Synthetic *C*-Glycosyl Nucleosides. A New Approach

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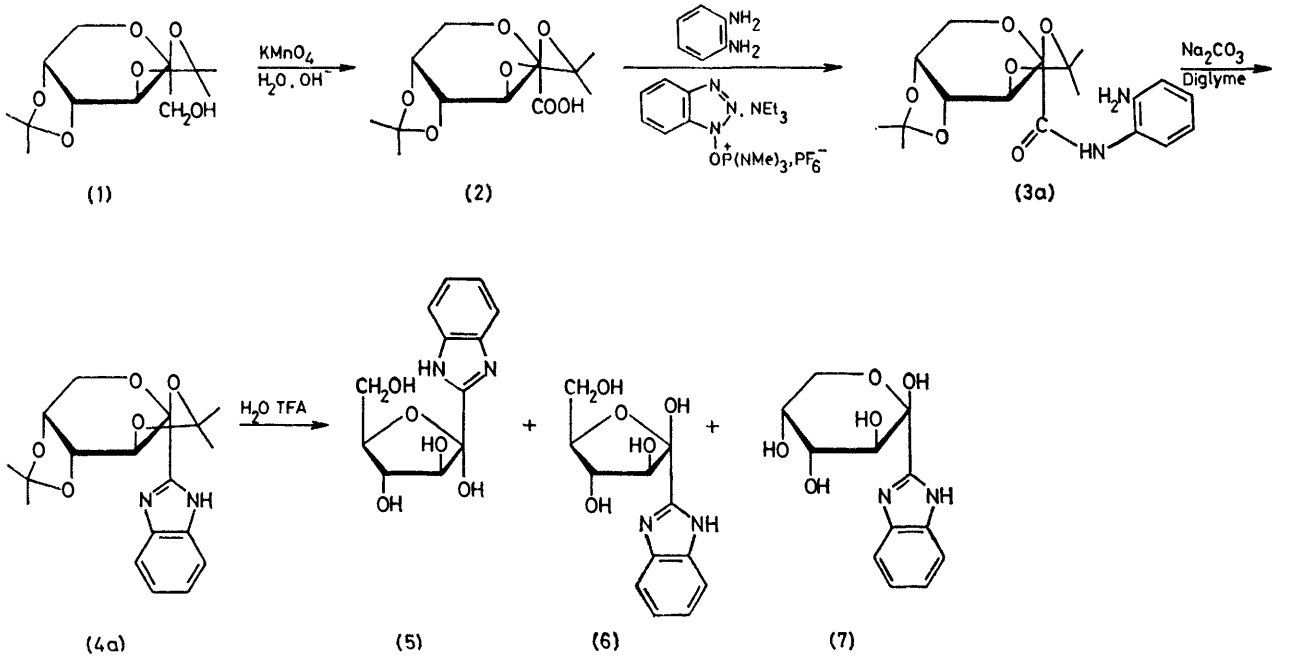
A synthesis of a series of *C*-nucleoside analogues is described starting from readily available hexulosonic acid derived from fructose. The construction of imidazolo-pyridine and -pyrimidine heterocycles under mild conditions is described for five derivatives. ^{13}C N.m.r. analysis of one product shows equilibrium between anomeric furanose and pyranose forms, depending upon the solvent.

SEVERAL synthetic studies directed towards *C*-nucleosides [1,2] have been reported. Precursors or analogues of them have been prepared by reaction of lithio heterocycles with sugar lactones [3,4] or aldehydes.[5] In the last case the compounds bore a hydroxy-group at the anomeric position. We report here our results dealing with the synthesis of such imidazolo-*C*-nucleoside analogues from the hexulosonic acid (2).



Compound (1), readily prepared from fructose,[6] was oxidized with aqueous potassium permanganate to afford the crystalline ulosonic acid (2) in 60% overall yield.[7]

A fusion reaction of a carboxylic acid and a diamino-heterocycle giving an imidazolo-*C*-nucleoside has been described by El Khadem *et al.*[8] who synthesized cordycepin C and AraA analogues. We found that a two-step procedure involving a preliminary formation of amide followed by cyclodehydration was much more satisfactory, amide formation being achieved by use of our peptide coupling reagent 'le BOP'.[9] Monoacylation of heterocyclic diamines was achieved quantitatively. In the case of diaminopyrimidine, regiospecific acylation at the 4-amino-group occurred.

Extraction of compound (3) was followed by direct cyclodehydration of the crude product. We found that among several methods including fusion reaction under vacuum, heating in refluxing diglyme in the presence of solid sodium carbonate afforded the best results. Table 1 summarizes our results.

