REACTIONS OF CARBENES WITH PYRIMIDINES AND ISOQUINOLINES. SYNTHESIS OF MODIFIED NUCLEOSIDES AND ALKALOIDS.

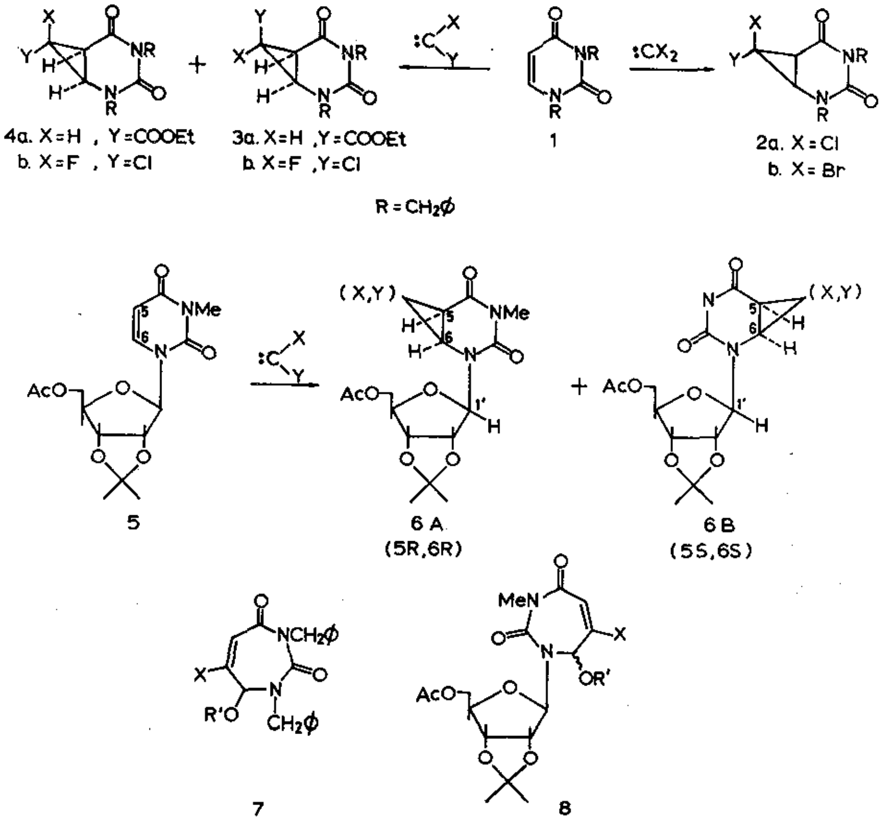
U.K. Pandit

Organic Chemistry Laboratory, University of
Amsterdam, Nieuwe Achtergracht 129, Amsterdam.
The Netherlands.

Reactions of carbenes with the olefinic function of heterocyclic systems[1] is of potential synthetic interest.
The primary addition products of such reactions can undergo diverse types of transformations[2] depending upon the nature of the hetero atom and its location with respect to the site of addition. With the objective of developing new, and hopefully convenient, approaches to the synthesis of modified nucleosides and alkaloids, the reactions of carbenes with suitable pyrimidine and isoquinoline derivatives have been studied in our laboratory.

Pyrimidines.

