Tetrahedron Letters No. 11, pp 951 - 954.
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0040-4039/79/0308-0951$02.00/0

NEW SYNTHESIS OF 5,6-CYCLOTHYMINE- AND 6-ALKYLURACIL-1-N-β-D-RIBOSIDES

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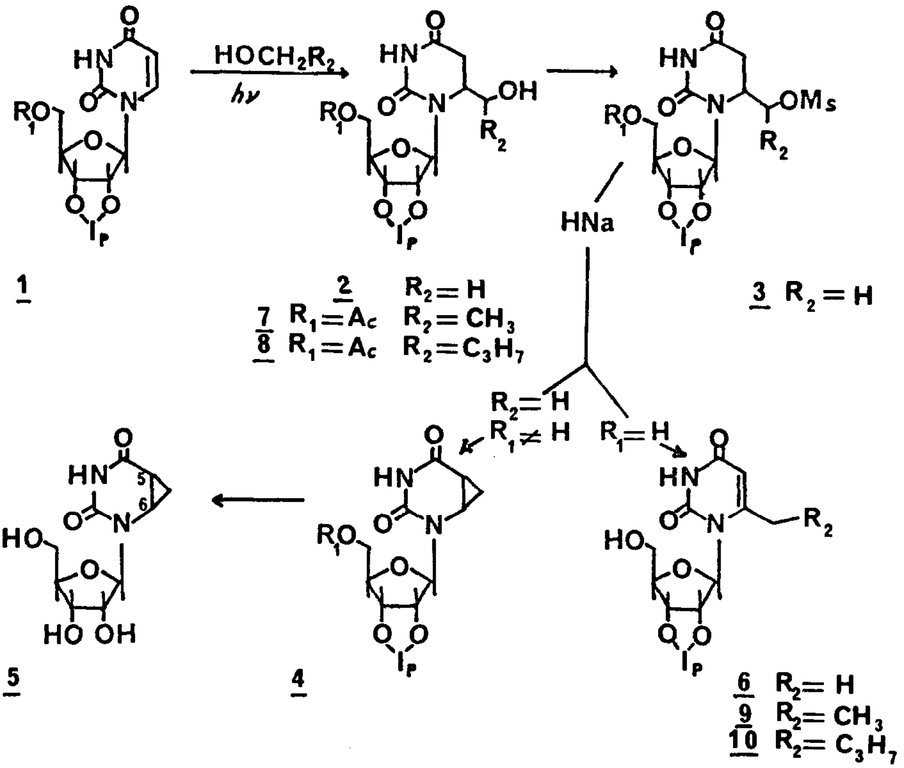
Many naturally occurring as well as synthetic nucleosides are known to manifest a variety of biological activities (1-3). Very often these compounds are pyrimidine type analogues of the normal nucleic acid constituents in which the C-5, C-6 double bond has been functionalized. Thus several C-5 substituted uracil and cytosine (deoxy-) ribosides are antiviral agents(4). Surprisingly, among this class of compounds two very attractive structural types, namely 5,6-dihydro-5,6-methylene- and 6-alkylpyrimidine nucleosides, have been little studies(5,6). This might be related to the fact that the procedures for their synthetic accessibility are not very practical. The preparation of cyclothymine ribosides requires N-3 protection and ends up with a partially separable mixture of diastereoisomers(7,8). Similarly, direct condensation of 6-alkyl uracils (silylated derivatives, $SnCl_4$) and peracetylated pentoses leads to nucleosides mixtures[9]. 6-alkyluridines (methyl and ethyl) have also been synthesized through the intermediacy of pentose 2-amino-1', 2'-oxazoline(10).

We wish to report a new convenient synthetic sequence to obtain these types of substances based on the addition of hydroxyalkyl radicals to 2',3'-O-isopropylideneuridine 1a.

Direct irradiation of a methanolic solution of 1a initiates the formation of hydroxymethyl radicals which add regioselectively at the C-6 position of the pyrimidine to yield 5,6-dihydro-6-hydroxymethyluridine 2a (diastereoisomeric mixture)(11). These compounds can also be obtained on a larger scale by using di-t-But-peroxide as a radical sensitizer. In the case of 5'-O-acetyl-2',3'-O-isopropylideneuridine(12) 1b, the corresponding diastereoisomers 2b$^+$ and 2b$^-$(13) are isolated, after silica gel chromatography in 25 and 50 % yields, respectively. With the 5'-O-trityl derivative 1c the overall yield is lower (58 %) but the ratio 2c$^+$/2c$^-$ is 1/3 ; this indicates that the stereoselective course of the reaction can be directed by introducing a bulky substituent at C-5'. Compounds 2b and 2c, whose spectral data are closely related to those previously reported for derivatives 2a, are easily converted into the cyclothymine