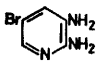
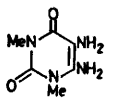
Removal of the protecting groups was achieved by reaction with wet trifluoracetic acid,[10] which one might expect to produce a mixture of the anomeric furanose and pyranose, the proportion of which should be variable. Indeed, measurements of the optical rotation showed rapid mutarotation. The isomeric composition was determined by integration of the anomeric carbon peaks [11,†] in the ^{13}C n.m.r. spectrum. Only three of the four possible isomers were present, the proportions of which, indicated in Table 2, were dependent upon the solvent.

These results demonstrate that use of a ulosonic acid readily available from fructose together with very mild

† Chemical shifts of carbon atoms have been assigned by comparison with those of fructose,[11d] both spectra being very close. Integration of the peaks of C-1′ and those of other signals are in good agreement.

reaction conditions allows rapid preparation of anomerizable *C*-nucleosides. On the other hand these compounds are precursors of natural *C*-nucleosides by reduction of the keto-group followed by cyclodehydration.[5]

TABLE 1

Diamine	Solvent [a]	Product	Reaction time/h [b]	Yield (%) [c]
	CH_2Cl_2	(4a)	14	75
	C_5H_5N	(4b)	40	44
	C_5H_5N	(4c)	21	62
	C_5H_5N	(4d)	22	58
	DMF	(4e)	16	52

[a] Solvent for monoamide formation. [b] For cyclodehydration. [c] From (2).

EXPERIMENTAL

Melting points were determined on a Kofler apparatus. ^1H N.m.r. spectra were recorded on Perkin-Elmer R 12 B 60 MHz and Cameca 250 MHz instruments, ^{13}C n.m.r. spectra on a Cameca spectrometer operating at 62.86 MHz with a pulse width of 4 μs, and optical rotations on a Perkin-Elmer 141 polarimeter. U.v. spectra were recorded on a

TABLE 2

Solvent		(5)	(6)	(7)
D_2O	δ_C (p.p.m.) [a]	102.6	98.64	95.43
	Integral (%)	10	14	76
DMSO	δ_C (p.p.m.) [a]	102.4	98.5	95.85
	Integral (%)	66	19	15

[a] Chemical shift downfield from Me_4Si.

Beckman DK 2A spectrometer and i.r. spectra on a Perkin-Elmer 457 instrument. Elemental analyses were obtained from the Service Central de Microanalyse du C.N.R.S. All evaporations were carried out on a rotatory evaporator below 40 °C.

Compound (1) was prepared according to refs. 6 and 7. It crystallized readily after evaporation of the solvent and had m.p. 103 °C (from ether–light petroleum), $[\alpha]_D^{20}$ −49.7° (*c*, 1 in acetone) [lit.,[6,7] −46.5° (*c* 1.3 in acetone)].