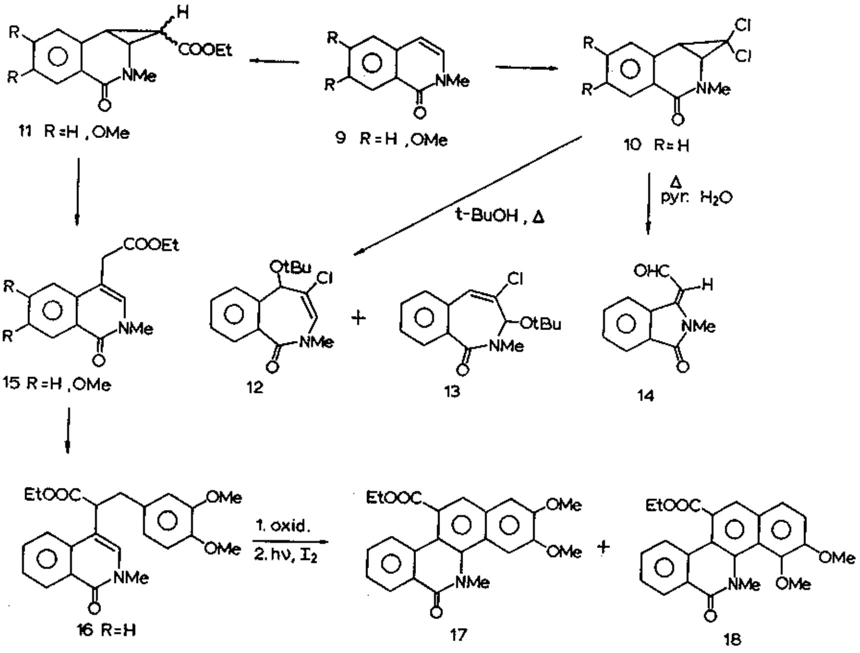
Dihalocarbenes ($:CX_2$, X=Cl, Br) react with 1,3-dialkylated uracil derivatives (1) by adding to the 5,6-double bond of the uracil ring, to form 1:1 adducts (2)[3]. The unsymmetrically substituted (methylene) carbenes ($X\ddot{C}Y$, X=Cl, Y=F; X=H, Y=COOEt) gave, as expected, mixtures of two isomeric adducts (3a,b and 4a,b; Scheme I). Similar reactions of dihalocarbenes with uridine derivative 5 resulted in diastereomeric addition products 6A and 6B[4a,b]. The absolute stereochemistry of the halocyclothymidines (6A,B) was established by X-Ray analysis of one of the adducts (6A, X=Y=Cl)[4b] and correlation within the A and B series by com-


4a. X=H , Y=COOEt
b. X=F , Y=Cl
3a. X=H ,Y=COOEt
b. X=F ,Y=Cl
1
:CX₂
2a. X=Cl
b. X=Br
R=CH₂ϕ
5
6 A
(5R,6R)
6 B
(5S,6S)
7
8

Scheme I

parison of their CD-spectra. The 5R,6R diastereomers exhibited a positive Cotton effect while their 5S,6S counterparts showed a Cotton effect with a negative sign. Particularly noteworthy was the observation that a significant difference existed between the chemical shifts of the C(1')-protons of the A- and B-series. The lower field resonance of the C(1')-proton in A, in comparison to the resonance of the corresponding proton in B indicated a difference in conformation about the glycosidic bond between the 5R,6R and the 5S,6S diastereomers. Consideration of the anisotropic influence of the C(2)-carbonyl group allows an assignment of anti- and syn-conformations to the A- and B-series, respectively. Unsymmetrical carbenes ($X \neq Y$) gave geometrical isomers (about the cyclopropane ring) corresponding to the two diastereomeric series.

The carbene adducts 2a,b and 6A,B (X=Y=Cl or Br) undergo a ring-expansion to the corresponding diazepinediones 7 and 8, respectively, upon heating in alcohols (R'OH)[5]. This reaction is subject to a stringent stereoelectronic control in accordance with the orbital symmetry rules. Thus, in the chlorofluorocarbene adducts (3b, 4b; 6A,B X=Cl, Y=F), while the endo-chloro isomers readily underwent conversion to the ring-expanded products (7, 8; X=F), the corresponding endo-fluoro adducts were totally inert under the same reaction conditions. In the case of uridine adducts, the reaction is, in addition, influenced by the conformation of the heterocyclic base with respect to the sugar moiety.


11 R=H, OMe
9 R=H, OMe
10 R=H
t-BuOH, Δ
Δ
pyr. H₂O
15 R=H, OMe
12
13
14
16 R=H
1. oxid.
2. hν, I₂
17
18

Scheme II

Isoquinolines.

Carbenes add to the 3,4-double bond of the isoquinoline system 9 to yield 1:1 adducts (10 and 11) in good yield. The dichlorocarbene adduct 10 undergoes cyclopropane ring-opening to different products (i.e. 12 + 13 and 14) depending upon the conditions of the reaction. These results throw light upon the mechanism of the ring-opening process.

The endo- and exo-ethoxycarbonyl adducts 11 undergo a thermal transformation to 15; the exo-isomer requiring a higher temperature (245°) than the endo-compound (190°). Refluxing in ethanol, in the presence of acid, converted both isomers, quantitatively, into 15. The β,γ-unsaturated ester 15 can be smoothly alkylated to the seco-benzphenanthridine system 16. Oxidation of 16, followed by a photo-oxidative cyclization, resulted in a mixture of benzphenanthridine derivatives 17 and 18, which were separated by chromatography. The cyclization step resulted in the two isomers (17 and 18) in a total yield of 85%.

The mechanisms of the reactions shall be presented and their potential scope in the synthesis of modified nucleosides and alkaloids will be discussed.

References.

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