 g. (20 mmoles) of III, in 15 cc. of anhydrous pyridine, 6 cc. of acetic anhydride was added slowly, with shaking. The mixture was kept at room temperature overnight and was then poured into 130 cc. of ice-water. This solution was extracted with three 50-cc. portions of chloroform, and the combined extracts were washed with three 25-cc. portions of saturated aqueous sodium bicarbonate solution and then with 20 cc. of water. The organic solution was dried over magnesium sulfate and evaporated *in vacuo* on the steam-bath. The residue was distilled *in vacuo* and 4.11 g. of a viscous oil with b.p. 124–127° (0.2 mm.) was obtained. This material crystallized partially on standing. It was triturated with ether, filtered, and the solid was recrystallized from a small amount of ether with Norit to afford 1.14 g. (20.5% based on 20 mmoles of III), m.p. 93–96°. For analysis, the solid was crystallized once more from ether (m.p. 100–101°) and was then sublimed *in vacuo* at 0.1 mm. and 95–98° bath temperature; m.p. 100–101°, $[\alpha]^{25}D$ −26.8° (*c* 2.05 in chloroform).

*Anal.* Calcd. for $C_{11}H_{15}FO_7$: C, 47.48; H, 5.44; F, 6.83. Found: C, 47.68; H, 5.67; F, 6.84.

(23) Examples of the formation of purine ribonucleosides with established β-configuration can be found in the following papers: J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 1650 (1951); reference 11; H. M. Kissman and M. J. Weiss, *J. Org. Chem.*, **21**, 1053 (1956); B. R. Baker, R. E. Schaub, J. P. Joseph and J. H. Williams, THIS JOURNAL, **77**, 12 (1955); B. R. Baker and J. P. Joseph, *ibid.*, **77**, 15 (1955).

(24) Nucleosides having the $C_1$–$C_2$ *cis* configuration (*i.e.*, α-ribonucleosides) have been isolated as minor by-products in a few cases: B. R. Baker, R. E. Schaub and H. M. Kissman, *ibid.*, **77**, 5911 (1955); L. Goldman, J. W. Marisco and R. B. Angier, *ibid.*, **78**, 4173 (1956); references 1 and 4.

(25) $C_1$–$C_2$ refer to the sugar carbons. With a ribose derivative a $C_1$–$C_2$ *trans* configuration is, therefore, the β-configuration.

(26) Melting points were taken on a Kofler micro hot-stage and are corrected. Ultraviolet absorption spectra were determined on a Cary recording spectrophotometer, and refractive indices on a Bausch and Lomb Abbe-type refractometer. Boiling points are uncorrected.

(27) Norit is the trade mark of the American Norit Co. for activated charcoal.

(28) In our large-scale-preparations laboratory, this reaction has been carried out with 262 g. of II to afford approximately the same yield of III.

(29) Celite, a product of the Johns-Manville Corporation, is the trade mark for diatomaceous earth. The material used for partition chromatography was Celite 545 which had been washed with 6 *N* hydrochloric acid, with distilled water until neutral and finally with methanol. The material was dried at 50°.

(30) Spots were located by spraying with alkaline, blue tetrazolium or by dipping into a solution prepared by the addition of 1 cc. of 0.3 *M* aqueous potassium permanganate to 30 cc. of acetone.

From the mother liquors an oil was isolated, which was redistilled to afford 2.9 g. with b.p. 140–145° (0.3 mm.). The major fraction (1.6 g.) having b.p. 142–145° (0.3 mm.) and $n^{11.5}D$ 1.4481, $[\alpha]^{25}D$ +12° (*c* 2.16 in chloroform), was used for analysis[31]; this oil is probably in part the α-anomer of IV.

*Anal.* Calcd. for $C_{11}H_{15}FO_7$: C, 47.48; H, 5.44; F, 6.83; OMe, 0.00. Found: C, 48.66; H, 6.04; F, 2.17; OMe, 6.89.

