NOVEL BASE-MODIFIED NUCLEOSIDES[1] 祝

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Addition of halocarbenes to uridine derivatives leads to the formation of C_5-C_6 adducts, which upon heating yield novel 1,3-diazepine nucleosides.

In connection with our continued interest in the synthesis of unconventional nucleoside analogues[1] we have recently investigated the general synthesis[2] and transformations[3] of 1,3-disubstituted uracil-carbene adducts. This communication describes the utility of the observed reactivity-patterns in the synthesis of novel 1,3-diazepine nucleosides.

Reaction of 5'-acetoxy-2',3'-O-isopropylidene-3-methyluridine (1) with appropriate phenylmercurymethyl trihalides[4], in refluxing benzene, yielded diastereomeric mixture of adducts 2-5 in yields ranging from 50 to 70%. The diastereomers were separated by chromatography (silica gel column; eluents: ethyl acetate/cyclohexane) and classified as belonging to the A or B type depending upon the sign

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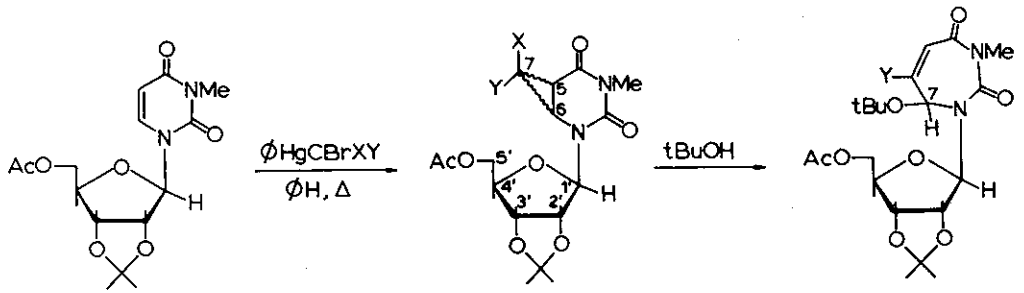
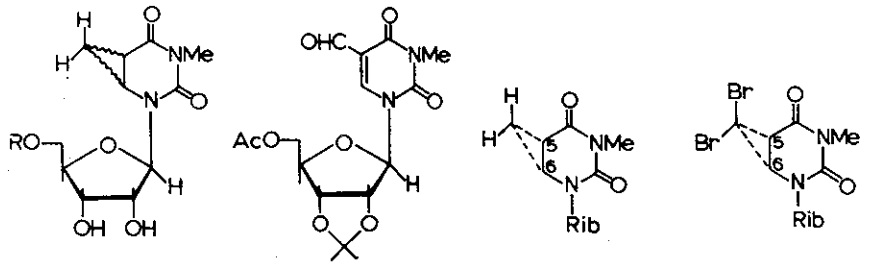
祝 Dedicated to Dr. K. Takeda on his 70th birthday.



1

2 (A,B) X=Y=Cl
3 (A,B) X=Y=Br
4 (A,B) X=Cl, Y=F
5 (A,B) X=F , Y=Cl



6 R=H
7 R=Ac

10

11(5S,6R)

12(5S,6S)

of the CD maximum and the chemical shift of the $C_{1'}$-H in the product. Diastereomers of type A exhibited the $C_{1'}$-H proton in the narrow range of δ 5.58 - 5.64 while those of class B showed the same proton in the region δ 6.03 - 6.16 (Table I). CD spectral curves of diastereomers A and B possessed, in the range 248 - 262 nm, negative and positive maxima, respectively. The structures assigned to the carbene-adducts were fully substantiated by their microanalytical and/or spectral (ir and nmr) data.

Reduction of diastereomers 3A and 3B with $(n\text{-}C_4H_9)_3SnH$, followed by hydrolysis, led to the formation of nucleosides 6 and 7, respectively. Since these transformations would not affect the configuration of the cyclopropane ring, 6 should belong to the A series and 7 to the B series. Kunieda and Witkop[5] have reported a positive Cotton effect (ORD spectrum) at 260 nm, for the 5R,6S diastereomer of 6. Since 3A was converted to the diastereomer of 6 with a negative Cotton effect at 258 nm (Table I), the latter can be, consequently, assigned the 5S,6R (11) configuration. It would follow from this correlation that the starting dibromo-adduct 3A possesses the corresponding 5S,6S (12) configuration. Accordingly, the series of diastereomers A and B may be assigned the configurations 5S,6S and 5R,6R, respectively.

