REACTION OF CARBENES WITH 1,3-DISUBSTITUTED URACIL DERIVATIVES

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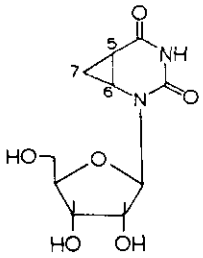
A general approach for the synthesis of 7-substituted 5,6-methano-5,6-dihydrouridine (1) derivatives is described.

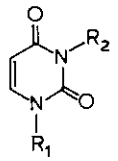
It has been recently reported that the 5'-diphosphate of modified nucleoside 1 is capable of copolymerization with ADP, IDP, UDP or CDP under influence of polynucleotide phosphorylase[2]. In view of the general interest in modified nucleosides represented by structure 1 - as potential substrates or antimetabolites in (poly)nucleotide biosynthesis - the availability of a procedure by which a functionalized carbon could be spanned across the 5,6-double bond of suitable pyrimidine derivatives would be of great value. The resulting products, and the ring-modified systems accessible via them, would constitute a novel class of nucleoside analogues. This communication presents an approach by which the desired operation can be conveniently accomplished.

The simplest method of introducing a carbon across the ends of a multiple bond is via the addition of a carbene or a carbenoid intermediate. Although Witkop et. al[3] report that methylene

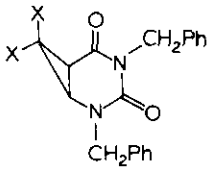


1

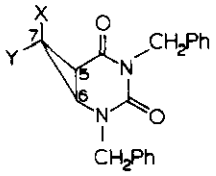
2	X	Y
a.	Cl	Cl
b.	Br	Br
c.	Cl	F
d.	H	COOEt



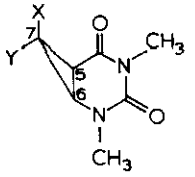
3	R_1	R_2
a.	Me	Me
b.	CH_2Ph	CH_2Ph



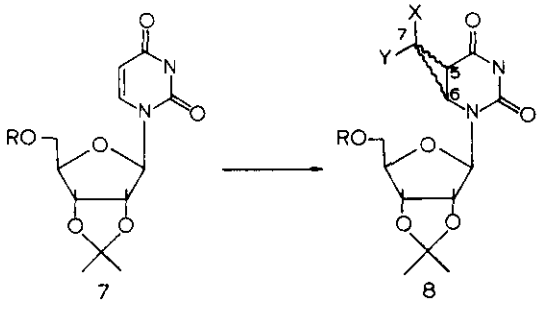
4
a. X = Cl
b. X = Br



5	X	Y
a.	Cl	F
b.	F	Cl



6	X	Y
a.	COOEt	H
b.	H	COOEt



7

a. R = Ac
b. R = H

8

	R	X	Y
a.	Ac	Cl	Cl
b.	CH_2COOEt	COOEt	H

(: CH_2) does not add to uracil derivatives, it seemed to us that such a reaction could be achieved if electrophilic carbenes were allowed to react with analogous substrates. Consequently, we undertook the examination of the reaction of carbenes[4] 2a-d with a variety of uracil derivatives.

Reaction of 1,3- dimethyluracil (3a) with dichlorocarbene (2a), generated by decomposition of either sodium trichloroacetate (thermally) or chloroform (under influence of base), led to intractible mixtures in which the anticipated adduct could not be identified. However, when the analogous dibenzyl derivative 3b was allowed to react with $PhHgCCl_2Br$ in benzene (reflux), the adduct 4a was isolated as a crystalline product (m.p. 96-98°) in 80% yield. Structure of 4a followed from its spectroanalytical data. [PMR δ 2.69 d, J=10 (1H, H_5), 3.22 d, J=10 (1H, H_6), 4.71 q, AB pattern, δ_{AB}=0.6, J=15 (2H, N_1-CH_2Ph), 4.89 s (2H, N_3-CH_2Ph), 7.02-7.45 m (10H, aromatic protons)].