**6-Chloro-9-(2,3-di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine (VI).**—A solution of 8.34 g. (30 mmoles) of 1,2,3-tri-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranose (IV)[32] in 200 cc. of ethereal hydrogen chloride (saturated at 0°) and containing 6 cc. of acetyl chloride was kept at 3° for 60 hours and was then evaporated under reduced pressure. The residue was evaporated three times with toluene to remove hydrogen chloride and acetic acid. The residual sirupy[33] chloro sugar V was dissolved in 50 cc. of xylene and was added to an azeotropically dried suspension of 11.67 g. (30 mmoles) of chloromercuri-6-chloropurine[10] in 200 cc. of xylene. The mixture was stirred under reflux for 3 hours and was filtered when cool. The filtrate was evaporated *in vacuo*. The dark brown residue was dissolved in 200 cc. of chloroform, and the solution was washed with two 30-cc. portions of 30% aqueous potassium iodide solution and then with 50 cc. of water. The dried (magnesium sulfate) chloroform solution was once more evaporated and the residue was mixed with 80 cc. of ether. Agitation caused the mixture to crystallize. The light yellow solid was filtered and from the filtrate there were obtained two additional crops of crystals to give a total of 6.8 g. This was recrystallized from ether with Norit to afford 6.06 g. (54%), m.p. 116–119°. An analytical sample, recrystallized once more from ether and dried at 74° *in vacuo*, showed m.p. 121–123°, $[\alpha]^{24}D$ −33.8° (*c* 2.12 in chloroform); $\lambda_{max}^{methanol}$ 263 mμ (ε 9,550 in acid), 262 mμ (ε 8,980 in methanol), 262 mμ (ε 8,910 in base).[34]

*Anal.* Calcd. for $C_{14}H_{14}FClN_4O_5$: C, 45.11; H, 3.78; F, 5.09; Cl, 9.51; N, 15.03. Found: C, 45.35; H, 4.00; F, 5.02; Cl, 9.56; N, 15.12.

**5'-Fluoroadenosine[6-Amino-9-(5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine, IX].**—A mixture of 2.5 g. (6.71 mmoles) of the blocked 6-chloronucleoside (VI) and 60 cc. of methanolic ammonia (saturated at 0°) was heated in a stainless steel bomb for 7 hours in a 100° bath. When cool, the bomb was opened and the contents were washed out with methanol. The light brown solution was filtered through Norit and the filtrate was evaporated *in vacuo*. A solid started to crystallize as the solution became more concentrated. After total evaporation and trituration with ethanol, 2.5 g. of solid was obtained. This was recrystallized from 30 cc. of hot water with Norit to afford 1.03 g. (64%) which had m.p. 201–203° (softened at 165° and resolidified) after drying at 110° *in vacuo*. The material absorbed water readily and, after exposure to air for some time, it had m.p. 165–167°. For analysis the compound was recrystallized twice more from methanol and dried as before; m.p. 205–206° (no previous softening), $[\alpha]^{25}D$ −56° (*c* 0.43 in water); $\lambda_{max}^{water}$ 256 mμ (ε 14,970 in acid), 258 mμ (ε 15,340 in water), 258 mμ (ε 15,360 in base).

*Anal.* Calcd. for $C_{10}H_{12}FN_5O_3 \cdot {}^1/_2CH_3OH$: C, 44.20; H, 4.95; F, 6.66; N, 24.56. Found: C, 44.31; H, 4.80; F, 6.83; N, 24.53.

**6-Chloro-9-(5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine (X).**—A solution of 744 mg. (2 mmoles) of the blocked 6-chloronucleoside (VI) in 40 cc. of methanolic ammonia (saturated at 0°) was kept at 3° for 16 hours. The solution was evaporated below room temperature; the residue was further evaporated with several portions of ethyl acetate and then was dried *in vacuo* to afford 623 mg. of gum. This was dissolved in 5 cc. of the lower and 5 cc. of the upper phase of the solvent system ethyl acetate–heptane–water (2:1:1) and 10 g. of Celite was added to the solution. The mixture was packed on top of a column prepared from 250 g. of Celite which had been mixed thoroughly with 125 cc. of the lower phase of the solvent system. The column [74.5 × 3.0 cm., hold-back volume (h.b.v.),[35] 465 cc.] was eluted with the upper phase, and the effluent was allowed to pass through a recording spectrophotometer (set at 263 mμ). Material with absorption at this wave length was eluted after 140 cc. of the second h.b.v. had come off the column and through the first 380 cc. of the third h.b.v. The relevant fractions were pooled and evaporated under reduced pressure. The residual gum (350 mg.) was crystallized and recrystallized from small amounts of ethyl acetate to afford 287 mg. (48%) of a white crystalline substance, m.p. 127–128°. An analytical sample was obtained after an additional recrystallization from ethyl acetate, m.p. 127–128°, $[\alpha]^{25}D$ −22.5° (*c* 1.07 in methanol); $\lambda_{max}^{methanol}$ 264 mμ (ε 9,530 in acid), 263 mμ (ε 9,240 in methanol), 262 mμ (ε 8,950 in base).

