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SYNTHESIS AND CHEMISTRY OF 5, 6-DIHYDRO-6-METHOXYURIDINE DERIVATIVES. ACCESS TO O^6, 5'-CYCLO-5, 6-DIHYDROURIDINE

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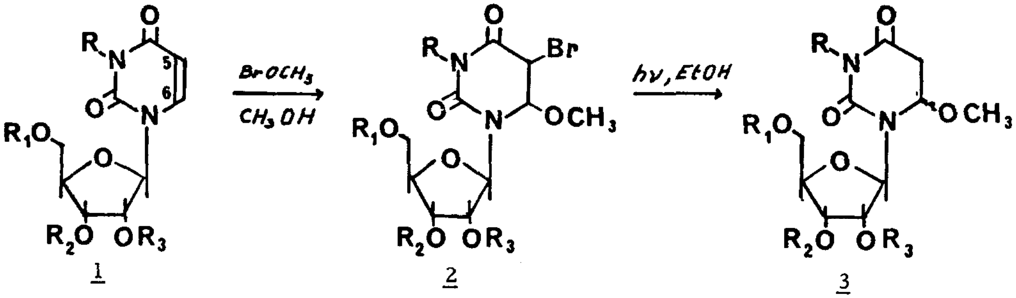
Irradiation of uridine 1a (or of its derivatives) in methanol produces three major photoproducts[1]. One of these, which eliminates methanol after heating, was supposed to be 5, 6-dihydro-6-methoxyuridine 3a. To confirm this structural assignment we have devised a two-step synthesis of this compound and of its derivatives 3b, 3c and 3d. We have studied the chemical behaviour of 3a and more particularly its transformation into O^6, 5'-cyclo-5, 6-dihydro-2', 3'-O-isopropylideneuridine 5 which is described for the first time.

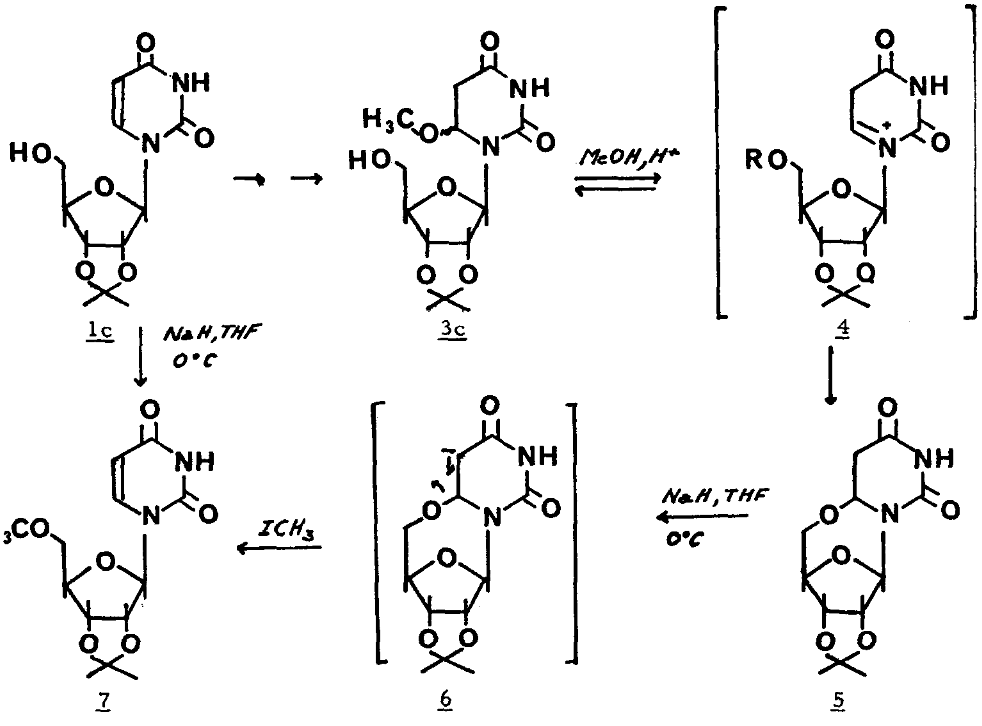


a $R=R_1=R_2=R_3=H$
b $R=H \quad R_1=R_2=R_3=Ac$
c $R=R_1=H \quad R_2, R_3 = >C(CH_3)_2$
d $R=CH_3 \quad R_1=H \quad R_2, R_3 = >C(CH_3)_2$

A methanolic solution of 2', 3'-O-isopropylideneuridine 1c was treated with bromine[2] at 0°C to give after addition of Ag_2CO_3/celite a 2:1 mixture[3] of diastereoisomers 2c which were not separated. The reduction of these bromo derivatives was accomplished by irradiating 2c in ethanol at -20°C[4]. Silica gel column chromatography of the reaction mixture obtained after neutralisation of the ethanolic solution with Amberlite IR-45 afforded the two main photoproducts 3c(-) [Dec. 155-160°C, $[\alpha]_D(CHCl_3)$ -80°] and 3c(+) [Dec. 138-142°C $[\alpha]_D(CHCl_3)$ + 38°]. Structures 3c are in agreement with analytical and spectral data (Table). Both epimers 3c (-) and 3c (+) lose methanol upon warming to yield 2', 3'-O-isopropylideneuridine 1c ; the rate of this thermal elimination is enhanced by the addition of acid.

