SYNTHESIS OF 5-ALKYL- AND 5-ACYL-URIDINES VIA 6-MERCAPTOURIDINE (NUCLEOSIDES AND NUCLEOTIDES. XVII[1])

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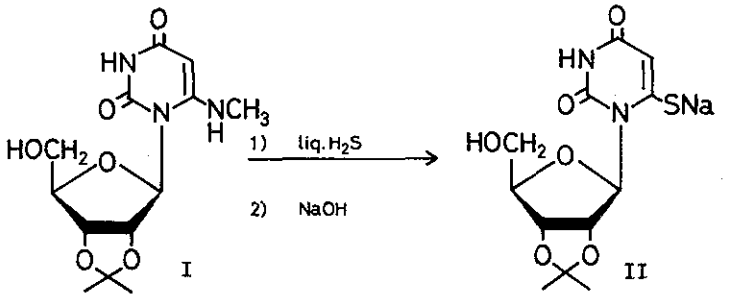
Several 5-alkyl- and 5-acyl-uridines have been prepared by the allylation or acylation of 2',3'-O-isopropylidene-6-mercapto-uridine followed by the desulfurization.

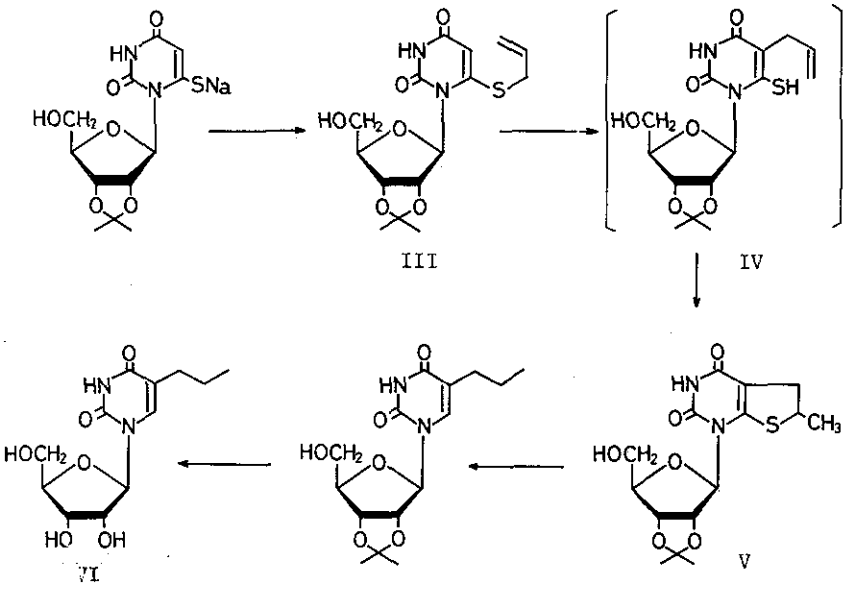
Certain pyrimidine nucleosides substituted at the position 5 of the pyrimidine ring exhibit biological activities. For example, 5-iodo-2'-deoxyuridine[2] and 5-ethyl-2'-deoxyuridine[3] showed marked antiviral activities. We wish to report the versatile method of introducing carbon units, namely alkyl and acyl groups, to the position 5 of a naturally occurring pyrimidine nucleoside , uridine, by the use of a 6-mercaptouridine derivative as the reactive intermediate.

The method already reported for the introduction of an alkyl(alkenyl) or an acyl group on the position 5 or 6 of the pyrimidine ring includes the Claisen rearrangement of 5-allyloxyuridine to the 6-allyl derivative[4], a thio-Claisen rearrangement of 1,3-dimethyl-4-allylthiouracilium salt to the 5-allyl-4-thio derivative[5], and acetylation of 6-amino-[6] and 6-hydroxy-[7]1,3-dimethyluracils to the respective 5-acetyl derivatives. Recently, 5-alkyl derivatives of uridine and 2'-deoxyuridine were prepared from the respective 5-chloromercuri derivatives and alkenes, via the organopalladium intermediate[8]. Photo-cycloaddition of alkenes to 2',3',5'-tri-O-acetyluridine was also reported[9].

Since a 6-mercaptouridine derivative[10] became readily accessible by the sulfhydrolysis of 6-methylaminouridine derivative, we attempted the thio-Claisen rearrangement and acylation of 6-mercaptouridine derivative.