*Anal.* Calcd. for $C_{10}H_{10}FClN_4O_3$: C, 41.60; H, 3.56; F, 6.58; Cl, 12.29; N, 19.41. Found: C, 41.70; H, 3.74; F, 6.32; Cl, 12.42; N, 19.60.

**6-Mercapto-9-(2,3-di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine (VII).**—A mixture of 372 mg. (1 mmole) of the 6-chloronucleoside VI and 84 mg. (1.2 mmoles) of thiourea in 10 cc. of absolute alcohol was heated on the steam-bath until the solids had dissolved (10 minutes). Additional heating caused the precipitation of a fluffy white solid. After 1.5 hours of reflux, the thick suspension was filtered and the precipitate was washed with ethanol and dried at 74° *in vacuo* to afford 300 mg. (81%), m.p. 241–244° (slight dec.). The substance was recrystallized from methanol with Norit, m.p. 244–245° (slight dec.), $[\alpha]^{25}D$ −84° (*c* 4.89 in acetone), $\lambda_{max}^{methanol}$ 323 mμ (ε 25,750 in acid), 323 mμ (ε 24,080 in methanol), 310 mμ (ε 24,200 in base).

*Anal.* Calcd. for $C_{14}H_{15}FN_4O_5S$: C, 45.40; H, 4.09; F, 5.13; N, 15.13; S, 8.66. Found: C, 45.48; H, 4.32; F, 4.79; N, 15.06; S, 8.90.

**6-Mercapto-9-(5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine (XI).**—To 960 mg. (2.59 mmoles) of the di-*O*-acetate VII was added 25 cc. of cold methanolic ammonia solution (saturated at 0°), and the solution was kept at 3° overnight. Evaporation under reduced pressure left a residue which was evaporated twice with small amounts of ethanol in order to remove traces of ammonia. The residue was then triturated with ether and collected. The solid was washed with ether and dried at 74° *in vacuo* to afford 767 mg., m.p. 227–228° dec. Recrystallization from methanol with Norit gave 659 mg. (80%), m.p. 229–230° dec., $[\alpha]^{25}D$ −76.0° (*c* 0.50 in water); $\lambda_{max}^{methanol}$ 322 mμ (ε 26,450 in acid), 323 mμ (ε 26,150 in methanol), 310 mμ (ε 25,800 in base).[36]

*Anal.* Calcd. for $C_{10}H_{11}FN_4OS \cdot CH_3OH$: C, 41.50; H, 4.75; F, 5.97; N, 17.66; S, 10.07. Found: C, 41.48; H, 4.54; F, 5.86; N, 17.91; S, 10.45.

**9-(2,3-Di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-purine (VIII).**—The blocked 6-chloronucleoside VI (2.42 g., 6.5 mmoles) was dissolved by warming in 60 cc. of methanol. To the solution was added 262 mg. (6.5 mmoles) of magnesium oxide[11] and a suspension of 325 mg. of palladium-on-charcoal catalyst (10%) in 6 cc. of ethylene glycol monomethyl ether. The stirred mixture was hydrogenated at room temperature and atmospheric pressure until the calculated amount of hydrogen (167 cc.) had been taken up (50 minutes). The mixture was filtered through Celite, and the precipitate was washed with a little methanol. Filtrate and washings were combined and evaporated under reduced pressure. The residual gum was dissolved partially in 120 cc. of chloroform, and the solution was washed with two 15-cc. portions of water. The organic phase was dried

(31) Attempts to anomerize the oil with acetic anhydride and acetic acid containing catalytic amounts of concentrated sulfuric acid [N. K. Richtmyer and C. S. Hudson, THIS JOURNAL, **63**, 1727 (1941); **65**, 740 (1943)] were not successful.

(32) The results from these condensation reactions were much more satisfactory when the crystalline tri-O-acetate IV was used instead of the distilled and presumably anomeric mixture.

(33) In some experiments the chloro sugar started to crystallize at this stage. However, because of instability, it was not possible to actually isolate V as a crystalline solid.