A similar reaction of 3b with $PhHgCBr_3$ yielded the dibromo adduct 4b (m.p. 114-117°) in 38% yield (based upon recovered 3b).

Reaction of 3b with the unsymmetrical carbene :CFCl (2c), generated from $PhHgCCl_2F$, led, as expected, to the formation of a mixture of isomeric adducts 5a (m.p. 84-86°) and 5b (140-142°) in yields (based upon recovered starting dibenzyluracil) of 43% and 37%, respectively. Configurational assignment of the isomers followed from their PMR spectra. The endo-chloro isomer 5a exhi-

bited two sets of double doublets at δ 2.84 $J_{5,6}$=10.5, $J_{H,F}$=17 and 3.33, $J_{6,5}$=10.5, $J_{H,F}$=7.5 for H_5 and H_6, respectively. The exo-chloro isomer 5b, on the other hand, showed a pattern of signals - δ 2.65, dxd, $J_{5,6}$=10 (H_5); $J_{H,F}$=3.5; δ 3.14, d, $J_{6,5}$=10, $J_{H,F}$=0 (H_6) - which attested to a trans location of the C_7-F and the C_5- and the C_6-protons[5]. Ethoxycarbonylcarbene 2d - generated by heating ethyl diazoacetate in refluxing DME - added to 3a to yield endo-adduct 6a, 70.5-71.5° (29%) and exo-adduct 6b, 82-83.5° (43%). Configuration of the adducts was derived from the chemical shifts and coupling patterns of the ring protons of the cyclopropane moiety. Particularly revealing were the signals for the C_7-H, which in 6a appeared as a double doublet at δ 2.20, $J_{7,5}$=10, $J_{7,6}$=6 and in 6b as an analogous pair of doublets at δ 2.01, $J_{7,5}$=5 and $J_{7,6}$=3.

With the aim of applying the reaction to the synthesis of nucleoside analogues of type 1, uridine derivative 7a was treated with excess of $PhHgCCl_2Br$ in refluxing benzene. Workup of the reaction resulted in a mixture of diastereomers (named A and B), corresponding to structure 8a, in 72% yield. The diastereomers were separated by column chromatography (A/B = 1). Although available data does not allow the assignment of absolute configurations to A and B, significant differences in their PMR spectra are noted. Diastereomer A: δ 1.4 and 1.6 2xs (6H, isopropylidine methyls), 2.11s (3H, CH_3CO), 3.02 d, J=10 (1H, H_5), 3.21 s (3H, N-CH_3), 3.69 d, J=10 (1H, H_6), 4.36 coleasced m (3H, C_5, (H_2) + C_4,H), 4.65-5.15 m (2H, C_2,H + C_3,H), 5.68 d, J=2 (1H, C_1,H); diastereomer B: δ 1.4 and 1.61 2xs (6H, isopropylidine

methyls), 2.10 s (3H, CH_3CO), 3.05 d, J=10 (1H, H_5), 3.22 s (3H, N-CH_3), 3.84 d, J=10 (1H, H_6), 4.37 coleasced m (3H, C_5, (H_2) + C_4,H), 4.61-5.00 m (2H, C_2,H + C_3,H), 6.16 d, J=2.5 (1H, C_1,H).

Reaction of uridine system 7b with the precursor of carbene 2d, resulted in a product, albeit in low yield (< 5%), which was identified as 8b. The endo-COOEt configuration of the compound was attested by its PMR spectrum; the C_7-proton appeared as a double doublet centred at δ 2.27, $J_{7,5}$=10, $J_{7,6}$=6.5. Formation of 8b involves, besides addition of the carbene across the 5,6-double bond, an insertion reaction of the same at the C_5,(H_2) - O-H bond. The exact sequence of the latter reactions is not known, however, general considerations of the reactivity of the carbene at the two sites prompts one to predict that the insertion reaction constitutes the first step.

Synthesis of diverse nucleoside analogues corresponding to 1 via the abovementioned general reaction is currently in progress.

REFERENCES

* To whom all inquiries should be addressed.

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4 For sake of convenience the word carbene is also used to indicate carbenoid reagents.

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