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A SYNTHESIS OF URACIL NUCLEOSIDE OF 2-DEOXY-D-ARABINO-HEXOPYRANURONIC ACID

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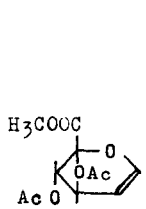
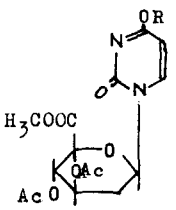
Recently, three antibiotic nucleosides, gougerotin (1 - 3), blasticidin S (4 - 5) and polyoxin complex (6) which contain hexouronic acid derivatives as the sugar moiety have been isolated. The finding of these nucleosides led the authors to a study of the pyrimidine and purine nucleosides of hexouronic acid derivatives. In the previous papers (7), the authors described the synthesis of pyrimidine and purine nucleosides of D-glucuronic acid, which is an indispensable component of a higher animal. This communication deals with a synthesis of uracil nucleoside of 2-deoxy-D-arabino-hexopyranuronic acid.

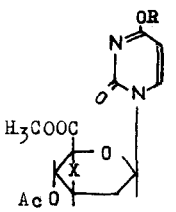
In order to explore the preparation of 2'-deoxy-D-arabino-hexopyranuronosyl-uracil (V), the authors utilized a protected glycal derivative (I) (8) as the starting material. A solution of (I) in anhydrous benzene was saturated with dried HCl or HBr at 10 - 15°.



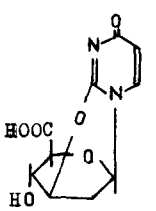
(I)



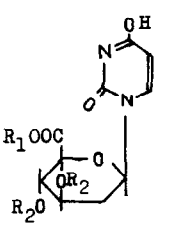
(II)



(IIIa): R=CH_3, X=Cl
(IIIb): R=C_2H_5, X=Cl
(IIIc): R=C_2H_5, X=Br



(IV)



(V): R_1, R_2=H
(VI): R_1=CH_3, R_2=Ac

After evaporation of the solvent, the remaining acid was removed completely by distillation with anhydrous benzene several times. The sirupy product thus obtained was mixed with

2,4-dialkoxypyrimidine and the mixture was heated under slightly reduced pressure (ca. 20 - 25 mmHg) at 90 - 95° for 35 - 60 hr, during which times crystalline crops were separated from the reaction mixture. Recrystallisation from EtOH afforded colorless needles melting at 235 - 237°, $[\alpha]_D^{25}$ +42.0° (c = 0.97, MeOH) (IIIa), 224 - 225°, $[\alpha]_D^{25}$ +57.6° (c = 1.0, MeOH) (IIIb) and 220 - 221°, $[\alpha]_D^{25}$ +72.1° (c = 0.97, MeOH) (IIIc) in 30 - 40% yields. In contrast to the authors' expectation, each of the compounds gave a positive Beilstein's halogen test. Their elemental analyses were not consistent with that of the 2'-deoxy-sugar nucleoside (II), but in quite agreement with that of $C_{14}H_{17}O_7N_2Cl$, $C_{15}H_{19}O_7N_2Cl$ and $C_{15}H_{19}O_7N_2Br$, respectively. The loss of one acetyl group was also observed in the nmr spectra of (IIIa) - (IIIc). Proof of the configuration of the sugar moiety in compound (IIIa), (IIIb) and (IIIc) was obtained by chemical methods and nmr spectroscopy.

Reduction of (IIIc) with $NaBH_4$ in aqueous methanol followed by heating with 1N HCl and sequential acetylation in an usual manner afforded the crystalline product (m.p. 82°, $[\alpha]_D^{23}$ +56.3° (c = 1.1, $CHCl_3$)). Its physical constants were in good agreement with those of 3-bromo-2,3-dideoxy-1,4,6-tri-O-acetyl-α-D-arabino-hexopyranose, which has been recently synthesized by Maki and Tejima (9). Therefore, the configuration of the sugar moiety in compound (IIIc) other than that of the anomeric carbon atom was ascertained to be 3-bromo-2,3-dideoxy-D-arabino-hexopyranuronosyl. There is not definite evidence for the residence of the chlorine at C-3' in compound (IIIa) and (IIIb), however, (IIIa) or (IIIb) might be presumably formed from an analogous precursor with that of (IIIc) and hence the position of the chlorine in (IIIa) and (IIIb) was tentatively assigned to C-3'. This was supported by the fact that (IIIa) and (IIIc), on treatment with methanolic hydrogen chloride and subsequent aqueous alkali, yielded the same anhydride (IV).