(34) Ultraviolet absorption spectra at different *p*H levels were obtained as follows. The substance was dissolved in the solvent indicated. Aliquots were diluted 1:10 with 0.1 *N* aqueous hydrochloric acid for the acid spectrum and 1:10 with aqueous 0.1 *N* sodium hydroxide for the base spectrum.

(35) Hold-back volume (h.b.v.) is defined as the volume of solvent necessary to fill the packed column.

(36) Johnson and Thomas[12] reported $\lambda_{max}$ 322 mμ (ε 22,500 at *p*H 1), 320 mμ (ε 21,500 at *p*H 6.7) and 310 mμ (ε 22,130 at *p*H 13) for 6-mercapto-9-β-D-ribofuranosylpurine. We have no explanation for the higher extinction values found for our compound.

over magnesium sulfate and the filtered solution was evaporated under reduced pressure. The residue crystallized when triturated with ether. The solid was collected by filtration, and was washed with cold ether and dried *in vacuo* at 74°; 1.69 g. (77%), m.p. 128–129°. After recrystallization from ether, the material had m.p. 129–131°, $[\alpha]^{25}D$ −19° (*c* 1.52 in methanol); $\lambda_{max}^{methanol}$ 262 mμ (ε 6,090 in acid), 262 mμ (ε 7,450 in methanol), 263 mμ (ε 7,780 in base).

*Anal.* Calcd. for $C_{14}H_{15}FN_4O_5$: C, 49.70; H, 4.47; F, 5.61; N, 16.57. Found: C, 49.71; H, 4.64; F, 5.90; N, 16.37.

**9-(5-Deoxy-5-fluoro-β-D-ribofuranosyl)-purine [5'-Fluoronebularine, XII].** (A) *Via* **De-*O*-acylation of VIII.**—To 1.35 g. (4 mmoles) of VIII was added 100 cc. of methanolic ammonia (saturated at 0°), and the solution was kept at 3° overnight. It was then evaporated in a 50° bath. The residual sirup crystallized spontaneously, and was collected with a little acetone and filtered. The dried solid weighed 882 mg. (87%), m.p. 151–153°. Material prepared in a similar reaction was crystallized twice from acetone, m.p. 152–153°, $[\alpha]^{25}D$ −31° (*c* 2.09 in methanol); $\lambda_{max}^{methanol}$ 263 mμ (ε 5,850 in acid), 262 mμ (ε 7,380 in methanol), 262 mμ (ε 7,380 in base).

*Anal.* Calcd. for $C_{10}H_{11}FN_4O_3$: C, 47.24; H, 4.37; F, 7.48; N, 22.04. Found: C, 47.39; H, 4.43; F, 7.18; N, 21.78.

(B) *Via* **Hydrogenolysis of X.**—To a solution of 288 mg. (1 mmole) of the deblocked 6-chloronucleoside X in 20 cc. of ethanol was added 50 mg. of magnesium oxide and a suspension of 56 mg. of palladium-on-charcoal catalyst (10%) in 2 cc. of ethylene glycol monomethyl ether. The stirred mixture was hydrogenated at room temperature and atmospheric pressure until the calculated amount of hydrogen (25 cc.) had been taken up (2 hours). The mixture was filtered through Celite and the filtrate was evaporated *in vacuo* to leave 302 mg. of gum. This was dissolved in 5 cc. of the lower phase and 5 cc. of the upper phase of an ethyl acetate–water mixture, and 10 g. of Celite was added to the solution. The mixture was packed on top of a column prepared from 100 g. of Celite and 50 cc. of the lower phase. The column (141 × 3 cm.; h.b.v. 171 cc.) was developed with the upper phase of the solvent system. The effluent was passed through a recording spectrophotometer set at 260 mμ. The second h.b.v. contained material with such absorption. This was isolated by evaporation and recrystallized from acetone, 140 mg. (55%), m.p. 151–153°. Admixture of 5'-fluoronebularine as prepared by method (A) did not lower the m.p.