Using the same synthetic route (1→2→3) we have successfully prepared the 5, 6-dihydro-6-methoxyderivatives 3a, 3b and 3d which, as 3c, were found identical to those obtained after irradiation of the corresponding uridine derivatives in methanolic solution.

Treatment of 3c (-) and 3c (+) in acidic methanol below 10°C led to a new derivative which must be O^6, 5'-cyclo-5, 6-dihydro-2', 3'-O-isopropylideneuridine 5 [Dec. 156-160°C $[\alpha]_D$ $(CHCl_3)$ $-60°]^5$. Structure 5 is based on the following arguments : the new compound 5 is an isomer of 2', 3'-O-isopropylideneuridine 1c which shows no UV absorption above 230 nm. It reverses to 2', 3'-O-isopropylideneuridine 1c upon warming. The NMR spectrum of 5, characterized by the absence of OCH_3 signal, is fully consistent with the structural assignment. In this spectrum the singlet due to H-1' is strongly deshielded which results from the anisotropy effect of the carbonyl at $C\text{-}2^6$ and confirms the anti-conformation of this novel cyclonucleoside.



The behaviour of 3c (-) and 3c (+) to give 5 is not unexpected. It is well known that 2', 3'-O-isopropylidene derivatives of uridine prefer the anti-conformation[7] thus favouring interaction between 5'-OH and C-6 for which there are several examples[8-10]. We have monitored the transformation of 3c (-) and 3c (+) into 5 by NMR spectroscopy using CD_3OD containing DCl as solvent. These experiments showed that the reaction was faster for 3c (+)

TABLE : NMR data (δ ppm)

	H 1'	H 2'	H 3'	H 4'	H 5'	H 5	H 6
3c(-)	5.52 d $J_{1'2'}$ = 2.6 Hz	4.92 q	4.78 q	4.08 m	3.74 dd	2.84 q	5.01 q
3c(+)	5.37 d $J_{1'2'}$ = 2.1 Hz	5.09 q	4.75 q	4.10 m	3.68 dd	2.96 dd 2.66 dd J_{gem} = 16.7 Hz	4.98 q
5	6.20 s	4.73 s	4.73 s	4.82 d	4.05 d 3.72 dd J_{gem} = 12.6 Hz	3.00 dd 2.66 dd J_{gem} = 17.5 Hz	5.07 q
7	5.83 s	4.78 s	4.78 s	4.33 m	3.60 d	5.67 d	7.43 d

OCH_3 : 3c(-), 3.76 ; 3c(+), 3.37 ; 7, 3.37
d = doublet, m = multiplet, q = quartet, s = singlet
solvent : $CDCl_3$

than for 3c (-) and that deuterium was not incorporated at C-5. Compound 3c (+) was acetylated yielding 3e ; when this acetate was dissolved in acidic CD_3OD progressive disappearance of the OCH_3 signal could be followed by NMR (it gave rise to a new signal due to methanol). Under these conditions there was no other significant spectral modifications (at least up to 60 % conversion) ; accordingly, a solvent promoted exchange took place to yield 5'-O-acetyl-5, 6-dihydro-2', 3'-O-isopropylidene-6-methoxy-d_3-uridine. This nucleophilic substitution, which occured with retention of configuration at C-6, presumably involves an immonium species such as 4 (R = Ac) which might be also (R = H) a precursor of 5.

When 1c was treated in THF with NaH in the presence of CH_3I at 0° C it underwent a slow reaction to give, surprisingly, 2', 3'-O-isopropylidene-5'-O-methyluridine 7 (oil). This novel specific reactivity of the 5'-OH towards CH_3I/NaH in THF does not involve a cyclic intermediate such as 5 since this methylation could be extended to 5, 6-dihydro-2', 3'-O-isopropylideneuridine. However, it is noteworthy that 5 gave rise, almost immediately, to product 7 when treated under the same conditions. In this case the rate enhancement might be ascribed to the higher reactivity of the anionic intermediate 6[11].

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3 - This ratio was estimated by inspecting the NMR spectrum of the mixture.

4 - We used a Hanau TQ 150 lamp with a filter to cut off wavelenghts < 280 nm ; with higher temperature (~ 10° C) the major photoproduct was compound 5.

5 - The cyclonucleoside 5 can be obtained directly from 2',3'-O-isopropylideneuridine 1c. Thus when a neutral 10^{-3}M methanolic solution of the latter is irradiated 5 is produced in 8 % yield, while in tBuOH it is the major photoproduct.

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11 - We thank M. G. Henry for skillful technical assistance.