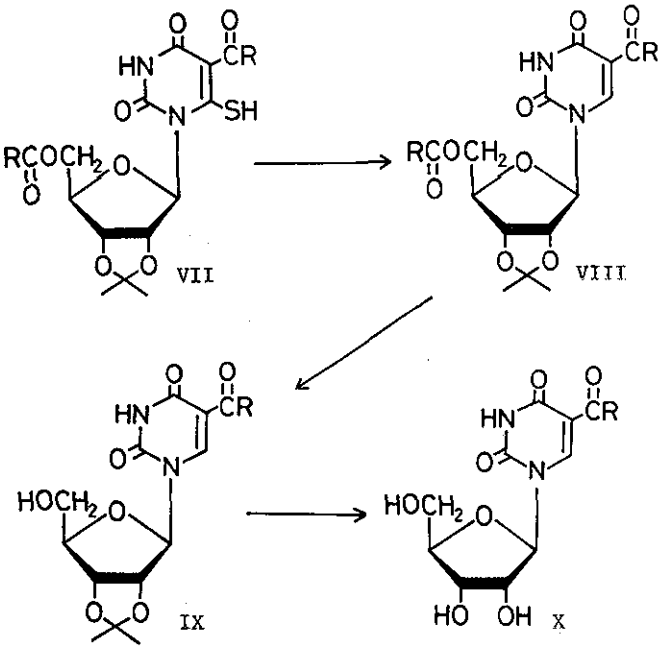


Treatment of 2',3'-O-isopropylidene-6-methylaminouridine(I)[11] with liquid hydrogen sulfide in pyridine at 60° for 24 hr in a sealed tube afforded the 6-mercaptouridine which was crystallized as a sodium salt(II, mp 228-30°(dec), UV λ_{max}^{EtOH}: 237, 315 nm, NMR δ, 5.40(H-5), 7.72(H-1'))in 79% yield. Treatment of II with an equivalent amount of allyl bromide at room temperature afforded the 6-allylthio derivative(III) in a yield of 63%, which without purification, was refluxed in dimethylformamide for 30 min to give the dihydrothiophenopyrimidine riboside(V, Mass m/e, 356(M^+), UV λ_{max}^{EtOH} 295 nm, NMR δ, 1.50(d, CH_3)) in quantitative yield. It is apparent that the thio-Claisen rearrangement of III to IV had occurred which rapidly cyclized to furnish V. Desulfurization of V with Raney Ni in refluxing ethanol and successive de-



acetonation in 50% formic acid afforded 5-propyluridine(VI, mp 193-195°, UV λ_{max}^{EtOH} 268 nm, NMR δ, 5.84(H-1'), 7.80(H-6), Mass m/e, 286(M^+)) in 70% yield. 5-Isobutyluridine(UV λ_{Max}^{EtOH} 267 nm, NMR δ, 0.83(d, gem-dimethyl), 7.72(H-6), Mass m/e, 300(M^+)) was similarly prepared by reacting II with β-methylallyl chloride to give the 6-methylallylthio derivative which was followed by thio-Claisen rearrangement, desulfurization, and deacetonation.

Since the method involving thio-Claisen rearrangement is restricted in the variety of alkyl groups to be introduced, acylation was undertaken as the alternative. Treatment of II with acetic anhydride in pyridine at room temperature for 4 hr afforded 5-acetyl-6-mercapto derivative(VII). Without purification, VII was treated with Raney Ni in refluxing ethanol to leave 5'-O-acetyl-2',3'-O-isopropylidene-5-acetyluridine(VIII, R=Me). Compound VIII(R=Me)



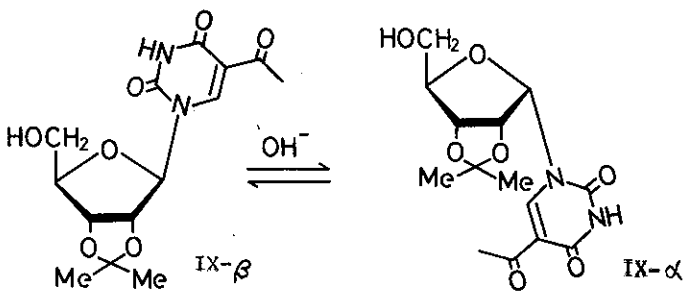
was deacetylated with methoxide in methanol at room temperature to give 2',3'-O-isopropylidene-5-acetyluridine(IX, R=Me). Deacetonation of IX(R=Me) in 50% formic acid afforded 5-acetyluridine(X, R=Me). By using anhydrides of propionic and butyric acid in place of acetic anhydride, 5-propionyl and 5-buty-

ryl-uridine were prepared from II. The results including physical constants of acyluridine derivatives were summarized in Table 1. The overall yields of these 5-acyluridines from II were over 44%. The reduction of the acyl carbonyl groups of X should give the respective 5-alkyluridines and experiments on this point are currently undertaken.