**1-(2,3-Di-*O*-acetyl-5-deoxy-5-fluoro-β-D-ribofuranosyl)-4-ethoxy-2(1H)-pyrimidinone (XV).**—The chloro sugar V obtained as a sirup from 6.95 g. (25 mmoles) of the crystalline triacetate IV was added in 50 cc. of xylene to an azeotropically dried suspension of 9.85 g. (26.2 mmoles) of chloromercuri-4-ethoxy-2(1H)-pyrimidinone[19] in 150 cc. of xylene. The mixture was stirred under reflux for 3 hours and was then allowed to cool. The brown solution was decanted from a small amount of tar, and xylene was removed by evaporation under reduced pressure. The residue was taken up in 200 cc. of chloroform, and the solution was washed twice with 30-cc. portions of 30% aqueous potassium iodide solution and then with 30 cc. of water. The chloroform solution was dried and partially decolorized over magnesium sulfate and Norit, and the filtered solution was evaporated *in vacuo* to leave 8.25 g. of brown gum which could not be made to crystallize. The material was dissolved in 20 cc. of methylene chloride and was added to the top of a column prepared from 160 g. of silica gel[37] and methylene chloride. The column was developed with 300 cc. of methylene chloride, 250 cc. of methylene chloride–chloroform (3:1), 200 cc. of methylene chloride–chloroform (1:3), 100 cc. of chloroform and 200 cc. of chloroform–acetone (95:5). These solvents eluted small amounts of gums and oils which were discarded. Further elution with 350 cc. of chloroform–acetone (9:1) brought down 720 mg. of yellow gum which also was discarded. Development was continued with this solvent mixture and the next 750 cc. eluted 5.7 g. of a viscous, yellow gum which was shown to contain two substances ($R_f$ 0.46 and 0.76) by paper chromatography in heptane–benzene–methanol–water (6.5:3.5:8.2, v./v.).[38] However, this gummy material could not be purified further and was used as such in the next step.

**5'-Fluorocytidine [1-(5-Deoxy-5-fluoro-β-D-ribofuranosyl)-cytosine, XIII].**—Crude XV (900 mg.) was dissolved in 30 cc. of methanolic ammonia (saturated at 0°) and the solution was heated in a stainless steel bomb at 100° for 8 hours. The bomb contents were washed out with methanol and the solution was evaporated *in vacuo* to afford 630 mg. of a brown gum which could not be made to crystallize and which was, therefore, chromatographed on a cellulose column. The column was prepared by packing 160 g. of cellulose powder[39] in 10-g. increments as tightly as possible into a glass tube. The completed column (34 × 4 cm.) was washed with 2,000 cc. of the one-phase system, butanol–ethanol–water (4:2:5). The product was dissolved in 3 cc. of the solvent mixture and 5 g. of Celite was added to the solution. The resulting mixture was packed on top of the cellulose column which was developed with the solvent system described. The effluent was allowed to flow through a recording spectrophotometer which had been set at 280 mμ. The first 275 cc. of solvent did not contain ultraviolet-absorbing material and was discarded; the following 200 cc. contained material with such absorption, and this was collected and evaporated *in vacuo*. The residue was crystallized from ethanol with Norit and 137 mg. with m.p. 195–200° was obtained, $R_f$ 0.36 in ethyl acetate–ethanol–water 1:4:3. The substance was recrystallized twice from ethanol; 70 mg., m.p. 205–207° (some sintering above 200°), $[\alpha]^{25}D$ +51.8° (*c* 1.1 in methanol); $\lambda_{max}^{methanol}$ 280 mμ (ε 13,630 in acid), 271 mμ (ε 8,680 in methanol), 272 mμ (ε 9,070 in base).

*Anal.* Calcd. for $C_9H_{12}FN_3O_4$: C, 44.08; H, 4.94; F, 7.75; N, 17.14. Found: C, 44.25; H, 4.92; F, 7.73; N, 16.97.

In a larger experiment, the remainder of crude XV (4.8 g.) was heated with 70 cc. of methanolic ammonia in a bomb at 100° for 8 hours. The bomb contents were evaporated *in vacuo* and the residue was redissolved in ethanol. The solution was passed through a layer of Norit. The dark red filtrate was condensed to a small volume and seeded with XIII obtained in the first experiment. The solid material which formed was collected (1.78 g.) and recrystallized twice from ethanol with Norit; 1.52 g., m.p. 205–207°. The 1.52 g. (adjusted for 5.7 g. of crude XV) represents a 30% yield over-all from 25 mmoles of the triacetyl sugar IV.