a $R_1=H$; b $R_1=COCH_3$; c $R_1=C(C_6H_5)_3$; d $R_1=CH_3$; e $R_1=C_5H_9O=THP$

ribosides 4b and 4c. Mesylation (MsCl, Pyridine) of 2b and 2c gave 3b and 3c whose NMR spectra show the signal due to Me-SO$_3$- as a characteristic singlet (3H) at 3.0 ppm. Treatment of mesylates 3b$^+$ and 3b$^-$ in the presence of a base (NaH ; DMF : THF, 1:9) produced the corresponding cyclothymines 4b in 45 % yield together with a minor amount of 2',3'-O-isopropylidene-6-methyl-uridine 6. Starting from compounds 3c-3e the corresponding 5,6-methylene-uridine derivatives 4c-4e were isolated in 60 % yields, exclusively. Compounds 4b-4e display a UV maximum at 240 nm. The NMR data for compounds 4b and 4c which are given in the Table are consistent with the proposed structures. Acidic treatment of derivatives 4c and 4d gave the free nucleosides 5$^+$ and 5$^-$ whose spectral data were found identical to those previously reported by Witkop and Kunieda(7).

The fact that the formation of 6 is avoided by introducing an alkali stable protecting group at position C-5' suggests that the elimination reaction leading to 2',3'-O-isopropylidene-6-methyl-uridine 6 must take place with the participation of the alcoholate at position C-5'. Earlier observations(14) having indicated that in THF this alcoholate undergoes specific reactions, we have treated 3a with NaH in this solvent to obtain 2',3'-O-

Table : ^{1}H NMR data of compounds 4b, 4c, 5, 6, 9 and 10

	$4b^-$	$4c^+$	5^+	$4b^-$	$4c^-$	5^-	6	9	10
NH	7.26	8.25	-	8.10	8.15	-	10.3	-	9.9
$H_{1'}$	5.73	6.15	5.95	5.62	5.90	5.90	5.58	5.52	5.48
$H_{2'}$	5.07	5.20	4.40	5.00	5.00	4.34	5.20	5.18	5.25
$H_{3'}$	4.72	4.80	4.13	4.60	4.70	4.10	4.92	4.95	4.90
$H_{4'}$	4.25	4.25	3.90	4.25	4.30	3.90	4.18	4.18	4.12
CH_2OR_1	4.26	3.40	3.73	4.26	3.40	3.70	3.80	3.80	3.75
H_6	3.20	3.35	3.50	3.15	3.15	3.30	-	-	-
H_5	2.05	1.80	2.03	2.05	2.0	2.05	5.50	5.52	5.50
H_7	1.50	1.20	1.50	1.30	1.20	1.60	-	-	-
	1.10	0.90	1.00	0.94	0.90	0.95	-	-	-
Ip	1.36	1.40	-	1.36	1.40	-	1.33	1.33	1.32
	1.57	1.60	-	1.56	1.60	-	1.52	1.52	1.54
R_1	2.08	7.7	-	2.09	7.6	-	-	-	-
	-	7.4	-	-	7.3	-	-	-	-
CH_2R	-	-	-	-	-	-	2.26	2.60	2.50
	-	-	-	-	-	-	-	1.25	1.30
	-	-	-	-	-	-	-	-	0.92

Chemical shifts in ppm. Solvent $CDCl_3$ (compounds 5^+ and 5^-, solvent CD_3OD)

isopropylidene-6-methyl uridine 6 exclusively (yield 60 %).

This procedure for obtaining 6-alkyluridine was extended to prepare readily other 6-substituted derivatives. Thus, irradiation of 1b in alcohol (ethanol, n-butanol) in the presence of di-*tert*-butylperoxide led to mixtures of diastereoisomeric 5,6-dihydro-6-hydroxyalkyluridines 7 and 8 (yield over 80 %) resulting from the regiospecific addition of hydroxyalkyl radicals to the nucleoside. Mesylation (MsCl, Pyridine), deacetylation (NaOMe/MeOH) and treatment with NaH in THF produced the 6-alkyl derivatives 9 ($M^{+\cdot}$ 312) and 10 ($M^{+\cdot}$ 340) in overall yield of 45 % from 1b. The spectral data of these two compounds are very similar to those of 2',3'-isopropylidene-6-methyluridine 6 (Table). It may be noted that 6-ethyluridine has been previously prepared by Holy by total synthesis(10). Whereas, to the best of our knowledge, higher 6-alkyl homologues have never been described.

We are currently preparing several other derivatives of the above compounds in view of their biological evaluation.

Acknowledgements : We are very grateful to Dr J. Polonsky for her encouragements and support throughout this work.

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12 - A 12 mM solution of 2b in methanol containing 1% of di-*tert*-butylperoxide was irradiated during 18 hours at 0°C through Pyrex with a Hanau TG 150 lamp.

13 - The sign attributed to compounds 2b corresponds to the sign of the C.D. curve of each diastereoisomer at 245-250 nm.

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(Received in UK 4 January 1979)