BASE CATALYZED SELECTIVE DISPROPORTIONATION REACTIONS OF 3',5'-DI-O-AROYL DERIVATIVES OF 1-β-D-ARABINOFURANOSYLURACIL

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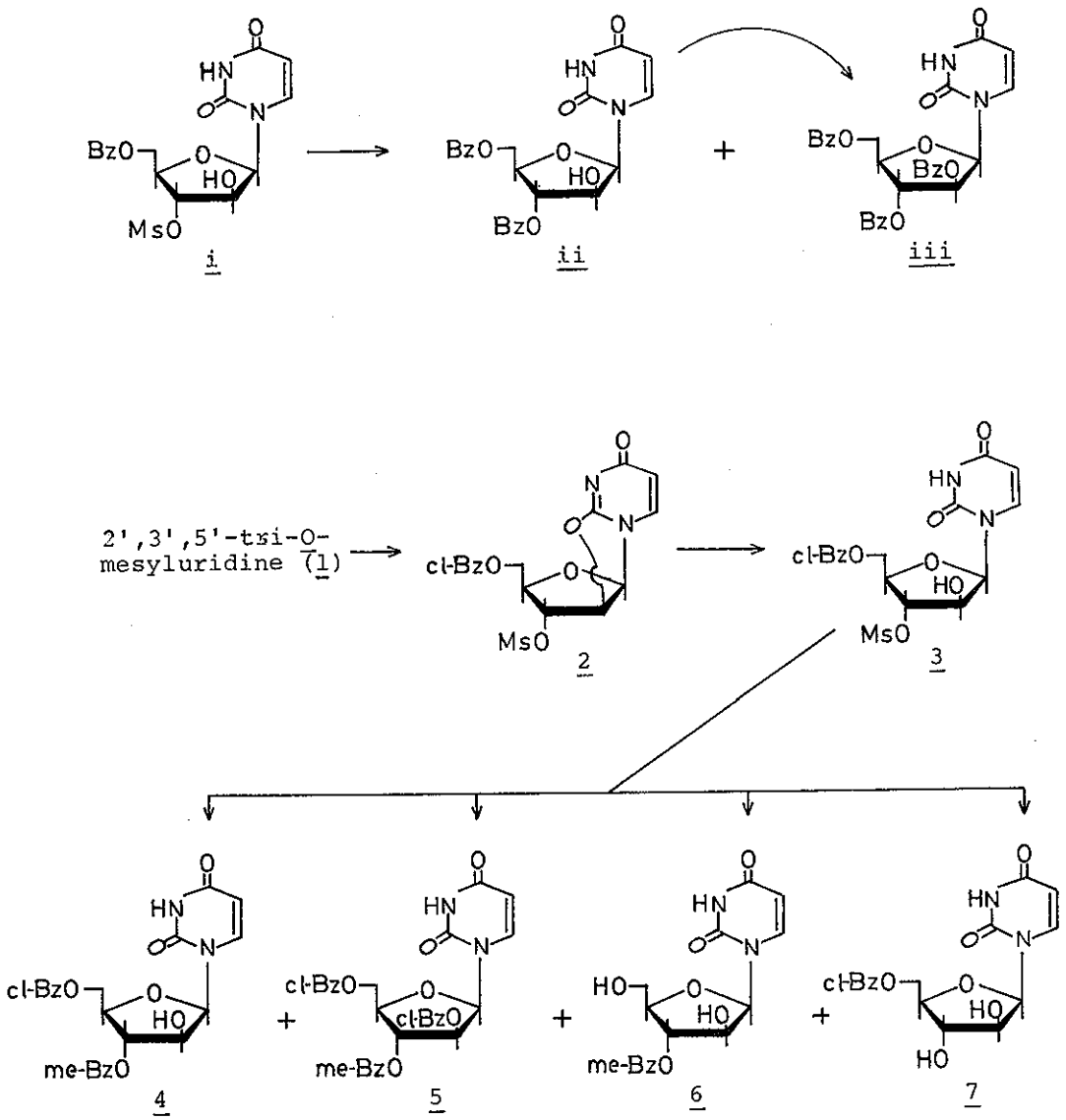
The mechanism for the base catalyzed formation of a 2',3',5'-tri-O-aroyl derivative (iii) of spongouridine from the corresponding 3',5'-di-aroyl derivative (ii) was concluded to be an intermolecular disproportionation reaction of the latter, the first observed example in the nucleoside area.