General Procedure for Amide and Dehydration Reactions.—Compound (2) (1 mmol), the diamino-compound (1.1 mmol), and ' le BOP ' reagent (1.1 mmol) were dissolved in the appropriate solvent (see Table 1). After complete dissolution of the reactants, NEt_3 (1.2 mmol) was added. Immediate reaction occurred, often with change of colour. After 5 min t.l.c. showed complete disappearance of the acid (2). Removal of the solvent under reduced pressure afforded a crystalline residue which was passed through a 10 cm silica gel column, with ethyl acetate (200 ml) as eluant. Evaporation afforded a crude amino-compound which was used immediately. The residue was dissolved in dry diglyme (15 ml) and sodium carbonate (200 mg) was added. The mixture was heated at 160 °C until complete disappearance of the starting material. After removal of the solid residue the solvent was evaporated under vacuum. The residue was chromatographed on silica gel with ether–light petroleum as eluant. 1-C-(*Benzimidazol-2-yl*)-1,2:3,4-*di*-O-*isopropylidene*-β-D-arabino-*pentopyranose* (4a) (259 mg, 75%) had m.p. 210 °C, $[\alpha]_D$ −42.2° (*c*, 1 in $CHCl_3$), $\lambda_{max.}$ (EtOH) 209, 274, and 281 nm; δ($CDCl_3$) 1.3—1.6 (2 s, 12 H, isopropylidene), 4—5.2 (m, 5 H, cycle), 7.2—7.4 (m, 4 H, aromatic), and 7.8 (m, 1 H, N*H*) (Found: C, 62.5; H, 6.5; N, 8.1. $C_{18}H_{22}N_2O_5$ requires C, 62.4; H, 6.3; N, 8.09%). 1-C-(1H-*Imidazo*[4,5-b]*pyridin-2-yl*)-1,2:3,4-*di*-O-*isopropylidene*-β-D-arabino-*pentopyranose* (4b) (152 mg, 44%) had m.p. 170 °C, $[\alpha]_D$ −41.4° (*c*, 1 in $CHCl_3$), $\lambda_{max.}$ (EtOH) 203 and 286 nm, δ($CDCl_3$) 1.1, 1.25, 1.6, and 1.7 (4 s, 12 H, isopropylidene), 4—5 (m, 5 H, cycle), 7—8.5 (m, 3 H, aromatic), and 13br (1 H, NH) (Found: C, 58.5; H, 6.0; N, 12.1. $C_{17}H_{21}N_3O_5$ requires C, 58.7; H, 6.0; N, 12.1%). 1-C-(5-*Bromo*-1H-*imidazo*[4,5-b]*pyridin*-2-*yl*)-1,2:3,4-*di*-O-*isopropylidene*-β-D-arabino-*pentopyranose* (4c) (265 mg, 62%) had m.p. 145 °C, $[\alpha]_D^{20}$ −48.9° (*c*, 1 in $CHCl_3$), $\lambda_{max.}$ (EtOH) 206 and 299 nm, δ($CDCl_3$) 1, 1.13, 1.51, and 1.55 (4 s, 12 H, isopropylidene), 3.75—5.1 (m, 5 H, cycle), and 8.23—8.70 (m, 2 H, heterocycle) (Found: C, 48.1; H, 4.8; N, 9.7; Br, 18.6. $C_{17}H_{20}BrN_3O_5$ requires C, 47.88; H, 4.7; N, 9.8; Br, 18.7%). 1-C-(7H-*Purin*-8-*yl*)-1,2:3,4-*di*-O-*isopropylidene*-β-D-arabino-*pentopyranose* (4d) (201 mg, 58%) had m.p. 248 °C, $[\alpha]_D^{20}$ −97.5° (*c*, 1.2 in $CHCl_3$), $\lambda_{max.}$ (EtOH) 205 and 268 nm, δ($CDCl_3$) 1.13, 1.29, 1.64, and 1.71 (4 s, 12 H, isopropylidene), 4.03—5.25 (m, 5 H, cycle), 9.14 (s, 1 H), and 9.23 (s, 1 H, heterocycle) (Found: C, 55.0; H, 5.8; N, 16.0. $C_{16}H_{20}N_4O_5$ requires C, 55.1; H, 5.7; N, 16.0%). 1-C-(1,3-*Dimethyl*-2,6-*dioxo*-7H-*imidazo*-[4,5-d]*pyrimidin*-8-*yl*)-1,2:3,4-*di*-O-*isopropylidene*-β-D-arabino-*pentopyranose* (4e) (321 mg, 52%) had m.p. 210 °C, $[\alpha]_D^{20}$ −24.1° (*c*, 1 in $CHCl_3$), $\lambda_{max.}$ (EtOH) 207 and 277 nm, δ($CDCl_3$) 1.3 (s, 6 H, isopropylidene), 1.6 (m, 6 H, isopropylidene), 3.5—3.62 (2 s, 6 H, CH_3), and 4—5 (m, 5 H, cycle) (Found: C, 53.2; H, 5.9; N, 13.7. $C_{18}H_{24}N_4O_7$ requires C, 52.9; H, 5.88; N, 13.7%).

Hydrolysis of Acetal Groups of (4a).—Compound (4a) (346 mg, 1 mmol) was dissolved in trifluoroacetic–water (9 : 1 v/v; 10 ml). Removal of the 4,5-isopropylidene group was instantaneous. Complete deprotection occurred within 2 h at room temperature. After thorough evaporation of the solvent under reduced pressure, toluene (20 ml) was added and the mixture co-distilled until dryness. Storage in a dry-box over potassium hydroxide pellets afforded a pale yellow *foam* (252 mg, 95%), $[\alpha]_D$ −5.3 (*c*, 0.4 in EtOH), −29.7 (0.4 in DMSO), and −18.7° (0.3 in H_2O) (all measured after 10 min in solution), $\lambda_{max.}$ (EtOH) 274, 280, and 202 nm (Found: C, 54.0; H, 5.25; H, 10.6. $C_{12}H_{14}O_5N_2$ requires C, 54.1; H, 5.2; N, 10.5%).

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