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SYNTHETIC ROUTES TO 4'-HYDROXYMETHYLNUCLEOSIDES*

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As a continuation of our interest in the chemistry of 4'-substituted nucleosides and of nucleoside-5'-aldehydes we have developed two complementary routes for preparing 4'-hydroxymethylnucleosides based upon the aldol coupling of furanose-5'-aldehydes with formaldehyde accompanied by Cannizzaro reduction by excess formaldehyde.[1] Attempted condensation of 2',3'-O-cyclohexylideneuridine-5'-aldehyde (1a)[2] with excess formaldehyde and potassium carbonate in aqueous dioxane led only to rapid decomposition apparently via elimination of the acetal.[3] A similar reaction using 0.6 M sodium hydroxide as the base, however, gave a 38% yield of the 4'-hydroxymethylnucleoside (2a), which was crystallized from methanol with mp 218-9°: NMR (MeOH-d_4) 5.94 ppm (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}H$), 4.31 (dd, 1, $J_{2',3'}$ = 5 Hz, $C_{2'}H$), 4.23 (d, 1, $C_{3'}H$), 3.75 and 3.62 (d, 2, J_{gem} = 11 Hz, $C_{4'}(\underline{CH_2}OH)$).[4] Hydrolysis of 2a with TFA-H_2O (9:1) gave 4'-hydroxymethyluridine (3a) as a homogeneous foam: $[\alpha]_D^{25}$ -12.1° (c 1, MeOH); λ_{max} (MeOH) 257 nm (ε 9,400). Condensation of unprotected uridine-5'-aldehyde with formaldehyde and sodium hydroxide was accompanied by epimerization at $C_{3'}$ giving roughly equal amounts of 3a and its 3'-epimer, which could be separated as their tetraacetates by preparative TLC. This epimerization is presumably due to reverse aldol cleavage of the initially formed β-hydroxyaldehyde followed by aldol cyclization and Cannizzaro reduction. A similar epimerization has recently been observed by others without explanation.[5]

Similar condensation of 1b[6] with formaldehyde and sodium hydroxide at room temperature for 5 hr led to the chromatographic isolation of 2b and the corresponding 2',3'-methylene derivative 2c as foams in yields of 39% and 8%. The methylene derivative (NMR singlets at 5.03 and 5.32 ppm in $CDCl_3$) 2c probably arises via elimination of the acetonide from 1b followed by reaction of the resulting $C_{2'}$-oxyanion with formaldehyde and intramolecular conjugate addition to the unsaturated aldehyde. The Cannizzaro reduction appears to be the rate limiting step since a reaction as above worked up after 15 min by addition of sodium borohydride gave 2b and 2c in yields of 57% and 12%. Hydrolysis of 2b using TFA-H_2O (9:1) followed by methanolic ammonia gave 4'-hydroxymethyladenosine (3b) with mp 218-9°: $[\alpha]_D^{25}$ -45.5° (c 0.5, MeOH); λ_{max} (MeOH) 259 nm (ε 13,900); NMR (Py-d_5) 6.64 ppm (d, 1, $J_{1',2'}$ = 7 Hz, $C_{1'}H$), 5.71 (dd, 1, $J_{2',3'}$ = 5 Hz, $C_{2'}H$), 5.17 (d, 1, $C_{3'}H$), 4.28-4.56 (m, 4, overlapping AB pattern, $C_{4'}(CH_2OH)_2$), 8.56 (s, 2, C_2H, C_8H).

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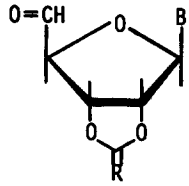
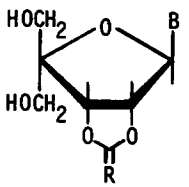
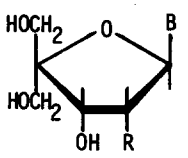


1 (a) B = Ur, R = $(CH_2)_5$
(b) B = N^6-Benzoyl Ad, R = Me_2



2 (a) B = Ur, R = $(CH_2)_5$
(b) B = N^{Bz}-Ad, R = $(Me)_2$
(c) B = N^{Bz}-Ad, R = H_2