**5'-Fluorouridine [1-(5-Deoxy-5-fluoro-β-D-ribofuranosyl)-uracil, XIV].**—The crude 4-ethoxy compound XV was prepared as described above from 25 mmoles of IV, and 5.74 g. of gum was obtained by silica gel chromatography. A solution of 850 mg. of this substance in 20 cc. of methanol was mixed with 9 cc. of methanolic hydrogen chloride (27% by weight), and the solution was kept at room temperature for 24 hours with exclusion of moisture. The solution was then evaporated under reduced pressure, and the residue was evaporated further with several portions of ethanol to remove hydrogen chloride. The residue crystallized from ethyl acetate–hexane 176 mg., m.p. 133–135°. Recrystallization from acetone with Norit afforded 148 mg., m.p. 141–142°, $[\alpha]^{25}D$ −1.9° (*c* 1.05 in water); $\lambda_{max}^{water}$ 261 mμ (ε 10,100 in acid), 261 mμ (ε 10,220 in water), 262 mμ (ε 7,430 in base).

*Anal.* Calcd. for $C_9H_{11}FN_2O_5$: C, 43.90; H, 4.51; F, 7.42; N, 11.38. Found: C, 44.07; H, 4.72; F, 7.70; N, 11.55.

When the same reaction was carried out with the remaining 4.8 g. of crude XV, it was found that the 24-hour reaction period with methanolic hydrogen chloride was insufficient insofar as only a small amount of crystalline XIV would be isolated after that time. When the reaction was allowed to proceed for three 24-hour periods, and crystalline material was harvested after each period, a total of 1.23 g. of solid material was obtained which was recrystallized to give 1.02 g. (when adjusted to 5.74 g. of crude XV this represents a 19.8% over-all yield from 25 mmoles of IV), m.p. 140–142°.

**5'-Fluoro-β-ribazole [1-(5-Deoxy-5-fluoro-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole, XVI].**—The crystalline triacetate IV (6.95 g., 25 mmoles) was converted to the chloro

(37) Davison Silica Gel, mesh size 200, a product of the Davison Chemical Co., was used as such.

(38) We are grateful to Mr. W. S. Allen for suggesting this solvent system to us. He has used it for the chromatography of non-polar steroids.

(39) Whatman standard grade cellulose powder was used.

sugar V as described above. Sirupy V in 50 cc. of xylene was added to an azeotropically dried suspension of 15.1 g. of chloromercuri-5,6-dimethylbenzimidazole[22] on Celite[40] (the mixture contained 10.48 g., 27.5 mmoles, of the chloromercuri-salt) in 200 cc. of xylene. The stirred mixture was kept under reflux for three hours and was then filtered while hot. The precipitate was washed with a little xylene and the filtrate was evaporated *in vacuo*. The dark colored residue was dissolved in 200 cc. of chloroform, and the solution was washed with two 15-cc. portions of 30% potassium iodide solution and then with 30 cc. of water. The chloroform solution was dried over magnesium sulfate and the filtrate was evaporated under reduced pressure. The residue was partially decolorized by solution in 100 cc. of ether and filtration through Norit. Evaporation *in vacuo* left a dark yellow oil which could not be made to crystallize. This was dissolved in 40 cc. of absolute methanol containing 0.4 cc. of a 1 *N* methanolic sodium methoxide solution. The solution was allowed to reflux for a few minutes and another 0.4 cc. of the sodium methoxide solution was added. The mixture was then kept under reflux on the steam-bath for 30 minutes. It remained at *p*H 8 throughout this time. The dark red solution was evaporated *in vacuo* to a small volume until crystallization started. The solid was collected and washed with ethanol to remove the color. A second crop was obtained by concentrating the mother liquors. The combined solids were recrystallized from ethyl acetate–acetone to afford 3.33 g. (47%), m.p. 173–175°. An additional recrystallization gave 2.63 g., m.p. 175–176°. Further recrystallizations did not change the m.p.; $[\alpha]^{25}D$ −43.3° (*c* 1.1 in methanol); $\lambda_{max}^{methanol}$ 277 and 285 mμ (ε 7,830 and 7,380 in acid); 248, 279 and 287 mμ (ε 7,420, 4,760, and 4,900 in methanol); 250, 280 and 288 mμ (ε 7,280, 4,920 and 4,760 in base).

*Anal.* Calcd. for $C_{14}H_{17}FN_2O_8$: C, 59.99; H, 6.12; F, 6.78; N, 10.00. Found: C, 60.00; H, 6.38; F, 6.47; N, 10.20.