It should be pointed out that the chemical shifts of the $C_{1'}$-protons (Table I) in the series A and B suggest a syn-conformation for the former and an anti-conformation for the latter class of diastereomers. Such preferred conformations could arise as a result of steric interactions of the halogen atoms with the ribose frame-work. This suggestion is borne out by the close similarity of the $C_{1'}$-hydrogens in the nucleosides 6 and 7 (Table I), which

TABLE I

Chemical Shifts (δ)[a] of significant protons and CD[6] (ORD) data of compounds 1-10.

Compound	C(5)H	C(6)H	C(7)H	NMe	C(1')H	C(2')H[d]	C(3')H[d]	Ac	$\lambda_{max}[\theta]$	
1	5.82	7.33		3.32	5.70	5.05	4.88	2.09		
2A	3.00	3.63		3.15	5.60	5.02	4.81	2.07	255	-26000
2B	3.04	3.81		3.17	6.10	4.80	4.71	2.08	255	+22000
3A	3.07	3.76		3.16	5.62	4.84	4.72	2.08	262	-9600
3B	3.10	3.80		3.21	6.16	4.6-4.9(m)		2.11	262	+9900
4A	3.08dd	3.70dd		3.16	5.58	5.02	4.81	2.09	248	-29000
4B	3.08dd	3.90dd		3.16	6.03	4.6-4.9(m)		2.03	249	+27500
5A	2.84dd	3.55		3.16	5.64	4.93	4.78	2.07	248	-24000
5B	2.87dd	3.66		3.18	6.04	4.6-4.8(m)		2.06	249	+22000
8	6.51		5.33	3.26	5.59	4.7-4.9(m)		2.10		
9	5.82dd		5.41dd	3.23	5.51	4.83	4.57	2.07		
10		8.25	10.05	3.37	5.9	4.7-4.9(m)		2.12		
7	2.19	3.32		3.12	5.95			2.07	244	+26000
									$\lambda_{max}[\Phi]^c$	
6[c]	2.26	3.37		3.14	5.99				230	+27200
									258	-7500

Spectra taken in: a. $CDCl_3$; b. ethanol. c. The NMR and ORD spectra of compound 6 were taken in D_2O and H_2O, respectively, for comparison with the reported data (ref.5)
d - centres of multiplets.

lack the halogens, and is further supported by the nmr data[5] for the two diastereomers of 6. In contrast to this configuration-conformation correlation, models of the 5R,6R and 5S,6S diastereomers of 2 appear to sterically favour the syn- and the anti-conformations, respectively. This observation, coupled with the assumption that the cyclopropane ring contributes to a cotton effect (at 260 nm) which is opposite in sign to that due to the methyl group in 5S-5-methyl-5,6-dihydrouridine, made by Kunieda and Witkop[5] in assigning the 5R,6S configuration to 6, cautions against a definitive configurational assignment of the diastereomers of adducts 2-5. An X-Ray analysis of the diastereomers of 2 has been undertaken in order to settle this question.

When 3(A,B) were heated in t-butanol (110°, sealed tube) diazepinone derivative 8 and the aldehyde 10 were isolated in variable yields. The formation of 8 can be rationalized in terms of an electrocyclic ring-opening process[6] such as has been previously proposed[3] for the ring-expansion of uracil-carbene adducts. In line with this proposal, both diastereomers of 4 gave nucleoside 9 upon heating in t-butanol (110°) while 5A and 5B were unaffected under the same conditions. As expected, a concerted disrotatory cyclopropane ring-opening is sterically prohibited in the case of the exo-chloro adducts 5 (A,B)[7].

The mechanism of formation of 10 from 3 (A,B) is not clear at present. The role of the ribose moiety in the latter transformation is suggested by the absence of the aldehyde product (10) in an analogous reaction of the 1,3-dibenzyluracil-dibromocarbene adduct[3]. A possible role of the $C_{5'}$-acetate group in the formation of 10, via catalysis of the C_6-C_7 bond-cleavage in 3 (A,B),

has been eliminated by studies involving the 5'-deoxy analogue of 3[8]. The mechanism of this reaction is receiving further attention.

The transformation of uridine derivatives to novel nucleosides, of which 8 and 9 constitute the first examples, is currently in progress.

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* To whom all inquiries should be addressed.

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