3 (a) B = Uracil, R = OH
(b) B = Adenine, R = OH
(c) B = Thymine, R = H

A more versatile route to 4'-hydroxymethylribonucleosides called for the synthesis of a suitable derivative of 4-hydroxymethyl-D-ribofuranose that could be condensed with a variety of heterocycles. To this end 3-O-benzyl-1,2-O-isopropylidene-α-D-allofuranose[7] was oxidized with periodate giving the amorphous aldehyde 4 that was characterized as its 1,3-diphenylimidazolidine derivative [mp 144-5°; $[\alpha]_D^{23}$ 10.6° (c 1.0, $CHCl_3$)]. Condensation of crude 4 with formaldehyde and aqueous sodium hydroxide (20°, 4 days) gave crystalline 5a with mp 101-2°, $[\alpha]_D^{23}$ 82.9° (c 1.0, $CHCl_3$) in 67% yield, and palladium catalyzed hydrogenolysis of the latter gave 82% of 5b with mp 114-5°, $[\alpha]_D^{23}$ 17.2° (c 0.3, EtOH) (reported[5] mp 114-5°). Acetylation of 5b followed by acetolysis with acetic anhydride, acetic acid and sulfuric acid gave the key intermediate 4-acetoxymethyl-1,2,3,4-tetra-O-acetyl-D-ribofuranose (6) as an analytically pure 3:1 (β/α) anomeric mixture. The latter compound has also been mentioned by Rosenthal[8] via a different synthetic route and has been used in a preparation of 3b.

Condensations of 6 with a variety of heterocyclic bases have been achieved using conventional methods of nucleoside synthesis[9] and are summarized in the Table. Thus, for example, the condensation of 6 with 6-chloropurine in acetonitrile at 55° for 2 hr in the presence of mercuric cyanide and stannic chloride gave crystalline 9-(4-acetoxymethyl-2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-6-chloropurine (7a) in 84% yield. The site of ribosidation was confirmed by the ultraviolet spectrum of 7a and the β-configuration, which is to be expected on the basis of the "*trans* rule",[9] was confirmed by conversion, upon treatment with liquid ammonia, into 3b (7e) identical to that obtained from 2b. Upon treatment with thiourea, 7a was efficiently converted into the 6-mercaptopurine derivative 7b, which could either be directly deacetylated giving 7c or alkylated with methyl iodide to the 6-methylthiopurine nucleoside 7d. The pentaacetate 6 was also condensed with the *bis*-(trimethylsilyl) derivatives of 5-fluorouracil[10] and 6-aza-2-thiouracil[11] giving the protected nucleosides 8a and 9a, which were deacetylated to give the crystalline free nucleosides 8b and 9b. In each case the site of alkylation, and the β-configuration, was confirmed by comparison of the UV and ORD spectra with those of the known ribosides.[12] Finally, condensation of 6 with 3-methoxycarbonyl-1,2,4-triazole[13] followed by treatment with ammonia gave the 4'-hydroxymethyl derivative 10 of the antiviral agent Ribavirin®.

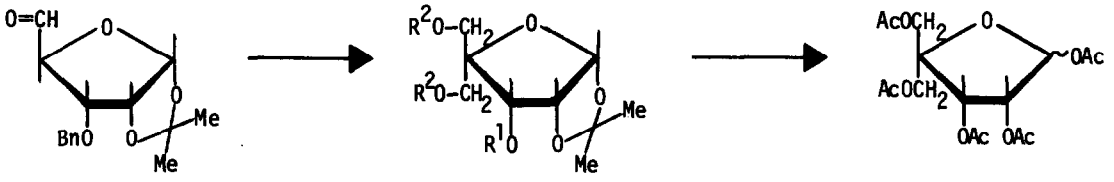
Compounds have also been prepared in the 2'-deoxy series. Thus oxidation of 3'-O-benzylthymidine[14] with DMSO-DCC-pyridinium TFA[15] gave the 5'-aldehyde that was purified as its 1,3-diphenylimidazolidine derivative[2,6] with mp 171-3°; $[\alpha]_D^{23}$ 47.2° (c 1.0, $CHCl_3$).