Assignment of anomeric configuration to each compound (IIIa - IIIc) was made on the basis of nmr spectra (e.g. IIIa, see Table I) and spin decoupling experiment. The anomeric proton quartet located at δ 5.99 was changed to a doublet with a splitting of 2.5 Hz by irradiating the multiplet at δ 2.08, which is assumed to be the H-2'ax signal. Irradiation of the octet centered at δ 2.82, which should be the H-2'eq signal, caused a collapse of the quartet at δ 5.99 to a doublet with $J_{H\text{-}1',\ H\text{-}2'ax}$ = 10.5 Hz. The large coupling constant of 10.5 Hz indicates that the anomeric proton must be axially oriented with bulky pyrimidine group assuming the equatorial position (10). Compound (IIIa) should exist with the sugar in the C-1 conformation, because there were observed the large values of the

Table I. The 100 MHz nmr spectral data for the ring protons in the carbohydrate moiety of compound (IIIa) and (VI) (in $CDCl_3$)

	Chemical Shifts (δ)*						Approx. J Values (Hz)			
Compd.	H-1′,	H-2′ax,	H-2′eq,	H-3′,	H-4′,	H-5′,	$J_{1',2'ax}$	$J_{1',2'eq}$	$J_{3',4'}$	$J_{4',5'}$
(IIIa)	5.99	2.08	2.82	4.0-4.4	5.17	4.18	10.5	2.5	9.5	9.5
(VI)	6.06	1.87	2.52	5.2-5.4	5.20	4.28	11.0	2.5	9.2	9.2

* Measured in ppm from internal TMS.

couplings (9.5 Hz) among the C-3′, C-4′ and C-5′ protons (see Table I) in the sugar moiety of (IIIa) which prove di-axial orientations of the C-3′ and C-4′ and, C-4′ and C-5′ protons. Therefore, the β-configuration of the anomeric center was established.

Up to date, many papers on the synthesis of 2′-deoxy-nucleosides starting from glycal derivatives have been presented, however, there has been no report on the halogen substituted nucleosides as described above. Recently, Maki and Tejima (9, 11) have reported that when 3,4,6-tri-O-acetyl-D-glucal or 6-tosyl-3,4-di-O-acetyl-D-glucal was treated with HBr in acetic acid, unexpectedly, 3-bromo-2,3-dideoxy-D-arabino-hexopyranosyl derivative which might be formed from substitution of the acetyl group at C-3 with bromine and simultaneous addition of HBr to the double bond at C-1 and C-2 was obtained, while on treatment with HBr in benzene, the same glycal derivative afforded a normal addition product, 2-deoxy-D-glycosyl bromide.

Treatment of (IIIa), (IIIb) or (IIIc) with methanolic hydrogen chloride followed by dissolving in 0.5N NaOH for 3 hr furnished colorless prisms (m.p. 230 - 235° (decomp), $[\alpha]_D^{24}$ +17.5° (c = 1.0, H_2O)) in ca. 45% yield. The UV absorption spectrum of this compound showed a maximum at 228 mμ (ε, 6710) and a shoulder at 245 mμ (ε, 4880), which strongly suggest the pyrimidine cyclonucleoside formation (12, 13). The 2,3′-anhydro nucleoside was assumed to be formed via 3′,4′-epoxide intermediate. (IV) was then hydrolysed with 0.5N NaOH at 50° to 2′-deoxy-β-D-arabino-hexopyranuronosyl-uracil (V) (did not show sharp melting point, but decomposed at 215 - 225° with effervescence, $[\alpha]_D^{25}$ +5.8° (c = 1.00, H_2O), UV: $\lambda_{max}^{H_2O}$ 260 mμ (ε, 5300); $\lambda_{min}^{H_2O}$ 228.5 mμ (ε, 1270)). The elucidation of the structure of (V) was as follows; Compound (VI) which was obtained by esterification of (V) with 0.1% methanolic hydrogen chloride and by subsequent acetylation was subjected to the $LiAlH_4$ reduction followed by hydrolysis with 0.1N HCl to give 2-deoxy-D-arabino-hexopyra-

nose (14, 15). The nmr spectrum of (VI) gave an anomeric proton quartet at δ 6.06 (see Table I). By irradiating the octet centered at δ 2.52, the quartet at δ 6.06 was collapsed into a doublet with $J_{H\text{-}1', H\text{-}2'ax}$ = 11.0 Hz, which indicates that the anomeric proton should occupy the axial position. Thus, the equatorial (β) orientation of the C-1′ substituent was confirmed.

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