In a recent publication[1], we have reported that 1-(2',3',5'-tri-O-benzoyl-β-D-arabinofuranosyl)uracil (iii) forms as a by-product in the synthesis of 1-(3',5'-di-O-benzoyl-β-D-arabinofuranosyl)uracil (ii) from 1-(5'-O-benzoyl-3'-O-mesyl-β-D-arabinofuranosyl)uracil (i) and sodium benzoate in hot DMF and that the immediate precursor of iii is compound ii. The unusual formation of iii has posed the question whether the 2'-O-benzoyl group in iii originates from the external benzoate anion or benzoic acid (released by the trapping of sodium cation by the base moiety) or iii forms by an intermolecular disproportionation

Scheme I.


i
ii
iii
2',3',5'-tri-O-mesyluridine (1)
2
3
4
5
6
7
cl-Bz=p-chlorobenzoyl
me-Bz=p-methylbenzoyl

reaction of ii. Another possibility that it results from an intramolecular benzoyl rearrangement with concomitant introduction of a second benzoyl unit from outside can not be ruled out immediately. To solve this problem, we designed a synthetic study using analogs of i and ii with different aroyl groups and sodium salts of substituted benzoic acids as basic catalysts. This report deals with the first evidence to support a disproportionation reaction in the formation of iii.

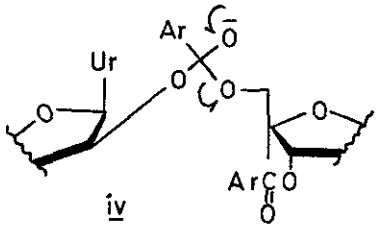
Treatment of 2',3',5'-tri-O-mesyluridine (1)[2] with sodium p-chlorobenzoate by the known method[2] gave 2,2'-anhydro-1-(5'-O-p-chlorobenzoyl-3'-O-mesyl-β-D-arabinofuranosyl)uracil (2) in 95% yield, mp 223-225°: λ_{max}^{MeOH} 242 nm (ε 23000). Acidic hydrolysis of 2 yielded 1-(5'-O-p-chlorobenzoyl-3'-O-mesyl-β-D-arabinofuranosyl) uracil (3) in 86% yield: mp 169-171°; λ_{max}^{MeOH} nm (ε) 243 (28000) and 263 (13200, shoulder). Treatment of 3 with 3 molar excess sodium p-methylbenzoate in DMF at 125° for 3.5 hr and separation of the reaction mixture by silica gel chromatography gave 1-(5'-O-p-chlorobenzoyl-3'-O-p-methylbenzoyl-β-D-arabinofuranosyl)uracil (4), mp 216-218°, 1-(2',5'-di-O-p-chlorobenzoyl-3'-O-p-methylbenzoyl-β-D-arabinofuranosyl)uracil (5), mp 245-246°, 1-(3'-O-p-methylbenzoyl-β-D-arabinofuranosyl)uracil (6), mp 226-229°, 1-(5'-O-p-chlorobenzoyl-β-D-arabinofuranosyl)uracil (7), mp 193-197°, in 37.2, 11.8, 7.3 and 2.9% yield, respectively. All these compounds showed uridine absorptions at 260-265 nm and NMR resonances of $H_{1'}$ as doublets ($J_{1',2'}$ = 3.2-3.75 Hz) (Table I) indicative of

Table I. NMR Resonances of the Sugar Protons of Uridine Derivatives at 60 MHz.

Compd	C_5',H	C_4',H	C_3',H	C_2',H	C_1',H
4[a]	4.48(m)	4.72(m)	5.35(s)	(in H_4', envelope)	6.28(d) $J_{1',2'}$=3.3 Hz
5[b]	4.85(d) J=~.5 Hz	4.58(m)	5.60(m)	5.80(dd) $J_{1',2'}$=3.75 Hz $J_{2',3'}$=1.6 Hz	6.45(d) $J_{1',2'}$=3.75 Hz
6[c]	3.95(d) J=3.4 Hz	4.32(m)	5.32(dd) $J_{2',3'}$= $J_{3',4'}$ 1.6 Hz	(in H_4', envelope)	6.19(d) $J_{1',2'}$=3.2 Hz
7[c]	4.1-4.3(m)		4.5-4.7(m)		6.19(d) $J_{1',2'}$=3.3 Hz

a: in $CDCl_3$/DMSO-d_6 (5:1). b: in $CDCl_3$. c: in $CDCl_3$/DMSO-d_6(3:1).

their arabino configuration. Compound 5 was also obtained by treatment of 4 with p-chlorobenzoyl chloride. The isolation of 2 and 6 directly led to the conclusion that there was involved a base catalyzed disproportionation reaction of 4 initially formed from 3[3] through a 2',3'-epoxide, as visuallized in formula iv. The reason for the formation of the much minor product, 7, is not clear at present, since we did not detect any trace of another counterpart (triaroyl compound) for 7. This sort of base-prompted disproportionation reaction has not been recorded in the nucleoside field and is interesting in view of the synthetically useful transacetylation between adenosine and its 2',3',5'-tri-O-acetyl derivative.[4]



iv

REFERENCES AND NOTES

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2. J. F. Codington, R. Fecher, and J. J Fox, J. Am. Chem. Soc., 82, 2794 (1960).

3. That 4 forms with a much less amount of its xylo isomer was evidenced in a separate experiment.

4. L. Szabo, Bull. Soc. Chim. France, 1966, 3159.

Received, 11th July, 1977