Regeneration of the aldehyde with *p*-toluenesulfonic acid followed by reaction with formaldehyde and sodium hydroxide gave 3'-O-benzyl-4'-hydroxymethylthymidine (mp 186-7°) in 66% yield. Palladium catalyzed hydrogenolysis then gave 4'-hydroxymethylthymidine in 55% yield: $[\alpha]_D^{25}$ 26.3° (c 0.5, MeOH); λ_{max} (MeOH) 267 nm (ε 9,300).

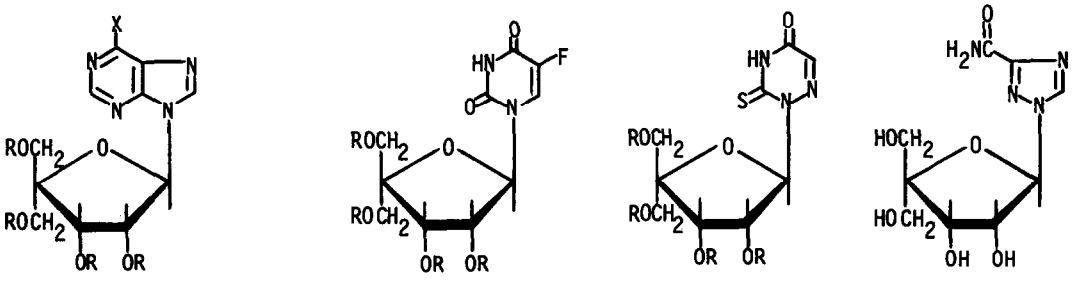
The methods described above make the synthesis of a wide range of 4'-hydroxymethylnucleosides possible and suggest the preparation of further derivatives of interest for biological studies.

Condensation Reactions

Cpd	Synthetic Method	% Yield	mp	$[\alpha]_D^{23}$ (c 1.0, solvent)	λ_{max} (ε)
7a	Free base, $Hg(CN)_2$, $SnCl_4$, MeCN, 55°, 2 hr	84	166-7°	-13.6° ($CHCl_3$)	EtOH, 264 (8,400), 250 (sh, 6,600)
7b	7a + thiourea, *n*PrOH, 100°, 3 hr	84	232-3°	----	pH 13, 311 (22,000), 232 (14,400)
7c	7b, NH_3/MeOH	91	222-4°	-66.9° (Py)	pH 13, 310 (23,000), 232 (14,100)
7d	7c, MeI, NaOH, 40°, 2 hr	84	132-4°	-55.3° (Py)	pH 13, 292 (18,600), 287 (18,600), 223 (11,700)
7e	7a, liq. NH_3, 20°, 18 hr	76	218-9°	-45.5° (MeOH)	MeOH, 259 (13,900)
8a	$(Me_3Si)_2$-base, $SnCl_4$, 60°, 1 hr, $(ClCH_2)_2$	~80	68-71°	----	MeOH, 263 (8,800)
8b	8a, NH_3/MeOH	62	197-9°	-31.9° (Py)	pH 1, 269 (10,000)
9a	$(Me_3Si)_2$-base, $SnCl_4$, MeCN, 55°, 1 hr	80	oil	----	MeOH, 272 (16,600), 217 (12,900)
9b	9a, NH_3/MeOH	43	173-5°	-152.6° (Py)	pH 1, 270 (16,600), 218 (14,300)
10	Free base, $Hg(CN)_2$, $SnCl_4$, MeCN, 50°, 2 hr and then NH_3/MeOH	50	Hygroscopic	-36.2° (Py)	End absorption



4 5 (a) R^1 = Bn, R^2 = H (b) R^1, R^2 = H 6



7 (a) X = Cl, R = Ac (b) X = SH, R = Ac (c) X = SH, R = H (d) X = SMe, R = H (e) X = NH_2, R = H: ≡ 3b

8 (a) R = Ac (b) R = H

9 (a) R = Ac (b) R = H

10

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