**Paper Chromatography.**—Circular paper chromatograms were run in the apparatus described by Kawerau.[41] The apparatus (26-cm. diameter) was purchased from the Shandon Scientific Co., London, England. It was found that the plastic holder[41] sold with this apparatus was attacked by solvents; it was replaced by a similarly shaped, glass holder. A special Whatman #1 filter paper was used (KCT-26) which had been slotted for the Kawerau apparatus. Solvents were mixed just before use, and the paper was not equilibrated with the solvent mixture. Unless stated otherwise, spots were detected by inspection under ultraviolet light.

(40) In all probability the Celite could have been left out of this reaction without affecting the results.

(41) E. Kawerau, "Chromatographic Methods," Vol. 1, No. 2, [published by H. Reeve Angel and Co., 52 Duane Street, New York 7, N. Y., 1956, p. 7]. The Kawerau apparatus has been found to be a very useful improvement for running paper chromatograms. The apparatus is not very bulky and it can be used to run 5 chromatograms at the same time. In general, circular paper chromatography takes less time and probably gives better resolution than paper strip or sheet chromatography.

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[JOINT CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, GEORGETOWN UNIVERSITY, AND THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE]

# 2-Deoxy Sugars. I. 3,4-Di-*O*-*p*-nitrobenzoyl-1-chloro (and 1-Bromo)-1,2,6-trideoxy-D-*ribo*-hexose. Two Crystalline 2-Deoxy Acylglycosyl Halides[1]

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Certain acylated derivatives of 2-deoxy-D-*ribo*-hexose (2-deoxy-D-allose) and 2,6-dideoxy-D-*ribo*-hexose (D-digitoxose) were prepared and investigated in an effort to secure corresponding crystalline acylglycosyl halides. 1,3,4-Tri-*O*-*p*-nitrobenzoyl-2,6-dideoxy-D-*ribo*-hexose was converted to 3,4-di-*O*-*p*-nitrobenzoyl-1-chloro (and 1-bromo)-1,2,6-trideoxy-D-*ribo*-hexose, both of which are crystalline, reasonably stable under anhydrous conditions, and display a high reactivity.

The role of 2-deoxy sugars as constituents of important biologically active compounds, *e.g.*, cardenolides, is well known. The synthesis of such compounds, partial or otherwise, is therefore of immediate interest; hence, a method for the preparation of reasonably stable, crystalline, acylated glycosyl halides of 2-deoxy sugars should have considerable import. It was in this connection that we turned to a study of 2,6-dideoxy-β-D-*ribo*-hexopyranose (D-digitoxose) (I), which is the chief carbohydrate constituent of the important cardenolide digitoxin. 2-Deoxy-D-*ribo*-hexopyranose (2-deoxy-D-allose) (II) was simultaneously investigated because of its close structural relationship with I.

The 2,6-dideoxy-D-*ribo*-hexopyranose (I) is tentatively assigned a β-configuration at $C_1$ based on the knowledge that the β-anomeric forms of D-hexoses as well as 2-deoxy-D-hexoses[3] invariably mutarotate in the direction of more positive values. This is found to be the case with I,[4] but it was necessary to establish that the mutarotation involved only a simple α,β-pyranoside interconversion. Accordingly, a rate study was carried out which disclosed a straight line plot of log $(\alpha_t - \alpha_\infty)$ *vs.* *t*, and which may be regarded as evidence for a simple anomerization.

Further support to this assignment may be gained from a comparison of various hexose and 2-deoxyhexose anomers and their corresponding methyl pyranosides,[5] which reveals that the molecular rotational shift produced in proceeding from a given anomeric form of a hexose to the methyl pyranoside with the same anomeric configuration is

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(2) This paper is taken from a dissertation presented to the Graduate School of Georgetown University, Washington, D. C., in partial fulfillment for the degree of Doctor of Philosophy in Chemistry.

(3) F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," U. S. Government Printing Office, Washington, D. C., 1942, p. 712.

(4) H. R. Bolliger and P. Ulrich, *Helv. Chim. Acta*, **35**, 97 (1952).

(5) (a) L. F. Fieser and M. Fieser, "Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 3rd ed., 1956, p. 377; (b) W. G. Overend and M. Stacey, *Adv. in Carbohydrate Chem.*, **8**, 94 (1953).