Table 1.

	RCO-	R=CH_3	R=CH_2CH_3	R=$(CH_2)_2CH_3$
VIII	mp	195.5~197.0°	147.0~147.5°	130.5~131.0°
	yield	69.6%	71.0%	58.0%
	NMR δ ($CDCl_3$)	2.13 (5'-$COCH_3$)	2.43(5'-$COCH_2$-)	2.38 (5'-$COCH_2$-)
		2.60(5-$COCH_3$)	3.05(5-$COCH_2$-)	3.01 (5-$COCH_2$-)
		8.39(H-6)	8.43(H-6)	8.40(H-6)
	MASS m/e	368(M^+)	396(M^+)	424(M^+)
IX	mp	192.0~195.0° (lit.181~190°)[12]	178.0~178.5°	164.0~164.5°
	yield	80.5%	85.2%	93.5%
	MASS m/e	326(M^+)	340(M^+)	354(M^+)
X	mp	194.5~196.5° (lit.165~167°)	186.0~187.0°	178.0~179.0°
	yield	93.5%	81.5%	81.4%
	NMR δ (DMSO-d_6)	2.49(5-$COCH_3$)	2.87(5-$COCH_2$-)	2.89(5-$COCH_2$-)
	MASS m/e	286(M^+)	300(M^+)	314(M^+)
II→X	yield	52.4%	49.2%	44.1%

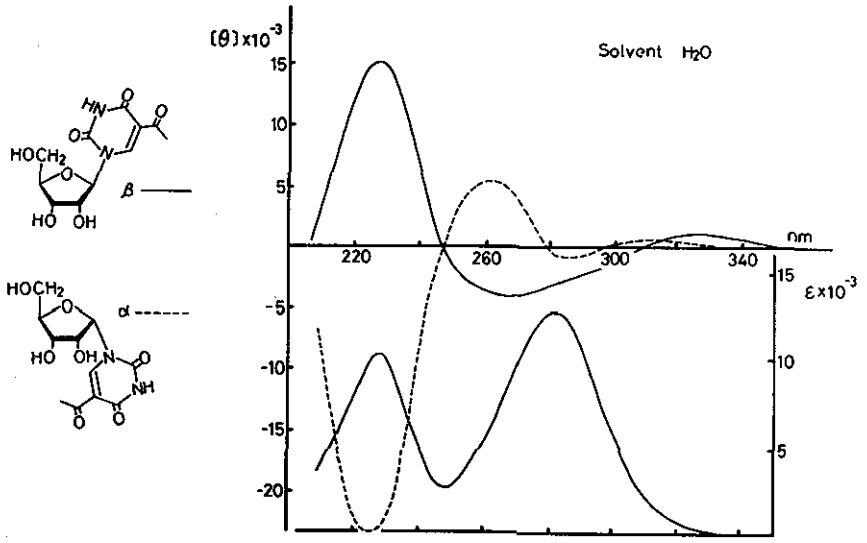
Eckstein and co-workers reported[13] that 5-formyluridine underwent anomerization in a strong alkaline medium. We confirmed similar anomerization when IX(R=Me) was dissolved in 2 N NaOH, in which the α-anomer being predonimating in a ratio of 2.5: 1. The differnces of chemical shifts($\Delta\delta$) of the two methyl signals of the isopropylidene moieties of IX-β and IX-α in NMR were 0.2 and 0.03 ppm, respectively, and consist with Imbach's proposal[14] for determination of the anomeric configuration of the isopropylidene nucleosides.



Furthermore, as the CD spectra of α- and β-5-acetyluridines show(Fig. 1), the main patterns are in mirror images in each other, and reflect the difference in anomeric configurations between the two. The weak positive CD bands appearing at 320 nm are probably due to the $n \rightarrow \pi^*$ transition of the carbonyl of 5-acetyl group.

The method described may be effective for the preparation of various 5-alkyl- and acyl-pyrimidine 2'-deoxyribosides of potential biochemical interests.

Fig. 1. **CD Spectra of α- and β-5-Acetyluridine**



ACKNOWLEDGEMENT This work was supported, in part, by the Grant-in-Aid for Scientific Research from the Ministry of Education, and Welfare of Japan.

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Received, 26th August, 1977